CARDIAC METABOLISM PET: THE DO’S & DON’TS VARY

Amol M. Takalkar, MD, MS (Biomed Engr), MBA (Exec), FACNM

Medical Director, Center for Molecular Imaging & Therapy (CMIT), Biomedical Research Foundation of Northwest Louisiana
Clinical Prof. of Radiology, Assoc. Director of Research Dept. of Radiology, LSUHSC-S
Shreveport, LA

AMOL.TAKALKAR@CMITLA.ORG
FINANCIAL DISCLOSURES

Lilly USA, LLC

- Speaker Bureau (Amyvid Reader Training Program)
LEARNING OBJECTIVES

1. Review appropriate indications for cardiac PET metabolism
2. Evaluate the best patient preparation for specific indication for cardiac metabolism PET
3. Analyze scan patterns of cardiac metabolism PET with rest perfusion imaging in specific disease conditions
INTRODUCTION

NUCLEAR CARDIOLOGY TECHNIQUES

➢ Planar Cardiac Imaging
➢ SPECT Cardiac Imaging
   w/ ECG Gating
   w/ Attenuation Correction
➢ MUGA (Multigated acquisition) Study
➢ Positron Emission Tomography (PET)
Amol M. Takalkar, M.D.

Cardiac PET

Myocardial Perfusion Imaging

- Rest & Post-stress (pharmacologic/exercise)
  - Perfusion scan N-13 Nh3, Rb-83 Cl
- Evaluation of CAD, chest pain (for ischemia)

Cardiac Metabolism Imaging

- Rest Perfusion scan (N-13 Nh3, Rb-83 Cl) + FDG Metabolism Scan
- Evaluation of myocardial viability, scar (for EP ablation), Cardiac Sarcoidosis
MYOCARDIAL METABOLISM
CARDIAC PET TRACERS

MYOCARDIAL METABOLIC TRACERS:

➢ GLUCOSE METABOLISM

1. F-18 FDG (FDA approved)

➢ FREE FATTY ACID METABOLISM

1. C-11 PALMITATE
2. C-11 ACETATE
MYOCARDIAL METABOLISM

Myocardial Substrate Utilization

Normal fasting conditions
High plasma FFA levels
Low plasma glucose & insulin levels
Primary myocardial substrate: FFA

Post-prandial conditions
High plasma glucose & insulin levels
Ischemic & hypoxic myocardium
Primary myocardial substrate: Glucose

Amol M. Takalkar, M.D.
Normal Variation in Cardiac FDG Uptake

Mild to modest to intense
Variable Cardiac FDG Uptake in same patient over time
MYOCARDIAL FDG UPTAKE

Highly variable:

➤ Hormonal & metabolic milieu

➤ Available substrate concentration

Patient dietary preparation affects uptake significantly
Dietary prep differs based upon indication of study

To suppress or not to suppress is the question!
INDICATIONS FOR CARDIAC METABOLISM STUDY

Myocardial Viability
- Chronic ischemic heart disease with dysfunctional myocardium
- Determine need for invasive management
  - Encourage normal myocardial FDG uptake

Myocardial Scar
- Persistent arrhythmias
- Determine area of scar for ablation

Myocardial Infection/Inflammation
- Myocarditis
- Cardiac Sarcoidosis
  - Suppress normal myocardial FDG uptake
DIETARY PREP TO ENCOURAGE NORMAL MYOCARDIAL FDG UPTAKE

For evaluation of myocardial viability & scar
Shift myocardium to use glucose as metabolic substrate

➢ Dietary preparation
➢ Glucose loading (oral/intravenous)
➢ Insulin-Euglycemic Clamp
➢ Acipimox

At BRF:
➢ High carb, low fat diet on the day prior to scan
➢ High carb, low fat breakfast 1 hr prior to scan
➢ Oral Glucose loading, if necessary
ORAL GLUCOSE LOADING

4-6 hr fasting
Check BSL

BSL < 110 mg/dL, non-diabetic patient
- 25-100 g oral glucose
- Administer FDG 30-60 min later

BSL > 110 mg/dL, diabetic patient
- 25-100 g oral glucose with insulin supplementation (keep BSL 100-140 mg/dL)
- Administer FDG 30-60 min later
GLUCOSE LOADING

INTRA VENOUS GLUCOSE

• Unable to tolerate oral glucose
• Altered gastro-intestinal glucose absorption

HYPERINSULINEMIC-EUGLYCEMIC CLAMP

• Provides controlled metabolic conditions
• Very cumbersome & difficult to implement

ACIPIMOX

• Nicotinic acid derivative
• Indirectly promotes myocardial glucose uptake
• Successfully used in Europe, not available in the US
DIETARY PREP TO SUPPRESS NORMAL MYOCARDIAL FDG UPTAKE

For evaluation of myocardial inflammation/infection
Shift myocardial metabolism to FA and reduce physiologic glucose utilization & FDG uptake by myocytes

➢ Prolonged Fasting (up to 18 hrs)
➢ Dietary Modification
➢ Heparin (i.v.) pre-administration: activates lipoprotein & hepatic lipases => increases FFA => reduces glucose utilization by myocytes (50 IU/kg)

Combination of above maneuvers may be more effective.

At BRF:
Low carb, high fat diet, high protein followed by a extended fast
Patient Instructions for Cardiac Sarcoidosis/Myocarditis Imaging

Starting 24 hours before your scan:

- Keep carbohydrate intake to a minimum (see below).
- Eat a high fat and minimal carbohydrate diet.
- Take all your medicines as usual.

You May Have:

- Fatty, unsweetened (fried, broiled, or grilled, but not breaded) chicken, turkey, fish, red meats, meat-only sausages, and fried eggs
- Dairy foods such as milk, cheese cream, sour cream, ice cream
- Water, broth, club soda, plain seltzer, and clear liquids that do not contain milk or sugar. Tea, coffee, and diet sodas that are not sweetened with Splenda (sucralose)
- Sugar substitutes: Sweet’N Low, Equal, or Nutrasweet
- Nuts
- Vegetables: asparagus, beet greens, broccoli, cabbage, cauliflower, celery, spinach, cucumber, mustard greens, radishes, Swiss chard, and watercress

Do NOT Have:

- Any foods that contain added sugars, or Splenda
- Any starchy foods, including bread, muffins, bagels, cereal, cookies, pasta, crackers, rice, corn, potatoes, carrots, and legumes
- Candy
- Peanut butter
- Fruits, fruit juices, frozen ices, sorbet, and sherbet
- Chewing gum, mints, and cough drops
- Alcohol

Starting 12-14 hours before your scan:

- Do not eat anything.
- You may drink water, but no other fluids.

Starting 6 hours before your scan:

- No smoking of any kind
- No liquid medications, chewable tablets, diabetic medicines including insulin
- Drink plenty of plain water
MYOCARDIAL ISCHEMIA

- Acute occlusion of coronary artery
  - Chronic hypoperfusion
  - Repetitive Ischemia

  Ischemic insult to myocardium

  Myocardial Adaptive Responses
  (Hibernation, Stunning, Ischemic Preconditioning)

<table>
<thead>
<tr>
<th>Fully Viable</th>
<th>Partially Viable</th>
<th>Non-Viable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

  Dysfunctional Myocardium
  - Necrosed & Scarred
  - Stunned or Hibernating

  Non-viable
  Viable
CAD WITH LVD

Medical management

Revascularization

Cardiac Transplantation

Significant peri-procedure morbidity & mortality

Limited availability of donor hearts. Significant peri-procedure risks

Maximum benefit in patients with reversibly dysfunctional myocardium
MYOCARDIAL VIABILITY EVALUATION

- Stress Echocardiography with low-dose dobutamine
- Tl-201 rest-redistribution studies
- Tc-99m sestamibi SPECT Imaging
- PET with myocardial perfusion and FDG
- Cardiac CT
- Cardiac MRI
MYOCARDIAL VIABILITY BY PERFUSION IMAGING ALONE

Dysfunctional Myocardial Segment

- Relatively normal blood flow
  - Stunned Myocardium

- Intermediate decline in blood flow
  - Hibernating Myocardium or Necrosoed endocardial tissue mixed with relatively normal myocardium

- Significantly reduced blood flow
  - Scarred Myocardium

Amol M. Takalkar, M.D.
PET MYOCARDIAL VIABILITY EVALUATION

➢ Assessment of regional blood flow alone is insufficient

➢ Requires appraisal of myocardial blood flow in combination with evaluation of myocardial metabolism

➢ Blood flow is assessed by either SPECT or PET agents (N-13 NH$_3$ or Rb-82 Cl)

➢ Myocardial metabolism is assessed by FDG PET with glucose loading
$^{13}$N-$\text{NH}_3$ / $^{18}$F-FDG IMAGING

MYOCARDIAL VIABILITY/SCAR

10-15 mCi N-13 Ammonia i.v.  
10 mCi FDG i.v.

Glucose Loading  
Perfusion Image  
Metabolism Image

~30  ~5  10  50-60 min  10

Time (min)
PET MYOCARDIAL VIABILITY IMAGING

3 Possible Patterns

- Normal Blood Flow
  - Normal Metabolism
    - Normal, Viable Myocardium

- ↓ Blood Flow
  - Normal or ↑ Metabolism
    - Flow – Metabolism Mismatch
      - Dysfunctional but Viable Myocardium

- ↓ Blood Flow
  - ↓ Metabolism
    - Necrosed or Non-viable Myocardium
53 year old male with unstable angina pectoris, s/p recent cardiac catheterization showing chronic total obstruction proximally in the LAD with 70% stenosis in the high diagonal and mild to modest stenosis elsewhere. He has Q waves in inferior and anterior leads on EKG.

FDG PET myocardial viability study
61 yr F, h/o STEMI, multivessel CAD on LHC, Myocardial Viability Study
Total defect: 14% of total myocardium or 26 gm!

79% of defect is mismatched (viable): 11% of total myocardium or 21 gm!

21% of defect is matched (non-viable): 3% of total myocardium or 5 gm!
56 yrs M, h/o ischemic cardiomyopathy, low LVEF & significant CAD on LHC
Distal Ant/ Apical defect: 91% mismatched /viable; 6% of total myocardium or 7 gm
Inf/ Inf-lat defect: 66% matched /non-viable; 12% of total myocardium or 32 gm
MYOCARDIAL VIABILITY
CLINICAL IMPLICATIONS

VIABILITY EVALUATION PRE-REVASCULARIZATION

• Predicts functional recovery

• Predicts improvement in congestive heart failure symptoms, exercise capacity, & quality of life

• Predicts cardiac events, remodeling, & long-term survival

• Predicts peri-operative complications & short-term survival
Identification of viable myocardium indicates a need for prompt revascularization, failure of which can lead to suboptimal outcomes & more serious consequences including death.

Failure to definitely identify significant viable myocardium helps the physician to make a decision to treat these patients medically or by cardiac transplantation, if warranted.
# PATTERN EXAMPLES

<table>
<thead>
<tr>
<th>NH\textsubscript{3}</th>
<th>FDG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stress</strong></td>
<td><strong>Rest</strong></td>
</tr>
<tr>
<td>Fixed</td>
<td>Fixed</td>
</tr>
<tr>
<td>Fixed</td>
<td>Fixed</td>
</tr>
<tr>
<td>Partially Reversible</td>
<td>Partially Reversible</td>
</tr>
<tr>
<td>Partially Reversible</td>
<td>Partially Reversible</td>
</tr>
</tbody>
</table>
64 yr M, HTN, COPD, alcohol abuse w/ DOE => severely reduced EF & NSTEMI => multi-organ failure s/o cardiogenic shock. LHC: sig. RCA d’se (successful PCI with DES), CTO of prox LCx, Intermediate LAD d’se. Viability study for addressing LCx

Reduced FDG uptake in the lat/inferolateral wall, most pronounced in distal portion suggesting potentially no significant viability in this area.

Pt managed medically subsequently
54 yrs M, h/o nonischemic cardiomyopathy and persistent rhythm abnormalities
For evaluation of scar for ablation

Rest Tc-99m SPECT perfusion + FDG metabolism

Matched perfusion metabolism abnormality in the proximal/basal lateral/posterolateral wall suggesting presence of a scar in this region

During EP procedure: scar in basal posterolateral wall
Successful LV substrate mapping & ablation of posterolateral LV VT
PA and right lateral views of the LV. The mitral valve has been cut. Purple areas are healthy (> 1.5 mV) and red is scar with <0.5 mV signals. Within the area of scar, they can find an abnormal track causing the arrhythmia that needs ablation.
CARDIAC SARCOIDOSIS

Granulomatous disease of unknown etiology.
Pathological hallmark: non-caseating granulomas
Pulmonary involvement: most frequent
May also involve: heart, liver, peripheral LN, spleen, skin, eyes, phalangeal bones, parotid gland, or other organs and tissues.

Symptomatic cardiac involvement: in ~5% of the patients with pulmonary/systemic sarcoidosis (asymptomatic CS may be more common)
Clinical manifestations: dependent on location, extent, & activity of the disease. 3 principal sequelae of CS:
➢ conduction abnormalities
➢ ventricular arrhythmias
➢ heart failure
Patients with CS have poorer prognosis than patients without cardiac involvement

No currently accepted international guidelines for the diagnosis of CS.
2 proposed diagnostic guidelines:
➢ Japanese Ministry of Health and Welfare’s set of criteria
➢ National Institutes of Health’s A Case Control Etiology of Sarcoidosis Study set of criteria by the WASOG
Expert Consensus Recommendations on Criteria for the Diagnosis of CS

There are 2 pathways to a diagnosis of Cardiac Sarcoidosis:

1. Histological Diagnosis from Myocardial Tissue
   CS is diagnosed in the presence of non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable).

2. Clinical Diagnosis from Invasive and Non-Invasive Studies:
   It is probable* that there is CS if:
   a) There is a histological diagnosis of extra-cardiac sarcoidosis and
   b) One or more of the following is present
      - Steroid +/- immunosuppressant responsive cardiomyopathy or heart block
      - Unexplained reduced LVEF (<40%)
      - Unexplained sustained (spontaneous or induced) VT
      - Mobitz type II 2nd degree heart block or 3rd degree heart block
      - Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS)
      - Late Gadolinium Enhancement on CMR (in a pattern consistent with CS)
      - Positive gallium uptake (in a pattern consistent with CS) and
   c) Other causes for the cardiac manifestation(s) have been reasonably excluded

*In general, ‘probable involvement’ is considered adequate to establish a clinical diagnosis of CS.33
ROLE OF PET IN CS

3 basic patterns of FDG-PET uptake: diffuse, focal, and focal on diffuse

CS is most typically associated with focal FDG uptake either in isolation or on a background of mild diffuse uptake with or without resting perfusion defects and wall motion abnormalities.

Concomitant use of PET perfusion tracers can help exclude significant obstructive coronary artery disease.

In addition, FDG-PET may be able to identify ongoing active inflammation and thus potentially detect reversible stages of CS.

Patients with extra-cardiac sarcoidosis (bx proven) with suspicious ECG/Echo abnormalities should undergo CMR or FDG PET for screening for CS.

CMR or FDG PET can help confirm diagnosis of CS (without need for cardiac bx).

FDG PET can be used to assess response to therapy.
**Expert Consensus Recommendations on Screening for Cardiac Involvement in Patients With Biopsy-Proven Extracardiac Sarcoïdosis**

Class I
1. It is recommended that patients with biopsy-proven extracardiac sarcoidosis should be asked about unexplained syncope/presyncope/significant palpitations*.
2. It is recommended that patients with biopsy-proven extracardiac sarcoidosis should be screened for cardiac involvement with a 12-lead electrocardiogram (ECG).

Class IIa
1. Screening for cardiac involvement with an echocardiogram can be useful in patients with biopsy-proven extracardiac sarcoidosis.
2. Advanced cardiac imaging, CMR or FDG-PET, at a center with experience in CS imaging protocols can be useful in patients with one or more abnormalities detected on initial screening by symptoms/ECG/echocardiogram.

Class III
1. Advanced cardiac imaging, CMR or FDG-PET, is not recommended for patients without abnormalities on initial screening by symptoms/ECG/echocardiogram.
*Palpitations were defined as “a prominent patient complaint lasting > 2 weeks.”

---

**Biopsy proven extra-cardiac sarcoidosis**

Cardiac history, ECG, Echocardiogram

1. Symptom(s) positive (significant palpitations*/pre-syncope/syncope)
2. Abnormal ECG**
3. Abnormal Echocardiogram***

One or more of 1-3

Advanced cardiac imaging, CMR and/or FDG-PET

None of 1-3

Negative – Low probability of cardiac sarcoidosis

---

**Unexplained Mobitz II or 3rd degree AV block in adults aged < 60 years**

High resolution CT chest
Advanced cardiac Imaging (CMR or FDG-PET)

1. CT scan suggestive of pulmonary sarcoidosis
2. CMR or FDG-PET suggestive of CS

One or more of 1-2

Positive – High probability of CS

Biopsy
Extra-cardiac if feasible, otherwise Guided EMB* to confirm diagnosis

Negative – Low probability
Consider alternative diagnosis

Neither of 1-2

Negative – Consider further biopsy and/or interval repeat imaging (especially if cardiac deterioration in follow-up)
CARDIAC SARCOIDOSIS

### Proposed Diagnostic and Therapeutic Strategy in CS (24)

<table>
<thead>
<tr>
<th>Indications for screening</th>
<th>Findings leading to further work-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed extracardiac sarcoidosis</td>
<td>Bundle branch block, ventricular ectopy, second- or third-degree atrioventricular block (atrial arrhythmia, first-degree atrioventricular block)</td>
</tr>
<tr>
<td>Unexplained persisting second- or third-degree atrioventricular block and age &lt; 55 y</td>
<td>Global LV dysfunction, regional wall motion abnormalities (right ventricular dysfunction)</td>
</tr>
<tr>
<td>Unexplained monomorphic ventricular tachycardia</td>
<td>Runs of ventricular tachycardia, nonsustained ventricular tachycardia (frequent isolated premature ventricular contractions)</td>
</tr>
<tr>
<td>Nonischemic dilated cardiomyopathy</td>
<td></td>
</tr>
</tbody>
</table>

#### Routine screening procedures

- Clinical symptoms, physical examination
- 12-lead electrocardiogram
- Echocardiogram
- Holter monitoring

#### Further work-up

- CMR
- PET
- Invasive electrophysiologic study

#### Therapy

- Immunomodulation (prednisone [30-40 mg]; methotrexate
- Implantable cardioverter-defibrillator

#### Response evaluation

-Symptoms
- CMR (no implantable cardioverter-defibrillator)
-PET

### Table 1  Indications for Perfusion and $^{18}$F-FDG-PET for the Evaluation of Cardiac Sarcoid Disease

- Patients <55 years of age presenting with second- or third-degree atrioventricular block of unknown etiology.
- Unexplained monomorphic ventricular tachycardia.
- Patients with extra-cardiac sarcoidosis and abnormal ECG, Holter or Echocardiogram in whom cardiac sarcoidosis is suspected.
- Patients with established cardiac sarcoidosis for evaluation of response to treatment.

---


Amol M. Takalkar, M.D.
### Classification of cardiac PET perfusion & metabolism imaging

<table>
<thead>
<tr>
<th>Rest Perfusion</th>
<th>FDG</th>
<th>Frequency</th>
<th>Example</th>
<th>Interpretation / Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal (negative)</td>
<td>32 (27%)</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Diffuse (non-specific)</td>
<td>15 (12%)</td>
<td><img src="image2.png" alt="Image" /></td>
<td>Diffuse FDG most likely due to failure to suppress FDG from normal myocardium.</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>17 (14%)</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Rest perfusion defect may represent scar from cardiac sarcoidosis or other etiologies</td>
</tr>
</tbody>
</table>

### Category 1:
Normal perfusion and metabolism

### Category 2:
Abnormal perfusion or metabolism

- Normal Focal
- Positive Negative

### Category 3:
Abnormal perfusion and metabolism

- Positive Focal increase ("mismatch pattern")
- Positive Focal on diffuse
- Positive Focal increase (different area)


Amol M. Takalkar, M.D.
Perfusion and metabolism patterns in various stages of cardiac sarcoidosis

<table>
<thead>
<tr>
<th>STAGES</th>
<th>Perfusion Defect</th>
<th>FDG-Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>None</td>
<td>No/Low</td>
</tr>
<tr>
<td>Early</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Progressive</td>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>Peak active</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Progressive myocardial impairment</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Severe</td>
<td>Low</td>
</tr>
</tbody>
</table>

No FDG uptake (is expected w/ adequate pt. prep) or mild diffuse FDG uptake (non-specific) is –ve

Focal, focal/patchy on diffuse uptake is abnormal

47 yrs F, impaired LVEF but normal LHC; LBBB; concern for cardiac sarcoidosis
Incidental note of 9 mm moderately FDG avid lung nodule
Amol M. Takalkar, M.D.

**PET PERFUSION-METABOLISM IMAGING FOR CARDIAC SARCOIDOSIS**

- **Perfusion Image**
  - Adsorption: 10-15 mCi N-13 Ammonia i.v.
  - Imaging: ~5 min
  - Imaging: 10 min
  - Imaging: ~90 min

- **Metabolism Image (Cardiac)**
  - Adsorption: 10 mCi FDG i.v.
  - Imaging: 10 min
  - Imaging: ~20 min

**Dietary Prep**
- Low Carb - High Fat diet x 2 on prior day
- Extended Fast

**Imaging Time**
- 10-12 hrs

Amol M. Takalkar, M.D.
48 yrs F, h/o sarcoidosis, now w/ cardiomyopathy & decreased LVEF
Normal perfusion on SPECT; concern for cardiac sarcoidosis
Whole body images indicate presence of active sarcoidosis in the chest; but cardiac PET imaging did not indicate CS involvement.
27 yrs M, morbidly obese (BMI: 49), abnormal SPECT MI but normal LHC subsequently
Decreased EF & felt to have NICM but subsequently had NSTEMI
Then developed ECG abnormalities with concern for myocarditis/sarcoidosis

Suppressed FDG uptake (proper pt. prep) except for proximal lat wall & apex (where there is perfusion defect)
EF: 24%
Scan performed on 2 days
PET imaging in CS: Assessing Response

Baseline

After 6 months of high-dose steroid therapy

THANK YOU!