Cardiac Positron Emission Tomography: Tracers and Protocols

Johannes Czernin, M.D.

Ahmanson Biological Imaging Clinic
David Geffen School of Medicine at UCLA
Why PET Perfusion Imaging?

• Resolution
• Attenuation Correction
• Image Analysis
  – Qualitative/Semi-quantitative (polar maps)
  – Quantitative (ml/g/min): To study physiology in health and disease (interventions)
    • Risk factors
    • Risk factor Modifications
    • Transplant Vasculopathy
    • Balanced MVD
Imaging probes for Assessing Myocardial Perfusion

- O-15 Water
- N-13 ammonia
- 82-Rubidium
- 2-tert-Butyl-4-chloro-5-[4-(2-(18F)fluoro-ethoxymethyl)-benzyloxy]-2H-pyridazin-3-one (Mitochondrial Complex 1 (MC-1) Inhibitor)
Net Myocardial Uptake of $^{13}$N-ammonia


$^{15}$O Water

- “ideal” flow tracer; freely diffusible; first pass extraction approaches unity
- Gold standard for comparing other quantitative myocardial imaging approaches
- Cyclotron produced
- Physical half-life 75 seconds
  - Drawbacks: rapid decay; low count rates; also distributes in blood pool
  - Therefore correction methods (blood pool imaging by inhaling $^{15}$O-CO; Binds to Hb as carboxy-Hb)
$^{13}$N-Ammonia

- Cyclotron-produced
- Physical half-life 9.8 minutes
- Intravenous dose 30 to 40 mCi per injection
- Allow 30 to 40 minutes between injections
Blood: In blood mostly as ammonium ion (NH4+)

\[ ^{13} \text{NH}_4^+ \leftrightarrow ^{13} \text{NH}_3 \] (lipid soluble; freely diffusible (equilibrium 19 \( \mu \)sec)

K\(^+\)

Cation Exchange; active transport

1. \(^{13} \text{NH}_4^+\)

2. Diffusion

\[ ^{13} \text{NH}_3 \]

Glutamine synthase (if inhibited with L-methionine no retention)

Glutamate \( \rightarrow ^{13} \text{N-glutamine} \)

Intracellular space

Slides are not to be reproduced without permission of author.
Study Protocol for Rest Stress PET Myocardial Perfusion Imaging with $^{13}$N-ammonia

1. Transmission Imaging 10 min
2. $^{13}$N-ammonia iv (30 to 40 mCi)
3. Start image acquisition from 4 to 19 min
4. Start iv Adenosine (140μg/kg/min) for 4 min
5. $^{13}$N-ammonia iv at 2 min
6. Start image acquisition from 4 to 19 min

Minimize patient motion, needs to remain aligned with transmission images
<table>
<thead>
<tr>
<th></th>
<th>Stress</th>
<th>Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apex</strong></td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td><strong>Short Axis</strong></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td><strong>Base</strong></td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
<tr>
<td><strong>Septum</strong></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
</tr>
<tr>
<td><strong>Vertical Long Axis</strong></td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
</tr>
<tr>
<td><strong>Lateral</strong></td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
</tr>
<tr>
<td><strong>Inferior</strong></td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
</tr>
<tr>
<td><strong>Horizontal Long Axis</strong></td>
<td><img src="image15" alt="Image" /></td>
<td><img src="image16" alt="Image" /></td>
</tr>
<tr>
<td><strong>Superior</strong></td>
<td><img src="image17" alt="Image" /></td>
<td><img src="image18" alt="Image" /></td>
</tr>
</tbody>
</table>
Detection of Coronary Artery Disease with $^{13}$N-ammonia and PET

<table>
<thead>
<tr>
<th>Authors</th>
<th>year</th>
<th>Type</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schelbert</td>
<td>1982</td>
<td>Dip</td>
<td>45</td>
<td>97%</td>
<td>100%</td>
</tr>
<tr>
<td>Yonekura</td>
<td>1987</td>
<td>Ex</td>
<td>50</td>
<td>93%</td>
<td>100%</td>
</tr>
<tr>
<td>Tamaki</td>
<td>1989</td>
<td>Dip</td>
<td>48</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>Demer</td>
<td>1989</td>
<td>Dip</td>
<td>193</td>
<td>94%</td>
<td>95%</td>
</tr>
</tbody>
</table>
Serial Reoriented N-13 Ammonia Images
Arterial Input Function and Tissue Response

N-13 Ammonia Activity (cts / pixel / sec)

Myocardium
Arterial Blood

Time (sec)
**MBF by N-13 Ammonia in Dynamic PET**

Graph showing a linear relationship between MBF by Flow Model and MBF by Microspheres.

- **Equation:**
  
  \[ y = 1.02x - 0.08; r = 0.99 \]

- **Data:**
  
  \[ n = 12 \]

Ref: Kuhle et al, Circulation 1992
Quantitative $^{13}$N-ammonia Blood Flow Studies

- Transmission Images
- Start Serial Image Acquisition
- $^{13}$N-ammonia bolus injection (30 to 40 mCi over 10 sec)
- Image Acquisition Sequence
  - 12 frames, 10 sec each
  - 2 frames, 30 sec each
  - 1 frame, 60 sec each
  - 1 frame, 900 sec
- Reconstruct and reorient all serial images
LV Blood Pool  Myocardium  Time Activity Curves

Baseline

Adenosine
Pharmacologically Induced Hyperemia

MBF Reserve
Adenosine
4.3 ± 1.3
(range 2.0 to 8.4)
Dipyridamole
4.4 ± 0.9
(range 1.5 to 5.8)

Chan et al, JACC 1992; 20:979
Other Quantitative Flow Studies

- Diet and Exercise (Czernin et al)
- Lipid lowering (Schindler et al)
- Smoking (Campisi et al)
- Diabetes (Schindler et al)
- Cold Pressor Testing (Schindler et al)
- Mental Stress (Schoder et al)
- Beta-blockers (Mueller et al)
- Age (Uren et al)

Many papers by Camici’s group, S. Bergman, R. Beanlands, R. Gropler, M. Schwaiger, F. Bengel, R. Brunken, …and many more
Stenosis Severity and Hyperemic Blood Flow flow

$r=0.77; \ p<0.001$  \hspace{1cm}  $r=0.78; \ p<0.001$

Sources of Errors

- Patient Motion between Transmission and Emission Imaging
- Incorrect Reconstruction Parameters (i.e. decay)
- Low Count Transmission Images
- Filtered Backprojection vs Iterative Reconstruction
- Delayed tracer clearance from blood and/or lung
- Reduced uptake of $^{13}$N-ammonia in Lateral Wall of Left Ventricle
Quantification of Myocardial Blood Flow with $^{13}$N-ammonia

- Feasible in the clinical setting
- Does not require additional patient time
- Time for image processing and analysis less than one hour (rest and hyperemia study)
- May prove clinically useful
  - Unexplained anginal symptoms
  - Transplant vasculopathy
  - Therapy monitoring
Rubidium

- Generator-produced
- Parent Isotope: Strontium-82 (25 d)
- Physical half-life 1.26 minutes
- 30 to 60 mCi per injection
- Allow a few minutes between injections
Rubidium

- Cation that substitutes for K+ on the Na+/K+ trans-membranous ion exchange system
- Active transport into myocytes competes with back diffusion that is flow dependent; therefore first pass retention fraction decreases at high flow rates.
**82Rubidium Protocol**

**Rest:** 30 to 60 mCi (1480 to 2220 MBq): Appr. 90 s after injection, 5-minute resting perfusion

**Stress:** intravenous infusion of dipyridamole (0.142 / kg /min for 4 minutes); 3-4 minutes after completion, 40-60 mCi of 82Rb

Schenker et al; Circulation. 2008 Apr 1;117(13):1693-700
Short Axis

Vert. Long Axis

Horiz. Long Axid

Courtesy Dr. Marcello Di Carli
Impact of PET Perfusion Imaging

Hypothesis:
1) Noninvasive Strategy for CAD management using MPI free of attenuation artifacts with improved resolution and image contrast due to substantially higher counts provided by PET, lowers cost of CAD management

2) Reductions in unnecessary diagnostic and therapeutic procedures compared with standard exercise SPECT

Approach: Clinical outcomes, procedure utilization, costs in >2,000 sequential patients imaged with PET; 2 control groups (internal and external group (END trial; Shaw et al JACC 1999))

Patient matched for pretest likelihood of CAD
<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SPECT</td>
<td>PET</td>
<td>SPECT</td>
<td>PET</td>
</tr>
<tr>
<td>Stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Impact of Perfusion Imaging

<table>
<thead>
<tr>
<th></th>
<th>Angio rate</th>
<th>False + nuclear</th>
<th>REVASC rate</th>
<th>CABG rate</th>
<th>PTCI rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>End study (n = 5826) pCAD=0.39</td>
<td>0.340</td>
<td>Not reported</td>
<td>0.130</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>SPECT (n = 102) pCAD=0.37</td>
<td>0.310</td>
<td>0.156</td>
<td>0.114</td>
<td>0.078</td>
<td>0.029</td>
</tr>
<tr>
<td>PET (n = 2159) pCAD=0.39</td>
<td>0.130</td>
<td>0.052</td>
<td>0.060</td>
<td>0.034</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Cost Savings by 30% without Negative Impact on Outcome

![Graph showing cost savings and outcomes](image)

<table>
<thead>
<tr>
<th></th>
<th>Cardiac mortality rate (1 y)</th>
<th>Acute MI rate (1 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>END study (n = 5826)</td>
<td>0.010</td>
<td>0.010</td>
</tr>
<tr>
<td>II SPECT (n = 102)</td>
<td>0.020</td>
<td>0.029</td>
</tr>
<tr>
<td>PET (n = 2159)</td>
<td>0.008</td>
<td>0.011</td>
</tr>
</tbody>
</table>

## Cardiac PET: Diagnostic Accuracy

<table>
<thead>
<tr>
<th>Investigation</th>
<th>N</th>
<th>Sten</th>
<th>Tracer</th>
<th>Stress</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schelbert</td>
<td>45</td>
<td>&gt;50</td>
<td>NH3</td>
<td>DIP</td>
<td>97</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Demer</td>
<td>193</td>
<td>-</td>
<td>Nh3, Rb</td>
<td>DIP</td>
<td>94</td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td>Yonekura</td>
<td>50</td>
<td>&gt;50</td>
<td>NH3</td>
<td>Ex</td>
<td>93</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>Stewart</td>
<td>81</td>
<td>&gt;50</td>
<td>Rb</td>
<td>DIP</td>
<td>84</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>Go</td>
<td>202</td>
<td>&gt;50</td>
<td>Rb</td>
<td>DIP</td>
<td>93</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>Williams</td>
<td>287</td>
<td>&gt;67</td>
<td>Rb</td>
<td>DIP</td>
<td>87</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Simone</td>
<td>225</td>
<td>&gt;67</td>
<td>Rb</td>
<td>DIP</td>
<td>82</td>
<td>91</td>
<td>89</td>
</tr>
</tbody>
</table>
PET Assessment of Myocardial Perfusion
Current Limitations

NH3 and O-15 H2O: Production requires on-site cyclotron

Rb-82: Production is feasible by generator, cost?

- Extraction fraction is lower than NH3
- Positron range: resolution?
- Rest-exercise imaging is not feasible for 15-O water
- Absolute quantitation is possible
What do we need to Achieve?

- Unit dose from regional (not local) cyclotron (F-18)
- High extraction fraction
- Possibility of rest-exercise imaging
- Possibility of absolute quantitation
Chemical Structure of BMS-747158; Lantheus

Mitochondrial Complex 1 (MC-1) Inhibitor

2-tert-Butyl-4-chloro-5-[4-(2-\(^{18}\)F)fluoro-ethoxymethyl]-benzyloxy]-2H-pyridazin-3-one
First-pass extraction in isolated rabbit hearts
BMS-474158 vs. $^{201}$TI and $^{99m}$Tc-sestamibi

PET Imaging with BMS-747158 in Normal Rabbit

Brief Coronary Ligation/ Reperfusion in Rat

Short axis  Long axis Horizontal  Long axis Vertical

Histology  

Cardiac PET

Yu, M et al. J Nucl Cardiol 2007,
BMS-747158 in Non Human Primates

1-4 min PI

5-15 min PI

75-85 min PI

First human study of BMS-747158, a novel F-18 labeled tracer for myocardial perfusion imaging

J. Maddahi, MD; C. Schiepers, MD; J. Czernin, MD; H. Huang, PhD; H. Schelbert, MD; A. Wijatyk, MD; M. Hibberd, MD; J. Lazewatsky, PhD; R. Sparks, PhD; M. Phelps, PhD

UCLA and Lantheus Medical Imaging

SNM 2008
BMS-747158 Phase I Trial

Objectives

- **Primary**
  - To estimate the radiation dosimetry of a single dose in healthy subjects at rest

- **Secondary**
  - To assess the safety and tolerability
  - To examine the biodistribution of a single dose
First Human Study of BMS-747158

20 min

70 min
7-min Image Acquired 3 min After Injection
First Human Study of BMS747158

Time activity curve

Average SUV of Myocardium = 5.4+-0.3
Summary

BMS-747158

- Is safe and well tolerated
- Has acceptable dosimetry
- Has a high and stable myocardial uptake
- Has an excellent myocardial to background ratio
- Has a unique potential for myocardial PET imaging (its fluorinated!)
- Stress/rest study starts next week; 2 day protocol
PET Perfusion Summary

• O-15 water, N-13 ammonia, 82-Rubidium are well established tracers of myocardial blood flow
• Cost effective use has been documented
• Prognostic value has been documented
• Robust quantification in ml/g/min is feasible
• New fluorinated perfusion agents are emerging; this will be game changing event
The Future…

Diagnostic Accuracy of Rubidium-82 Myocardial Perfusion Imaging With Hybrid Positron Emission Tomography/Computed Tomography in the Detection of Coronary Artery Disease

Uchechukwu K. Sampson, MD, MPH, MBA, MSc(Oxon),* Sharmila Dorbala, MD, FACC,† Atul Limaye, MD, MRCP,* Raymond Kwong, MD,*† Marcelo F. Di Carli, MD, FACC, FAHA‡

Boston, Massachusetts

Objectives
Our objective was to determine the accuracy of rubidium-82 myocardial perfusion positron emission tomography-computed tomography (PET-CT) imaging for detecting obstructive coronary artery disease (CAD).

Background
Hybrid PET-CT is a new noninvasive imaging modality for evaluating patients with known or suspected CAD.

Methods
We evaluated 64 consecutive patients with suspected CAD undergoing rest-stress rubidium-82 cardiac PET-CT (CT was only used for attenuation correction) and coronary angiography within 7 days (range 1 to 180 days). Patients with known CAD, previous myocardial infarction, or revascularization were excluded. Thirty-eight patients with a low likelihood for CAD were also studied. Obstructive CAD was defined as ≥70% diameter stenosis on angiography.

Results
The mean age of the patients was 62 ± 15 years, with a body mass index of 31 ± 8 kg/m². Chest pain and/or dyspnea were the predominant reasons for evaluation. Stress perfusion defects were detected in 41 of 44 patients with obstructive CAD (sensitivity 90%, 95% confidence interval [CI] 87 to 99). The specificity of PET-CT was 83% (48 of 58, 95% CI 71 to 94), and its overall diagnostic accuracy was 87% (95% CI 79 to 93). All patients with a low likelihood for CAD showed normal scans, for a normalcy rate of 100% (38 of 38, 95% CI 91 to 100). The sensitivity for detecting CAD in patients with single- and multivessel (≥2 vessels) disease was 92% (22 of 24, 95% CI 74 to 99) and 96% (19 of 20, 95% CI 74 to 99), respectively.

Conclusions
Myocardial perfusion PET-CT affords high sensitivity and overall accuracy for detecting CAD, including patients with single-vessel disease, women, and obese patients. (J Am Coll Cardiol 2007;49:1052–8) © 2007 by the American College of Cardiology Foundation
First Human Study of BMS747158
Myocardial to Background Ratio Over Time

Minutes

%
Cardiac PET Imaging with BMS-747158
Rabbit Coronary Artery Ligation

35-45 min after injection