The Ring of Fire
Imaging Vascular Calcification and Inflammation Using PET/CT

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Introduction

• We have used PET/CT to study the pathology of 2 conditions

• Aortic stenosis: the most common form of heart valve disease in the western world

• Atherosclerosis: the most common cause of death
Similar Pathophysiology

Why are statin ineffective in aortic stenosis?
Positron Emission Tomography
PET Detector

Positron + Electron \rightarrow 2 \times 511\text{keV} \text{ photons}
Positron Emission Tomography (PET) Computed Tomography (CT) (PET/CT)

PET

FUSED PET/CT
PET Tracers Used

18F-Fluorodeoxyglucose (18F-FDG):
  - Inflammation

18F-Sodium Fluoride (18F-NaF):
  - Calcification Activity
18F- Fluorodeoxyglucose (18F-FDG)

- Glucose analogue: metabolic trapping within cells with high glucose requirements
  - Cancer imaging
  - Vascular inflammation
    - Macrophages have higher glucose requirement than surrounding cells
$^{18}$ Fluoro-Deoxy Glucose
Atherosclerosis

Rudd et al. *Circulation* 2002;105:2708-2711
\(^{18}\text{Fluoro-Deoxy Glucose}\) Correlates with carotid macrophage burden

Tawakol et al JACC 2006
18F-NaF

Calcification Activity

- Used as a bone tracer for 30 years
- Binds to hydroxyapatite, a key structural component of bone and vascular calcification
18F-NaF is a marker of Calcification Activity

| Volume μm³ | 8000 | 8000 | 8000 | 8000 |
| Surface area | 2400 | 4800 | 24,000 | ? |

24,000,000,000 μm²
Aortic Stenosis
Aortic Stenosis Background

- Burden is set in increase
  Nkomo et al, Lancet 2006

- No effective medical treatment

- Predicting disease progression is challenging

- Pathophysiology is incompletely understood
Aims

To use PET/CT to investigate

• The relative contributions of calcification (18F-NaF) and inflammation (18F-FDG) to the different stages of aortic stenosis

• The importance of calcification and inflammation to disease progression.
Methods

• 121 patients, age 72 ±8 years, 69% male
  – 20 Control; 20 Aortic Sclerosis; 25 Mild, 33 Moderate, 23 Severe Aortic Stenosis

• Echocardiogram, CT Calcium score & 2 PET /CT scans at baseline
  – 125MBq 18F-NaF
  – 200MBq 18F-FDG

• 20 patients: repeat echo and CT calcium scoring at 1 year
18F-NaF Activity: Aortic Valve

Field of View: 780mm
512 matrix size
Voxel size: 1.5 × 1.5 × 3.0mm
18F-NaF Correlates with Histological Markers of Calcification Activity

18F-NaF PET

Alkaline Phosphatase

Alk Phos Immunohistochemistry

Graph showing the correlation between Valve 18F-NaF Activity and the % surface area of the valve stained. The equation is R² = 0.82, P < 0.001.
Tracer uptake vs Aortic Stenosis Severity

Aortic Valve PET Activity (TBR)

Dweck et al Circulation 2012;125:76-86
Differences between Atheroma and Aortic Stenosis

- Calcification (18F-NaF) increased in the valve.

- Inflammation (18F-FDG) increased in aortic atheroma

Dweck et al. European Heart Journal. In press
18F-NAF Predicts Aortic Stenosis Disease Progression at 1 year

Good correlation between baseline PET activity and - change in calcium score (CT) $r^2=0.44$, $p<0.001$

Out performed the current gold-standard method: $r^2=0.36$, $p<0.001$

18F-FDG was not predictive of disease progression: $r^2=0.02$, $p=0.55$
Conclusions

• Positron emission tomography is a novel, feasible and repeatable approach to the evaluation of valvular calcification and inflammation in patients with aortic stenosis.

• PET/CT holds promise as a clinical tool for predicting disease progression and as a surrogate biomarker and end-point in studies of potential therapeutic agents.

SALTIRE 2

- Test whether putative anti-calcific therapies can reduce the 18F-NaF signal in the aortic valve and whether they can slow disease progression
  - Bisphosphonates
  - Denosumab
  - ACE inhibitors
Background

- The majority of MIs are caused by atherosclerotic plaque rupture

- Identifying lesions at risk of rupture is challenging

- Most are non-flow limiting
  - Therefore missed by conventional stress testing or invasive coronary angiography
Inflammation, Calcification & Vulnerable Plaque

**VULNERABLE PLAQUE CHARACTERISTICS**

**Inflammation**
- Macrophages
- Secrete MMPs

**Calcification**
- Healing response to inflammation
- Early stages increase vulnerability

**Spotty Calcification**

Adapted from Vancraeynest et al, JACC 2011
Hypothesis

18F-FDG and 18F-NaF PET might label high-risk coronary atherosclerotic plaques by identifying inflammation and spotty calcification respectively.
Coronary Atherosclerosis Cohort

• Patient population
  – 40 patients with stable angina
  – 40 patients post myocardial infarction

• All received
  – Invasive & CT coronary angiography
  – Calcium scoring
  – 18F-FDG & 18F-NaF PET
Measurement of Coronary 18F-FDG Activity was Difficult

- Not possible in >50% of the coronary vessel territories examined
- No important differences observed between our populations
18F-NaF Activity post STEMI

Coronary Angiogram (LCA)

Fused 18F-NaF PET CT
18F-NaF Activity post STEMI

Coronary Angiogram (LCA)

Fused 18F-NaF PET CT
18F-NaF Activity post NSTEMI

Coronary Angiogram (RCA)

Fused 18F-NaF PET CT
• 93% had increased $^{18}$F-NaF activity in the culprit plaque

• The remaining 7% were either young smokers or had an equivocal culprit
18F-NaF Identifies Culprit Plaque Post TIA

12 patients undergoing endarterectomy post TIA: 18F-NaF activity localised exactly to the area of plaque rupture on the excised plaques
18-NaF Uptake Associated with increased Histological Calcification Activity

**Alkaline Phosphatase**

<table>
<thead>
<tr>
<th>%Staining of vessel wall</th>
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<tbody>
<tr>
<td>NaF Positive Regions</td>
</tr>
<tr>
<td>NaF Negative Regions</td>
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p<0.0001

**Osteocalcin**

<table>
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<th>%Staining of vessel wall</th>
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<td>NaF Positive Regions</td>
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<td>NaF Negative Regions</td>
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</table>

p<0.0001
18F-NaF Identifies Vascular Calcification Activity & Culprit Plaque

What about stable coronary artery disease?
Stable Coronary Artery Disease

- Focal increased 18F-NaF uptake observed in 45%
18FNaF Activity in the Absence of Calcification on CT
VH-IVUS Features of 18F-NaF Positive and Negative lesions

- NaF -ive
  - 12% Necrotic core
  - 12% Calcification
  - 76% Fibrous/ Fibrofatty

- NaF +ive
  - 49% Necrotic core
  - 11% Calcification
  - 40% Fibrous/ Fibrofatty
18F-NaF Appears to Identify Vulnerable Plaque

VULNERABLE PLAQUE CHARACTERISTICS

- Spotty Calcification
- Large Necrotic Core
- Inflammation
- Thin Fibrous Cap
- Positive Remodeling

<table>
<thead>
<tr>
<th>Feature</th>
<th>NaF Positive</th>
<th>NaF Negative</th>
<th>P-value</th>
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<tbody>
<tr>
<td>NaF Positive:</td>
<td>73%</td>
<td>21%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimal Luminal Area mm²:</td>
<td>9 (6-14)</td>
<td>7 (5-10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque Area mm²:</td>
<td>24(21-29)</td>
<td>14 (12-18)</td>
<td></td>
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CONCLUSIONS

• Calcification appears to occur as a healing response to intense plaque inflammation

• 18F-NaF identifies high-risk plaque
  • Culprit plaques post myocardial infarction
  • In stable angina vulnerable plaques with multiple high-risk features
Marker of the Vulnerable Plaque?

Has the potential to change the way we treat coronary disease

Lesion Severity Ischaemia  Plaque Biology Vulnerability
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High sensitivity-Trop I in stable angina patients

\[ p = 0.047 \]
Excellent Interobserver Reproducibility

18F-NaF

A)
Average of Max 18F-NaF TBR measurements

Mean Difference

0 2 4 6 8
-1.4
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4

0.23
0.02
-0.19

18F-FDG

D)
Average of Max 18F-FDG TBR measurements

Mean Difference

-0.11
0.02
-0.15

-0.7
-0.6
-0.5
-0.4
-0.3
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
18F-NaF Predicts Change in Coronary Calcium Score

$r^2 = 0.52 \ p < 0.001$
Poor Reproducibility of Coronary 18F-FDG Measurements

- Not possible in 49% of the coronary vessel territories examined

Intra-class Correlation Coefficient = 0.67 (95% CI: 0.31 to 0.86)
18F-FDG Activity
Aortic Valve 18F-FDG activity Maps Closely to Macrophage Staining

18F-FDG PET

CD 68 Immunohistochemistry
Fluoro-Deoxy Glucose
Influence of Statins

Tahara et al. JACC 2006;48:1825-1831
Tawakol et al. JACC 2013; in press