Imaging of Atherosclerosis with PET-CT

Ahmed Tawakol, MD
Co-Director
Cardiac MR PET CT Program
Mass General Hospital
Assistant Professor
Harvard Medical School

Disclosures

• Research Grants:
  – NIH, Roche/Genentech, BMS

• Consulting
  – Cerenis, Novartis, Roche/Genentech

Case:
Middle Aged Woman w CP
Most Culprit Lesions Cause Insignificant Luminal Narrowing Prior to Onset of MI

**Imaging Atherosclerosis**

1) Stenosis evaluation is inadequate for atherosclerotic plaque evaluation and risk stratification.

2) The evaluation of the arterial wall composition and biology may provide important insights.

3) This can be achieved via a combination of molecular and structural imaging.

**Clinical PET/CT in Oncology: An Important Example for Cardiology**

- Combined molecular and structural imaging (PET-CT) more accurate than structural imaging alone (CT or MR) for tumor staging and localization
  - Lardinois, NEJM 2003,
  - Antoch, JAMA 2003

- FDG PET highly accurate for following response to chemotherapy

- Proliferation of PET

- Transformed Oncology practice and clinical trials
FDG-PET Accumulation: Measure of Tissue’s Glycolytic Rate

Up-Regulation of Glycolysis With Macrophage Activation

Glycolytic Flux Correlates with Human Macrophage Activation Regardless of Stimulus or O₂ Tension
FDG Uptake By Macrophages Important in Tumor Imaging

J.H.F. Rudd et al., Circulation 2002

FDG Uptake by Macrophages Important in Tumor Imaging

Distribution of FDG Within Human Plaques: Predominantly In Macrophages

FDG Uptake Vs. Inflammation In Atherosclerotic Rabbits

Jawad, et al. JNC 2006

FDG Uptake (% ID/gm*10^3)

0 20 40 60 80 100 120 140

Blood Activity

>0-5

>5-15

>15

Vessel Inflammation (% RAM-11 Staining)

P<0.001, r=0.79
FDG Uptake Correlates w Plaque Inflammation

FDG-PET vs. Histology and Gene Expression

Vascular FDG Uptake And Inflammation Vs. CT Morphological Imaging Features
Vascular inflammation at 6 Months ($\Delta$TBR, 6 months-baseline).

**Coronary FDG PET**

- ACS vs. Stable Syndrome:
  - New Stent: $p<0.01$
  - Old Stent: $p=0.32$

**Plaque Imaging as a Marker of Atherothrombotic Risk**
Aortic FDG Uptake Increased In ACS

PET CT Fused Image

Increased FDG Uptake Observed In Symptomatic Carotid Disease

Vasc FDG Signal Identifies Increased Systemic Risk of Future Atherothrombosis
TBR Levels By Framingham Risk Score


Vasc FDG Signal to Refine Risk

Risk Categories | NRI | Events correctly reclassified | Non-events correctly reclassified |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10% risk</td>
<td>29.44% [13.45, 48.42]</td>
<td>12.20%</td>
<td>17.24%</td>
</tr>
<tr>
<td>10-20% risk</td>
<td>12.20%</td>
<td>17.24%</td>
<td></td>
</tr>
<tr>
<td>&gt; 20% risk</td>
<td>17.24%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDG-PET Signal Contains Temporal Information

β coefficient -0.096, p<0.0001
Assessment of Interventions

Rapid Modulation of Signal

- Anti-Inflammatory Rx
- Pro-Inflammatory Cytokines

Monocyte Recruitment in Atherosclerosis
Statin Rx Reduces Vasc Inflammation (Assessed by PET)

Single Center, Open-label Study
Simva 5-20 vs diet

Baseline Follow-up
PET-CT
SUV

Diet
Simvastatin
BL Wk 4 Wk 12 BL Wk 4 Wk 12
Atorva statin 10 mg Atorva statin 80 mg

Δ=7% P=0.04
Δ=6% P=0.04
Δ=13% P=0.001
Δ=15% P<0.001

Vascular FDG Uptake TBR in MDS

Tawakol et al AHA 2011

Change in TBR in the Most Diseased Segment

Pre-study Baseline Wk 4 Wk 12 Final study

Change in LDL-C Over Time

Atorva 10
Δ=7%
P=0.04

Atorva 80
Δ=6%
P=0.04

% Reduction in MDS TBR at wk12

% Reduction in LDL-C at week 12

Tawakol et al AHA 2011

Change in LDL

Δ=13%
P=0.001

Δ=15%
P<0.001

* = significant reduction (p < 0.01) from baseline; # = significant reduction (p < 0.01) of Atorva 80 relative to Atorva 10

Tawakol et al AHA 2011
Response To Therapy: Pioglitazone

Mizoguchi et al. JACC-CV Imaging 2011

Effect of P38 MAP Kinase Inhibition on Vascular FDG Uptake

Elkhawad et al. JACC-CV Imaging 2012 in press

Anti-Tumor Necrosis Factor-α Therapy Reduces Aortic Inflammation in RA

Kaisa M. Mäki-Petäjä et al. Circulation 2012
Psoriasis: Reduction in Arterial Inflammation Correlates w Anti-inflam Drug Concentration

Kimball et al Am Academy of Dermatology 2012

Increases in HDL Correlates with Reductions in Carotid Inflammation (PET)

Fayad et al Lancet 2011

Fayad et al Lancet 2011, Tawakol et al ESC August 2012
DalOUTCOMES Trial

![Cumulative Incidence of Primary Outcome (% of patients)](image)

P=0.52 by log-rank test

<table>
<thead>
<tr>
<th>Year</th>
<th>No. at Risk Placibo</th>
<th>No. at Risk Dalcezudapib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>293</td>
<td>293</td>
</tr>
<tr>
<td>1</td>
<td>7386</td>
<td>7372</td>
</tr>
<tr>
<td>2</td>
<td>6551</td>
<td>6495</td>
</tr>
<tr>
<td>3</td>
<td>3743</td>
<td>3736</td>
</tr>
</tbody>
</table>

Additional CV Targets
FDG Uptake In The Aortic Valve

[Image: Image of aortic valve with FDG uptake highlighted]

Marincheva et al, JACC 2011

FDG Uptake and Aortic Valve Calcification

[Graph showing correlation between FDG uptake and aortic valve calcification]

Marincheva et al, JACC 2011

FDG Increased in Myocardial Inflammation After MI

[Graph showing increased FDG uptake in myocardial inflammation after MI]

Lee et al, JACC 2012
FDG Increased in Myocardial Inflammation After MI

Cardiac Sarcoidosis Imaging

Atherosclerosis Imaging as a Tool to Develop Novel Disease Insights

Aortic Inflammation in HIV Disease
**Obesity**

![Graph showing the relationship between BMI (kg/m²) and vascular inflammation (SU Vmax)].

*Figueras et al. AHA 2010*

**Periodontitis**

![Images and graphs showing changes in carotid and periodontal activity].

*Fifer et al. JACC 2011*

**Novel Pleiotropic Effect of Statins: High Dose Statins Reduce Periodontal Activity**

![Graphs showing the relationship between change in periodontal activity and change in carotid activity].

*Subramanian et al. IADR 2012*
Next Steps: Further Clinical Development

**Confirmatory Studies**
- Prospective studies to evaluate relation between signal and:
  - Events
  - Local progression

**Assess Role in Clinical Care**
- Triage of patients with carotid stenosis
- Aortic diseases
- CAD?

**Evaluation of Therapies**
- Validation in well-blinded multi-center trial setting
- Several on-going multi-center trials

Clinical Trial Designs Must Incorporate Imaging

- Current Clinical Trial Schema is unsustainable
- Phase III:
  - 15,000-30,000 patients over 3-5 yrs
  - $300-700 Million
  - <20% success rate
  - Major impediment to identification of new treatments
- Could imaging facilitate discovery of new treatments?
  - Bring greater confidence when initiating phase 3 trial
  - Approach works in oncology…
- At least half dozen new drugs soon reporting w this approach
- Additional >10 new compound studies w PET-CT & MR soon
- Usher the first new anti-athero drugs since statins?

Development of New Tracers

- RZD Receptor Imaging
- MMP Imaging
- Ado Receptor Imaging

Pugliese et al JACC 2010
Elmahdy et al PNAS 2006
### Improved Processing of Cardiac PET/CT Images Via Optical Flow Modeling

**Input Data**

CT image with three artificially added lesions:
- A: 3-mm radius
- B: 5-mm radius
- C: 2-mm radius

**Results**

<table>
<thead>
<tr>
<th></th>
<th>Conventional N/A</th>
<th>SuperRes</th>
</tr>
</thead>
<tbody>
<tr>
<td>True Area</td>
<td>26 69 12</td>
<td>37 86 21</td>
</tr>
<tr>
<td>Conventional processing</td>
<td>N/A 207 N/A</td>
<td></td>
</tr>
<tr>
<td>Super-resolution</td>
<td>37 86 21</td>
<td></td>
</tr>
</tbody>
</table>

Ambawani S et al, International Symposium on Biomedical Imaging 2011

---

### Future of Atherosclerosis Evaluation

**Multi-Modality Imaging**

- PET CT
- PET MR