PET and PET/CT in CLINICAL CARDIOLOGY

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Career Investigator, Program Director, Molecular Function and Imaging Program
Rob Beanlands

The following relationships exist related to this presentation:

Research grant support
  General Electric
  Lantheus Medical Imaging

Consultant
  Jubilant Draximage
  Lantheus Medical Imaging

Other declared potential conflicts:
  Institution produces Positron Emitting Radiopharmaceuticals
  Report SPECT and PET Cardiac Scans
PET and PET/CT in Cardiology

Questions

PET 101 – advantages / disadvantages

Accepted Indications – Ischemia - Hibernation

Emerging Indications - Flow - Inflammation

Future applications - Plaque - Neurohormonal
Which of the following creates a disadvantage for PET compared to SPECT?

a) Consistent attenuation correction
b) Accuracy
c) Radiation dose
d) Short half-life radioisotopes
e) Quantification of blood flow
 QUESTIONS

Which of the following are of proven prognostic value with PET perfusion imaging:

a) Defect extent and severity
b) Stress EF
c) Quantification of Blood Flow
d) All of the above
e) Don’t know for PET
Which is the most important for predicting improved clinical outcome with revascularization in patients with severe ischemic cardiomyopathy

a) Extent of scar

b) Contractile Reserve

c) Extent of Viability

d) Extent of Hibernation
Which of the following is not part of Japanese Criteria for the diagnosis of cardiac sarcoidosis

a) LGE on MRI
b) Perfusion Defect on SPECT
c) Positive Gallium-67 scan
d) Positive FDG PET
e) Wall motion abnormality on Echocardiography
f) Extra-Cardiac Sarcoidosis
PET in Canada
Positron Emission Tomography

Radioisotope

Nucleus

511keV γ-ray

Positron

+ve

Electron

-ve

511keV γ-ray

Klein 2006
Positron Emission Tomography

Coincidence Detector

Klein 2007
Advantages of PET

• Attenuation Correction - *High specificity*

• Coincidence Detection - *High Count Sensitivity*

• Quantification - *Potential Added utility*

• Positron Radioisotopes
  • short half-life - *Rapid testing, less radiation*
  • physiological tracers – *Flow, metabolism, inflammation, molecular/cellular function*
Limitations of PET

- Availability
- Cost

- Short half-life radioisotopes –
  - Requires Cyclotron / Generator
  - Difficult to do exercise stress

- Radiation (small)

- Anatomical Resolution (better with hybrid CT(MRI))
Perfusion Imaging using 99mTc Myoview SPECT

Case S

62 y.o Woman
Chest Pain
BMI 31.5

Stress
Rest
Stress
Rest
Stress
Rest
$^{82}\text{Rb}$ PET Images
82Rb PET Images

PET MPI corrects for Attenuation Artifact
Superior specificity and diagnostic certainty
Persantine Tc-99m Tetrofosminmin SPECT
-veECG, no TID, normal WM
Ischemia in the inferior wall and moderate-sev. Ischemia LAD. **High risk**
Coronary Angiogram

LAD (P,M,D): 90 % + 70 %
LPDA: 100 %
RCA (P): 90 %

Patient referred for CABG
PET

Pooled Sensitivity: 90% (0.88-0.92)
Pooled Specificity: 88% (0.85-0.91)
Rb-82 PET vs gated AC Tc-99m based SPECT

* P < 0.01 for Rb-82 PET vs gated AC SPECT

Mc Ardle et al; JACC Oct 2012
Annual Incidence of All-cause Mortality in Relation to Gated Rb-82 PET Results

N = 1441 pts
Mean Follow-up = 2.7 years

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Mean Follow-up = 2.7 years

The extent of the Stress PET MPI defects & the stress PET LV function Predict mortality

Prognostic Value of Stress Myocardial Perfusion Positron Emission Tomography: Results from A Multicenter Observational Registry

Dorbala et al, J Am Coll Cardiol 2013 Jan 15;61(2):176-8
Dynamic Cardiac PET

LV Blood Pool

RA/RV Blood Pool

Myocardium

Activity [Bq/cc] vs. Time [min]

- LV Blood
- Myocardium
- Myocardium - Modeled

Time [min]
Quantification of Myocardial Blood Flow (MBF)

\[ C_M(t) = C_A(t) \otimes K_1 e^{-k_2 t} \]
MBF in Multi-vessel disease

A) Short Axis

Stress

Rest

HLA

VLA

B) stressRubidium Flow

stresRubidium / restRubidium

restRubidium Flow

stresRubidium - restRubidium

C) LAD (mid) 70%

D2 100%

OM1 and OM2 90%

RCA (prox) 60%

RCA (mid) 99%

Rest MBF (mL/min/gr) 1.03

Stress MBF (mL/min/gr) 1.17

MFR 1.12

MFD 0.14

Ziadi et al. JNC 2011 (in press)
Myocardial Flow Reserve & Prognosis

Ziadi et al, JACC 2011

Murthy et al, Circulation 2011
Class I Indications (level B): Pharmacological PET MPI for diagnosis of CAD and/or risk stratification in patients:

a) with non-diagnostic non-invasive imaging tests or

b) prone to artifact such as obese patients or

c) unable to exercise or have LBBB or ventricular pacing.

(d) hemodynamic significance of a lesion
Typical Effective Doses of Cardiac Studies

Adapted from Einstein AJ, JACC 2011; in press
Dysfunctional Myocardium

- Viable (Recoverable)
- Remodeled ‘Normal’
- Stunning
- Hibernation
- Non-viable SCAR
Management Decisions in Patients With Severe LV Dysfunction and CAD

**Patient 1**

*Decision to revascularize straight forward:*
- 60 years old
- Severe angina
- LVEF 30%
- Normal LV size
- Three vessel CAD
- Good target vessels
- No co-morbidities

**Patient 2**

*Decision to revascularize more controversial:*
- 73 years old
- CHF class III w/o angina
- Prior CABG
- LVEF 20%
- Dilated LV
- Three vessel CAD
- Mediocre target vessels
- Impaired renal function
- COPD

FDG Uptake and Metabolism

Blood Capillary

Glucose

18F-FDG

Cell

Glucose

hexokinase

Glucose-6-P

Glycolysis

Glycogen

18F-FDG-6-P

Phelps et al, JNM 1978
Perfusion/FDG Viability Imaging
Cadre PT 01 378 BLST

PERFUSION/METABOLISM MATCH = SCAR
Match (Scar) = 36%
Perfusion/FDG Viability Imaging
Cadre PT 01 357 PEBR

Perfusion/Metabolism Mismatch = Hibernation
Perfusion/FDG Viability Imaging Polar Maps
Cadre PT 01 357 PEBR
Sensitivity and Specificity of Different Viability Techniques

* $p<0.05$ better vs others

* $p<0.05$ worse vs others

* $p<0.05$ vs others

Dobutamine Echo ** 41 st./1421 pts
FDG PET * 20 st./598 pts
TI-201 40 st./1119 pts
MRI 13 st./420 pts
Tc-99m 25 st./721 pts
Sensitivity and Specificity of Different Viability Techniques

Dobutamine Echo - Contractile Reserve – most specific;

FDG PET - most sensitive

* p< 0.05 vs others

Light micrograph

Transmission electron micrograph

Normal cardiomyocytes

Hibernating myocardium

PARR2 - Event Free Survival
Patients who Adhered to PET Recommendations

Hazard ratio = 0.62; 95% CI = (0.42,0.93); p=0.019

Beanlands et al., JACC 2007; 50: 2002-2012
Hazard ratio = 0.62; 95% CI = (0.42,0.93); p=0.019

Beanlands et al., JACC 2007; 50: 2002-2012
Adjusted outcome: Revascularization and Mismatch Interaction Hazard Ratios and 95% confidence intervals

D’Egidio et al, JACC Cardiovasc Imaging 2009 Sep;2(9):1060-8
Revascularization and Mismatch Interaction

Adjusted outcome: Revascularization and Mismatch Interaction Hazard Ratios and 95% confidence intervals

Increased Hibernation = Increased benefit from revascularization

D’Egidio et al, JACC Cardiovasc Imaging 2009 Sep;2(9):1060-8
% HIBERNATION vs RISK of Death

Ling, et al. Circulation: Cardiovascular Imaging 2013; Apr

648 pts
p =0.0009
Kaplan–Meier Analysis - Probability of Death According to Myocardial-Viability Status and Treatment

A. Without myocardial viability

- Medical therapy (33 deaths)
- CABG (25 deaths)

B. With myocardial viability

- Medical therapy (95 deaths)
- CABG (83 deaths)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without viability</td>
<td>114</td>
<td>58</td>
</tr>
<tr>
<td>With viability</td>
<td>487</td>
<td>178</td>
</tr>
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<tr>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
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<tr>
<td>0.70 (0.41–1.18)</td>
<td>0.53</td>
</tr>
<tr>
<td>0.86 (0.64–1.16)</td>
<td>0.53</td>
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Viability is not the only predictor of outcome.

Viability Testing is not needed in every patient with LV dysfunction.

DOES NOT indicate that viability imaging is not useful.

## STICH- Viability Substudy

### What’s Wrong with this picture?

<table>
<thead>
<tr>
<th></th>
<th>STICH</th>
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<tbody>
<tr>
<td>n</td>
<td>601</td>
<td>430</td>
<td>332</td>
</tr>
<tr>
<td>Follow-up (yrs)</td>
<td>1 - 6</td>
<td>1</td>
<td>0.5 - 2</td>
</tr>
<tr>
<td>randomized</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Mean age</td>
<td>59.5</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>Mean EF (%)</td>
<td>26</td>
<td>26</td>
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<tr>
<td>Diabetes (%)</td>
<td>39.5</td>
<td>38</td>
<td>41</td>
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<tr>
<td>Renal dysfunction (%)</td>
<td>7.5</td>
<td>34</td>
<td>21</td>
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<td>Prior CABG (%)</td>
<td>3</td>
<td>19</td>
<td>~22</td>
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<td>viability</td>
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<td>Perf/FDG PET (&gt;7% MM)</td>
<td>Perf/FDG PET (&gt;10% MM)</td>
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<td>$^{201}$TI-SPECT($&gt;11/17$)</td>
<td>Dob Echo CR ($&gt;5$ sg)</td>
<td></td>
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<td>assessed hibernation</td>
<td>No-SPECT; Yes-</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td>% of pts w viability</td>
<td>81</td>
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### Need More Comparative Effectiveness

**RCTs in viability imaging**

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Patients presenting with new or worsening symptoms/signs of HF (n=2039***)
(with one of three clinical questions)

I-A (n=1285)

Known CAD/LVEF <40%
Clinical Question: Is there ischemia/hibernation?

MRI/PET vs. STD**

Primary Outcome: Composite Clinical Endpoint

I-C (n=250)

Unknown Coronary Anatomy
Clinical Question: Is there obstructive CAD?

CTA vs. STD**

Not eligible for I-A or I-B

Primary Outcome: Resource utilization

I-B (n=504)

Known or suspected NICM or HFPSF
Clinical Question: What is the cause of CM* or HF?

Routine MRI vs. STD**

Primary Outcome: Specific Diagnosis

Follow-up all level one patients
Outcomes: composite clinical endpoints (cardiac death, MI, Arrest, hospitalization), QoL, LV Function, Cost, resource utilization, safety.

*CM = Cardiomyopathy
** STD = Standard care which is: I-A: SPECT perfusion; I-B Echo +/- selective CMR; I-C coronary angiography
***revised sample size calculations October 6, 2011
Who do I send for FDG viability imaging?

a) Known or strongly suspected IHD
b) > NHYA II
c) Moderate - severe LV dysfunction (EF ≤ 40%)
d) Moderate to large persistent perfusion defects – no significant ischemia

e) +/-significant co-mordities +/-or poor distal targets
f) +/-or equivocal viability results on another test.

Modified from CCS/CAR/CANM/CNCS/CanSCMR Position Statement CJC 2007; 23(2):107-19
Who do I NOT send for FDG viability imaging?

a) Predominantly Angina  CCS >II
b) Normal or mild LV dysfunction
c) Critical LMCA disease
d) Good targets
e) Documented moderate or severe ischemia
f) Minimal or no co-morbidities

Modified from CCS/CAR/CANM/CNCS/CanSCMR Position Statement CJC 2007; 23(2):107-19
Cardiac Sarcoidosis

Prednisone 30 mg po qd x 2 mo

Case 5
Case 8

74-year-old female presented with palpitations found to have VT due to CS.

Whole body FDG-PET

Baseline  

After 3 months of steroid therapy

82Rb-PET

FDG-PET

Case 4

44-year-old male with 3<sup>rd</sup> degree AV block due to CS

Baseline

Follow up (8 months later) without steroid therapy

*The pt rejected steroid therapy
Representative case with positive on FDG-PET and negative on CMR

57-year-old female with new onset 3rd degree AV block

FDG-PET Short Axis view

Cardiac MR Short Axis view

Focal FDG uptake in the septum

No LGE

LGE: late gadolinium enhancement
Representative cases with discordance between FDG-PET and CMR

(A) Focal FDG uptake in the septum and lateral walls of the LV and RV on FDG-PET (black arrows).

(B) No LGE on CMR.

35-year-old male with third degree AVB.

A case with positive on FDG-PET and negative on CMR.

(C) No FDG uptake on FDG-PET.

(D) LGE in the basal septum on CMR (white arrows).

57-year-old female with left anterior fascicular block.

A case with positive on CMR and negative on FDG-PET.
## Characteristics of CS patients and controls with conduction disease

<table>
<thead>
<tr>
<th></th>
<th>Patients with cardiac sarcoidosis</th>
<th>Control subjects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild conduction disease (n = 19)</td>
<td>Advanced AVB (n = 14)</td>
<td>Advanced AVB (n = 15)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>57.3 ± 16.8</td>
<td>54.9 ± 11.8</td>
<td>51.1 ± 6.7</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>15 (79)</td>
<td>9 (69)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>60.9 ± 14.3</td>
<td>60.6 ± 10.1</td>
<td>61.1 ± 6.6</td>
</tr>
<tr>
<td>Interval between FDG-PET and CMR, weeks</td>
<td>1.3 ± 2.3</td>
<td>1.1 ± 1.9</td>
<td>2.9 ± 5.1</td>
</tr>
<tr>
<td>FDG-PET positive, CMR negative, n</td>
<td>0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>CMR positive, FDG-PET negative, n</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>FDG-PET &amp; CMR positive, n</td>
<td>13</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>FDG-PET &amp; CMR negative, n</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>FDG-PET negative (CMR not done)</td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>FDG-PET sensitivity, %</td>
<td>68 (43,87)</td>
<td>93 (66,100)</td>
<td></td>
</tr>
<tr>
<td>specificity, %</td>
<td>NA</td>
<td>87 (59,98)</td>
<td></td>
</tr>
<tr>
<td>CMR sensitivity, %</td>
<td>100 (82,100)</td>
<td>64 (35,87)</td>
<td></td>
</tr>
<tr>
<td>specificity, %</td>
<td>NA</td>
<td>100 (59,100)</td>
<td></td>
</tr>
<tr>
<td>Prevalence adjusted bias adjusted kappa (PABAK)</td>
<td>0.3684</td>
<td>0.1429</td>
<td></td>
</tr>
</tbody>
</table>

- **Mild conduction disease:** RBBB and/or axis deviation
- **Advanced AVB:** second degree AVB type II or third degree AVB
Histological diagnosis group:
Cardiac sarcoidosis is confirmed when endomyocardial biopsy specimens demonstrate non-caseating epithelioid cell granulomas with histological or clinical diagnosis of extracardiac sarcoidosis.

Clinical diagnosis group:
Although endomyocardial biopsy specimens do not demonstrate non-caseating epithelioid granulomas, extracardiac sarcoidosis is diagnosed histologically or clinically and satisfies the following conditions and more than one in six basic diagnostic criteria:
1. Two or more of the four major criteria are satisfied
2. One in four of the major criteria and two or more of the five minor criteria are satisfied

Major Criteria:
- Advanced AV Block
- Basal thinning of the interventricular septum
- Positive Gallium-67 (or $^{18}$F-FDG*) uptake in the heart
- Depressed EF <50%

Minor Criteria:
- Abnormal ECG findings: ventricular arrhythmias (VT or multifocal or frequent PVC’s), complete RBBB, axis deviation, or abnormal Q-waves
- Abnormal ECHO; RWMA or morphological abnormality (aneurysm or wall thickening)
- Perfusion defects on nuclear imaging: Thallium-201, Technetium 99m SPECT (or Rubidium-82 or $^{13}$N-Ammonia PET*).
- DGE on Cardiac MRI
- Interstitial fibrosis or monocyte infiltration on cardiac biopsy
FDG PET/CT for Cardiac Sarcoidosis

* Sensitivity = 89%
Specificity = 78%
6 studies
164 patients

Symmetric SROC
AUC = 0.9328
SE(AUC) = 0.0348
Q* = 0.8685
SE(Q*) = 0.0424

Youssef JNM 2011 (in press)
PET and PET/CT in Clinical Cardiology
Where are we now?

- **ESTABLISHED CLINICAL INDICATIONS**
  - *Myocardial Perfusion Imaging* (Rb82, NH3, (H2O) ?Flurpirdaz)
  - *Detection of Hibernation / Viability* (FDG)

- **EMERGING CLINICAL APPLICATIONS**
  - Flow Quantification (Rb82, H2O, NH3): CAD/Microvascular Disease
  - Inflammation imaging (FDG): Sarcoidosis

- **POTENTIAL CLINICAL APPLICATIONS**
  - Neurohormonal Imaging (HED)
  - Vulnerable Plaque Imaging (FDG)

- **FUTURE APPLICATIONS**
  - Vast array of emerging imaging biomarkers require translation