Disclosures

E. Gordon DePuey, M.D.

Disclosures:

Grant Support: Michael J. Fox Foundation
Consultant: Adenosine Therapeutics

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Learning Objectives

- Describe advancements in imaging techniques and software for single photon emission computed tomography (SPECT) and positron emission tomography (PET) cardiovascular procedures.
- Discuss recent advances in the fields of cardiac molecular and vascular biology.
- Discuss developments in SPECT and PET targets for cardiovascular imaging.
- Compare SPECT and PET in terms of combined indices for patient care.

Self-Assessment Question 1

- Which of the following is NOT an effective advancement to decrease patient radiation dose?
  - A. Regadenoson vasodilator stress
  - B. Focused collimation
  - C. Solid state detectors
  - D. Stress only SPECT imaging
  - E. PET perfusion radiopharmaceuticals
Self-Assessment Question 2

• Which of the following radiopharmaceuticals hold promise in the early detection of atherosclerotic plaque?

A. Tc-99m tetrofosmin
B. I-123 BMIPP
C. I-123 MIBG
D. F-18 NaF
E. F-18 flurpiridaz

Advances in Cardiac SPECT and PET Imaging

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Mt. Sinai St. Luke’s and Mt. Sinai West Hospitals
Clinical Professor of Radiology
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Patient-Centered Imaging

• The goal of the ASNC Preferred Practice Statement is to help providers choose the proper imaging procedure for the individual patient

• One MPI test DOES NOT fit all

DePuey EG, Miller TD, Mahmarian JJ et al, JNC 2012

ASNC Initiatives to Decrease Patient Radiation Exposure

• Promote awareness of radiation exposure associated with various MPI imaging protocols

• Encourage adherence to MPI Appropriate Use Criteria and Image Wisely Recommendations

Recommendations for Reducing Radiation Exposure in Myocardial Perfusion Imaging: ASNC Information Statement

• Decrease MPI radiation dose to <9mSv in 50% of patients by 2014

Cerqueria MD et al. J Nucl Cardiol, May 2010
ASNC Patient-Centered Imaging Document

DePuey EG, Miller TD, Mahmarian JJ et al, JNC 2012

- Encourage stress-only imaging in low-intermediate likelihood patients

Stress-Only Tc-99m Protocol

Advantages
- Patient convenience/satisfaction and laboratory efficiency are improved.
- There is a marked reduction in patient radiation exposure by eliminating the higher rest Tc-99m dose.
  - In one recent study, the mean Tc-99m dose was significantly lower at 21.3±10.7 mCi with stress-only vs. 55.1±11.9 mCi with stress/rest imaging. This was particularly true for patients who received an initial low dose of Tc-99m as part of a same day stress/rest protocol (13.5±2 mCi).5
- Conservation of Tc-99m radiopharmaceuticals
- Reduced cost by eliminating injection of a second Tc-99m dose and the subsequent rest imaging

Disadvantages
- First, there is a requirement to assess each patient on arrival to the laboratory to choose the most appropriate imaging protocol rather than a "one test fits all" approach.
- Differentiation of artifact from a true perfusion abnormality is more difficult without a resting scan and therefore requires the expertise of an experienced reader.
  - In this regard, attenuation correction with either x-ray computed tomography (CT) or line sources may be advantageous if a stress-only protocol is used. Recent data indicate that a stress-only imaging protocol coupled with attenuation correction techniques can be effectively applied to obese patients where a normal study predicts an excellent outcome. Prone imaging can also be used to clarify inferior perfusion defects due to diaphragmatic attenuation observed on supine images.
- The perfusion images should be unequivocally normal by visual and, preferably, quantitative analysis- and LV cavity size, LVEF and regional wall motion and thickening should be normal.

ASNC Patient-Centered Imaging Document

- Encourage stress-only imaging in low-intermediate likelihood patients
- Encourage increased SPECT acquisition time, as tolerated by patients, in preference to weight-base dosing in large patients

DePuey EG, Miller TD, Mahmarian JJ et al, JNC 2012

• Encourage stress-only imaging in low-intermediate likelihood patients
• Encourage increased SPECT acquisition time, as tolerated by patients, in preference to weight-base dosing in large patients
• Discourage dual-isotope and stress/delayed Tl-201 protocols

DePuey EG, Miller TD, Mahmarian JJ et al, JNC 2012

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Patient Radiation Exposure Associated with SPECT and PET MPI Protocols

<table>
<thead>
<tr>
<th>PROTOCOLS</th>
<th>EDE (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-Day Tc-99m Rest/Stress or Stress/Rest Protocol</td>
<td>9.3 – 11.3</td>
</tr>
<tr>
<td>Two-Day Stress/Rest or Rest/Stress Tc99m Protocol</td>
<td>12.8 – 15.7</td>
</tr>
<tr>
<td>Stress-Only Tc-99m Protocol</td>
<td>6.6 – 7.9</td>
</tr>
<tr>
<td>One-Day Rest Tl-201/Stress Tc-99m Dual Isotope Protocol</td>
<td>29.2</td>
</tr>
<tr>
<td>One-Day Tl-201 Stress/Redistribution Protocol</td>
<td>22.0</td>
</tr>
<tr>
<td>One-Day Tl-201 Stress/Re-injection/Redistribution Protocol</td>
<td>31.4</td>
</tr>
<tr>
<td>Rest/Stress Rubidium-82 (PET/CT)</td>
<td>1.75 – 13</td>
</tr>
<tr>
<td>Rest/Stress N-13 Ammonia (PET/CT)</td>
<td>1.5</td>
</tr>
</tbody>
</table>

ASNC Patient-Centered Imaging Document

- Encourage stress-only imaging in low-intermediate likelihood patients
- Encourage increased SPECT acquisition time, as tolerated by patients, in preference to weight-base dosing in large patients
- Discourage dual-isotope and stress/delayed Ti-201 protocols
- Utilize focused collimation, new solid-state camera technology, and new reduced count-density software to decrease injected activity

DePuey EG, Miller TD, Mahmarian JJ et al, JNC 2012

Cardio-Focused Collimation

IQ SPECT Results

ACI - 38 y/o male, 95% mid LAD (Tc-99m)

1. Parallel stress AC
2. Parallel rest AC
3. IQ stress AC: ½ time, ½ dose
4. IQ rest AC: ½ time, ½ dose

Courtesy James Corbett, M.D

Advantages of Semi-Conductor Detectors vs. Sodium Iodide

- Scored detector size defines spatial resolution, obviating time-consuming positioning circuitry
  - Higher count rates
  - Improved spatial resolution
- Direct conversion of incident photon to electrical signal
  - Higher count rates
  - Improved energy resolution
- Lower maintenance
  - Stationary gantry
  - Semiconductor detectors resistant to physical damage and hydration
  - PMT energy “drift” avoided (although random high signals from semiconductor elements sometimes occur)

Spatial Response Comparison

Direct digital positioning provides for excellent intrinsic spatial resolution and enhanced image contrast.
Low Dose Tc-99m Protocol
CZT Solid State Detectors with Cardio-focused Parallel-hole Collimation

Hardware and Software Advancements to Accommodate Lower Cardiac Counting Statistics

- Cardio-focused collimation
  - Parallel hole collimator with central converging collimation
  - Multiple scanning parallel hole collimators
  - Multi-pinhole collimators
- Solid state CsI and CZT detectors
- Software to cope with lower counting statistics

Software Solutions: Preservation of SPECT Image Quality Despite Lower Counting Statistics

- Iterative Reconstruction
- Resolution Recovery
- Noise Reduction

Patient Radiation Dose (EDE):
Advantages of Reduced-Dose Protocols

Full-Dose Protocol
- Tc-99m tetrofosmin R/S SPECT = 8.6 mSv
- Tc-99m sestamibi R/S SPECT = 10.7 mSv

Half-Dose Protocol
- Tc-99m tetrofosmin R/S SPECT = 4.3 mSv
- Tc-99m sestamibi R/S SPECT = 5.4 mSv

Half-Dose Stress-Only Protocol*
- Tc-99m sestamibi S SPECT = 1.4 mSv

*Note: stress-only protocols should be used only in patients with no prior MI, normal LV function, and a low-intermediate likelihood of CAD
Hardware and Software Advancements to Accommodate Lower Cardiac Counting Statistics

- Cardio-focused collimation
  - Parallel hole collimator with central converging collimation
  - Multiple scanning parallel hole collimators
  - Multi-pinhole collimators
- Solid state CsI and CZT detectors
- Software to cope with lower counting statistics
- Encourage PET in preference to SPECT in obese patients and those unable to exercise

PET Advantages

- Compared to SPECT
  - Improved spatial resolution
  - Inherent attenuation correction
  - Superior diagnostic sensitivity and specificity
  - Lower patient radiation dose
- Quantification of myocardial blood flow reserve
  - Detection of balanced ischemia
  - Improved detection of multivessel disease
- Myocardial Viability
  - Unique diagnostic potential
  - Sarcoidosis
  - Amyloidosis
  - Prosthetic valve infection
- F-18 flurpiridaz
  - Higher, more linear extraction than Tc-99m agents, Rb-82, and N-13 ammonia
- Molecular imaging
  - Disease-specific targets

Improved Diagnostic Sensitivity with PET due to Higher Spatial Resolution, and Higher Myocardial Radiopharmaceutical Extraction

Case 1: Perfusion Imaging using Tc-99m Tetrofosmin SPECT

- SPECT images from 50 year old male with exertional chest pain showing a small area of reduced perfusion in the inferior wall of the heart at stress, partially reversible at rest. This small defect indicates only a mildly increased risk of cardiac events, which would not mandate referral for invasive angiography, stenting, or CABG.

Case 1: Perfusion Imaging using Rb-82 PET

- Rb-82 PET images from the same patient now showing extensive areas of abnormal at stress with normal perfusion at indicating high-risk multivessel coronary disease. The patient went on to have invasive angiography followed by bypass surgery.

Improved Specificity with PET due to Higher Counting Statistics and Inherent Attenuation Correction

ASNC 2014 PET Summit, Courtesy Rob Beanlands, M.D
Case 2: Perfusion Imaging Using Tc-99m Tetrofosmin SPECT

- SPECT images from an obese 62 year old woman complaining of chest pain.
  - A partially reversible anterior defect suggests the presence of significant coronary artery disease is the reason for this woman’s chest pain and may prompt referral for invasive angiography.
  - However this patient underwent Rb-82 PET scanning for further evaluation.

ASNC 2014 PET Summit, Courtesy Rob Beanlands, M.D.

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Dynamic PET (and Maybe SPECT)
Acquisition to Quantify Myocardial Blood Flow Reserve

Right and Left Ventricular and Myocardial Time-activity Curves and Corresponding 6-second Mid-Ventricular Short-axis Tomograms

Dynamic Protocol to Assess Coronary Flow Reserve
Dynamic Protocol to Assess Coronary Flow Reserve
Case Example

Patient 2:
- Male - 69 years old
- Previous inferior MI
- Pre-operative assessment for total knee replacement

→ Partial thickness inferior wall infarct, extending to apex and basal lateral wall with superimposed ischemia

D-SPECT®, Spectrum Dynamics

Dynamic Protocol to Assess Coronary Flow Reserve
Case Example

→ High risk of triple vessel disease

D-SPECT®, Spectrum Dynamics

Global CFR by PET
N = 2,783 patients
137 (5%) CV deaths

Cardiac Mortality

Years

0
1
2
3

CFR<1.5
hi risk

CFR=1.5-2.0
mod risk

CFR>2.0
LOw risk

Murthy et al. Circulation 2011;124:2215

ASNC 2014 PET Summit,
Courtesy Lance Gould, M.D

Coronary Artery Disease Occurs in Both
Epicardial and Small Vessels

Epicardial Coronary Conduit Vessels
Resistance Vessels (< 400 μ)

Source: Schelbert HR. In: Cardiac PET and PET/CT Imaging. Eds: Di Carli, Lipton. Courtesy M. DiCarli, M.D

Physiologic Assessment of the Coronary Circulation

FFR

CFR

ASNC 2014 PET Summit, Courtesy M. DiCarli, M.D
**PET Advantages**

- Compared to SPECT
  - Improved spatial resolution
  - Inherent attenuation correction
  - Superior diagnostic sensitivity and specificity
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- Quantification of myocardial blood flow reserve
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**F-18 flurpiridaz**
- Higher, more linear extraction than Tc-99m agents, Rb-82, and N-13 ammonia

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**Cardiac Sarcoidosis**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
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<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
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**Abnormal cardiac PET identifies sarcoid patients at higher risk of death / VT**

(Even after accounting for JMBW criteria, presence of extra-cardiac sarcoidosis and LVEF)

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**Focal inflammation involving right ventricle**

**Endomyocardial Biopsy**

**APAM 2014, Courtesy Ron Blankstein, M.D.**
Focal FDG uptake in right ventricle → highest risk of death / VT

Example of response to therapy

Baseline | After treatment
---|---
Whole Body FDG | ![Images]
Cardiac | ![Images]
Perfusion | ![Images]
FDG | ![Images]
Short axis | Horizontal Long axis | Short axis | Horizontal Long axis

Example of failure to respond to therapy

Baseline | After treatment
---|---
Whole Body FDG | ![Images]
Cardiac | ![Images]
Perfusion | ![Images]
FDG | ![Images]
Short axis | Horizontal Long axis | Short axis | Horizontal Long axis

PET/CT improves the diagnostic accuracy of IE, particularly in the subset of patients with possible infection

25 y.o. male with congenital heart disease p/w fever and lethargy

25 y.o. male with congenital heart disease p/w fever and lethargy
Radiopharmaceutical Advancements

**SPECT**

- I-123 MIBG
- I-123 BMIPP

**123I-mIBG Planar Imaging**

Survival during 24-mo follow-up more effectively stratified by H/M ratio than LVEF

Control End stage HF


123I-mIBG Defect in a Region with Preserved Myocardial Perfusion: Innervation-Perfusion Mismatch

SPECT images show significantly larger innervation than perfusion defects

**PET**

- F-18 Flurpiridaz (Investigational in Phase III trials)
- F-18 NaF

Example of BMIPP SPECT Imaging in a Patient With Suspected Acute Coronary Syndromes: A Multicenter Trial


ISCHEMIC MEMORY

Iodofiltic Acid I 123 (BMIPP) Fatty Acid Imaging Improves Initial Diagnosis in Emergency Department Patients With Suspected Acute Coronary Syndromes: A Multicenter Trial

Example of BMIPP SPECT Imaging in a Patient With Suspected Acute Coronary Syndromes: A Multicenter Trial

F-18 Flurpiridaz is Available as a Unit Dose from a Regional Cyclotron

<table>
<thead>
<tr>
<th></th>
<th>O-15 water</th>
<th>N-13 ammonia</th>
<th>Rb-82</th>
<th>F-18 flurpiridaz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half life (minutes)</td>
<td>2.06</td>
<td>9.96</td>
<td>1.25</td>
<td>109</td>
</tr>
<tr>
<td>Production</td>
<td>On-site cyclotron</td>
<td>On-site cyclotron</td>
<td>Generator</td>
<td>Regional cyclotron</td>
</tr>
</tbody>
</table>

PET Image Resolution with F-18 Flurpiridaz is Very high

<table>
<thead>
<tr>
<th></th>
<th>O-15 water</th>
<th>N-13 ammonia</th>
<th>Rb-82</th>
<th>F-18 flurpiridaz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positron range (mm)</td>
<td>4.14</td>
<td>2.53</td>
<td>8.6</td>
<td>1.03</td>
</tr>
</tbody>
</table>

ASNC 2014 PET Summit, Courtesy Jamshid Maddahi, M.D.

F-18 Flurpiridaz has Superior Image Resolution

ASNC 2014 PET Summit, Courtesy Jamshid Maddahi, M.D.

Effect of Tracer EF on Perfusion Defect Severity

Maddahi J, J Nucl Cardiol 2012;19:S30-37

Rest-Treadmill Exercise MPI

ASNC 2014 PET Summit, Courtesy Jamshid Maddahi, M.D.
**Phase 2 18F flurpiridaz Study**

**ROC Analysis for CAD Diagnosis**

ROC curve showing PET vs. SPECT analysis with PET: 0.82±0.05 and SPECT: 0.70±0.06, P<0.05.

Berman DS, Maddahi J, et al. JACC 2013;61:469

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**18F-NaF : the next big thing for coronary plaque imaging?**

- 18F-NaF is incorporated directly into hydroxyapatite crystals via an exchange mechanism with hydroxyl groups to form fluoroapatite.
- Uptake believed to reflect active calcifications (“microcalcifications”).

Chen, Dilisirian Cardiol Rep 2013

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**Increased 18F-NaF in Culprit Plaques**

Figure 1

PET/CT qualitative and quantitative analysis of the 3 plaque subtypes, hot spots, and control regions. Radiographically, less dense plaque (light) shows intense fluoride uptake, denser plaque (medium) shows less tracer accumulation, and plaque in the highest tertile of HU density (heavy) shows no visible uptake. The highest activity is in calcium-free arterial hot spots. Graph at bottom left shows distribution of uptake intensity vs. density of plaque subtypes, hot spots, and control regions, allowing appreciation of the distribution spread of each element and the inverse correlation between plaque density and TBR. Graph at bottom right shows the significant difference between different plaque types and the almost identical uptake of fluoride in heavy plaque and control regions. CR = control region; HP = heavy plaque; HS = hot spots; LP = light plaque; MP = medium plaque.

ASNC 2014 PET Summit, Courtesy Ron Blankstein, M.D.

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**Self-Assessment Question 1**

- Which of the following is NOT an effective advancement to decrease patient radiation dose?
  - A. Regadenoson vasodilator stress
  - B. Focused collimation
  - C. Solid state detectors
  - D. Stress only SPECT imaging
  - E. PET perfusion radiopharmaceuticals

Correct answer is A
Self-Assessment Question 2

- Which of the following radiopharmaceuticals hold promise in the early detection of atherosclerotic plaque?
  A. Tc-99m tetrofosmin
  B. I-123 BMIPP
  C. I-123 MIBG
  D. F-18 NaF
  E. F-18 flurpiridaz

- Correct answer is D