The Future of Nuclear Cardiology: Response to Threats

PET: Will It Change the Future?

Gary V. Heller, MD PhD
Research Officer, Intersocietal Accreditation Commission, Ellicott City MD
Consultant, Nuclear Cardiology Program, Morristown Medical Center, Morristown New Jersey
PET: The Future of Nuclear Cardiology?

- Improved diagnostic sensitivity and specificity and risk stratification with existing equipment and radiopharmaceuticals
- Quantification of myocardial blood flow
- New perfusion tracers with higher myocardial extraction and therefore higher diagnostic sensitivity
- Molecular Imaging
Low Diagnostic Yield of Elective Coronary Angiography

Manesh R. Patel, M.D., Eric D. Peterson, M.D., M.P.H., David Dai, M.S., J. Matthew Brennan, M.D., Rita F. Redberg, M.D., H. Vernon Anderson, M.D.,

CONCLUSIONS

In this study, slightly more than one third of patients without known disease who underwent elective cardiac catheterization had obstructive coronary artery disease. Better strategies for risk stratification are needed to inform decisions and to increase the diagnostic yield of cardiac catheterization in routine clinical practice.

From the Duke University, Durham, NC (M.R.P., E.D.P., D.D., J.M.B., P.S.D.); University of California at San Francisco, San Francisco (R.F.R., R.G.B.); and the University of Texas Health Science Center, Houston (H.V.A.). Address reprint requests to Dr. Patel at the Duke Clinical Research Institute, Duke University Medical Center, P.O. Box 17969, Durham, NC 27715, or at manesh.patel@duke.edu.


METHODS

From January 2004 through April 2008, at 663 hospitals in the American College of Cardiology National Cardiovascular Data Registry, we identified patients without known coronary artery disease who were undergoing elective catheterization. The patients’ demographic characteristics, risk factors, and symptoms and the results of noninvasive testing were correlated with the presence of obstructive coronary
Hospital Variation in the Use of Noninvasive Cardiac Imaging and Its Association With Downstream Testing, Interventions, and Outcomes
Kyan C. Safavi, BS; Shu-Xia Li, PhD; Kumar Dharmarajan, MD, MBA; Arjun K. Venkatesh, MD, MBA; Kelly M. Strait, MS; Haiqun Lin, MD, PhD; Timothy J. Lowe, PhD; Reza Fazel, MD, MSc; Brahmajee K. Nallamothu, MD, MPH; Harlan M. Krumholz, MD, SM

*JAMA Intern Med.*
Published online February 10, 2014.

**CONCLUSIONS AND RELEVANCE** Hospitals vary in their use of noninvasive cardiac imaging inpatients with suspected ischemia who do not have AMI. Hospitals with higher imaging rates did not have substantially different rates of therapeutic interventions or lower readmission rates for AMI but were *more likely to admit patients and perform angiography.*
Current State Of Nuclear Cardiology

• 95% of studies performed in US are SPECT
• 99% of SPECT studies are rest/stress, requiring 3-4 hours
• 99% of laboratories in 2014 do not meet ASNC recommendations of <9mSv in 50% of patients (ACC abstract, IAC data, Jerome, Tilkemeirer, Shaw)
• 50% of SPECT cameras are 10-20 years old (Bateman, IAC data presented at ASNC) and cannot perform radiation reduction, fast protocols
• Diagnostic accuracy, especially specificity, is in the tank (Krumholz, Patel, day-to-day experience)
• Referring physician confidence: all time low
The Way Out

- Shorten protocols
- Reduce radiation exposure
- Reduce cost
- Improve diagnostic accuracy
- Provide additional data/value
The Way Out

**SPECT**
- Shorten Protocols: new camera
- Reduce radiation exposure: new camera
- Reduce cost: new camera
- Improve diagnostic accuracy: attenuation correction
- Provide additional data/value: 1. new camera, myocardial blood flow? 2. mIBG imaging

**PET**
- Shorten Protocols: done
- Reduce radiation exposure: done
- Reduce cost: shortened protocol, increased efficiency
- Improve diagnostic accuracy: done
- Provide additional data/value: myocardial blood flow, FDG for sarcoid, metabolic viability, inflammation imaging
The Way Out: PET

- Shorten protocols
- Reduce radiation exposure
- Reduce cost
- Improve diagnostic accuracy
- Provide additional data/value
- New developments that make a difference
Growth of PET in the US: Rubidium Generators, Estimated
The Way Out: PET

- Shorten protocols
- Reduce radiation exposure
- Reduce cost
- Improve diagnostic accuracy
- Provide additional data/value
- New developments
Rest/Stress SPECT Protocol, circa 1991-2014

Elapsed Time: 2 ½-4 hours

Imaging time: 30 minutes

Radiation Exposure: 10-25 mSv

Time (minutes)

0 45 60 90 120 135

Radiopharmaceutical Injection (rest)

Radiopharmaceutical Injection (peak exercise/pharm stress)
Rubidium PET-CT Protocol, 2014

Elapsed Time: 25 Minutes
Imaging time: 10 minutes
Radiation Exposure: 2-5 mSv

CT-transmission

Rb-82 20-60 mCi

Pharmacologic stress*

Rb-82 20-60 mCi

Gated rest

Gated stress

CT-transmission: (optional)

Approx 1 min

Approx 7 min

Approx 6 min

Approx 7 min

Approx 1 min

* Dipyridamole, regadenoson, or dobutamine.
Recommendations for Reducing Radiation Exposure in Myocardial Perfusion Imaging


Favorable dosimetry (20 mCi Rb-82 ~ 0.9 mSv)


The Way Out: PET

• Shorten Protocols
• Reduce radiation exposure
• Reduce cost
• Improve diagnostic accuracy
• Provide additional data/value
• New developments
Cost in a Value System

- Time of study
- Efficiency of camera: daily throughput
- Repeat testing: down-stream procedures will now matter
Myocardial Perfusion PET in Patients with a Non-Diagnostic SPECT

- 73% Normal
- 25% Abnormal
- 2% Non-Diagnostic

233 consecutive pts with a non-diagnostic SPECT followed by MP PET ≤90 days

64% were women
Mean BMI 32
Mean age 62 yrs

Downstream Effects: PET vs SPECT

The Way Out: PET

• Shorten protocols
• Reduce radiation exposure
• Reduce cost
• Improve diagnostic accuracy
• Provide additional data/value
• New developments
Table 4. Summary of published literature on diagnostic accuracy of PET

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number</th>
<th>Tracer</th>
<th>Sensitivity (%)</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schelbert et al</td>
<td>1982</td>
<td>45</td>
<td>$^{13}$NH$_3$</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Tamaki et al</td>
<td>1985</td>
<td>25</td>
<td>$^{13}$NH$_3$</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>Yonekura et al</td>
<td>1987</td>
<td>50</td>
<td>$^{13}$NH$_3$</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Tamaki et al</td>
<td>1988</td>
<td>51</td>
<td>$^{13}$NH$_3$</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Gould et al</td>
<td>1986</td>
<td>50</td>
<td>$^{82}$Rb/$^{13}$NH$_3$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Demer et al</td>
<td>1989</td>
<td>193</td>
<td>$^{82}$Rb/$^{13}$NH$_3$</td>
<td>83</td>
<td>95</td>
</tr>
<tr>
<td>Go et al</td>
<td>1990</td>
<td>202</td>
<td>$^{82}$Rb</td>
<td>93</td>
<td>78</td>
</tr>
<tr>
<td>Stewart et al</td>
<td>1991</td>
<td>81</td>
<td>$^{82}$Rb</td>
<td>83</td>
<td>86</td>
</tr>
<tr>
<td>Marwick et al</td>
<td>1992</td>
<td>74</td>
<td>$^{82}$Rb</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Grover-McKay et al</td>
<td>1992</td>
<td>31</td>
<td>$^{82}$Rb</td>
<td>100</td>
<td>73</td>
</tr>
<tr>
<td>Laubenbacher et al</td>
<td>1993</td>
<td>34</td>
<td>$^{13}$NH$_3$</td>
<td>88</td>
<td>83</td>
</tr>
<tr>
<td>Wallhaus et al</td>
<td>2001</td>
<td>45</td>
<td>$^{64}$Cu-PTSM</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>Bateman et al</td>
<td>2006</td>
<td>112</td>
<td>$^{82}$Rb</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>Walsh et al</td>
<td>1988</td>
<td>33</td>
<td>$^{15}$O-H$_2$O</td>
<td>92</td>
<td>-</td>
</tr>
<tr>
<td>Williams et al</td>
<td>1994</td>
<td>287</td>
<td>$^{82}$Rb</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>Simone et al</td>
<td>1992</td>
<td>225</td>
<td>$^{82}$Rb</td>
<td>83</td>
<td>91</td>
</tr>
<tr>
<td>Sampson et al</td>
<td>2007</td>
<td>102</td>
<td>$^{82}$Rb</td>
<td>93</td>
<td>83</td>
</tr>
<tr>
<td>Husmann et al</td>
<td>2007</td>
<td>70</td>
<td>$^{13}$NH$_3$</td>
<td>96</td>
<td>-</td>
</tr>
<tr>
<td>Total weighted mean</td>
<td>1660</td>
<td></td>
<td></td>
<td>90</td>
<td>89</td>
</tr>
</tbody>
</table>

Diagnostic Accuracy: PET vs SPECT

**Diagnostic Accuracy by Gender**

- Men: 69% (SPECT) vs 84% (PET)  (*P = 0.55*)
- Women: 67% (SPECT) vs 88% (PET)  (*P = 0.009*)

**Diagnostic Accuracy by BMI**

- BMI < 30: 70% (SPECT) vs 87% (PET)  (*P = 0.05*)
- BMI > 30: 67% (SPECT) vs 85% (PET)  (*P = 0.02*)

**MVD Sensitivity**

- SPECT: 48%
- PET: 71%  (*P = 0.03*)

Diagnostic Accuracy of Cardiac Positron Emission Tomography Versus Single Photon Emission Computed Tomography for Coronary Artery Disease

A Bivariate Meta-Analysis

Matthew W. Parker, MD; Aline Iskandar, MD; Brendan Limone, PharmD; Andrew Perugini, PharmD; Hyejin Kim, PharmD; Charles Jones, PharmD; Brian Calamari, PharmD; Craig I. Coleman, PharmD; Gary V. Heller, MD, PhD
Clinical Implications of Improved Diagnostic Accuracy: PET

• Significantly fewer “cath normal” results: HH went from 40% before PET to 15% after PET

• Targeted Catherization: avoid cath in patients with Single vessel Ischemia by PET as no benefit

• Higher percentage of cath/revascularization

• Concentration on multi-vessel ischemia
The Way Out: PET

- Shorten Protocols
- Reduce radiation exposure
- Reduce cost
- Improve diagnostic accuracy
- Provide additional data/value
- New developments
Risk Stratification: PET Summed Stress Score Severity and Left Ventricular Dysfunction

Lertsburapa et al JNC 2007;14:S124
PET Prognosis Registry: Cardiac Mortality Rates by % the Abnormal Stress Myocardium with Rb-82 PET

Women (n=2,904)
Model $X^2=47$, $p<0.0001$

Men (n=3,133)
Model $X^2=71$, $p<0.0001$

Source: Kay J Am Coll Cardiol (in press)
Impact of LVEF Reserve in Predicting Cardiac Events

Figure 2. Event Rates in Patients With Normal and Abnormal LVEF Reserve

Annualized rates of cardiac events (CE) (cardiac death and nonfatal myocardial infarction) and all-cause death were lower in patients with left ventricular ejection fraction (LVEF) reserve $\geq 0\%$ compared to those with LVEF reserve $< 0\%$. $p < 0.001$ for CE and all-cause death.

Perfusion is Normal: What Does Normal Myocardial Flow Reserve Add?

1. Confirms that vasodilation occurred
   - Non-responder
   - Caffeine or other antagonist
2. Excludes balanced flow reduction
3. Excludes flow-limiting epicardial CAD
4. Excludes endothelial dysfunction
5. Excludes small-vessel CAD

6. Infers a better prognosis
Survival Curves Showing Added Value of CFR in Predicting Outcome Up to 3 Years After a Normal MPI PET Scan

Other Aspects of Cardiac PET

- Myocardial viability assessment
- Cardiac sarcoid assessment
- Inflammation assessment: ICD, etc
- Neuronal Imaging: future
- Cardiac amyloid: data emerging
- Unstable plaque assessment?
Conclusion: Added information

- Risk stratification with PET now documented
- Reversible wall motion predicts worse prognosis
- Normal blood flow provides additional confidence in normal study
- Abnormal blood flow implies worse prognosis and potential for therapy
- In contrast to SPECT, multiple options for non-CAD evaluation
The Way Out: PET

- Shorten protocols
- Reduce radiation exposure
- Reduce cost
- Improve diagnostic accuracy
- Provide additional data/value
- New developments that make a difference
Current Status: PET

• The two available PET perfusion tracers are limited in:
  • Availability: NH3 ammonia
  • Exercise patients: Rb-82
  • Cost

• Cardiac PET perfusion will never become mainstream until full spectrum of patients can be accommodated
Ideal PET MPI Imaging Agent: Glover and Gropler assessment

- High cardiac uptake with minimal redistribution
- Near linear myocardial uptake (high first pass extraction fraction)
- Usable for both exercise and pharmacologic stress
- Usable for quantitation of absolute/regional myocardial flow
- Available as unit dose (\(^{18}\)F-labeled compound)

Adapted from: Glover, D and Gropler, R., J. Nucl. Card 14:6 p765-8
F-18 Flurpiridaz

- Lantheus Medical Imaging
- Phase 2 complete, results published
- Phase 3 study 1 complete, ongoing evaluation of data
- Active discussions with FDA
First Pass Uptake in Isolated Rabbit Hearts

69 year old, male subject, low likelihood of CAD, exercise stress.

Courtesy, Cesare Orlandi, MD Lantheus Medical Imaging.
Clinical History
- 75 year old male
- BMI of 32.6
- No CAD on angiography

Flurpiridaz PET MPI over SPECT MPI

Reader:
- Definitely normal

SPECT
Reader:
- Probably abnormal
  (possible reversible defect in the basal inferior wall)

Phase 2
Patient Without Coronary Artery Disease

Improved Specificity in flurpiridaz PET MPI over SPECT MPI

Courtesy, Cesare Orlandi, MD Lantheus Medical Imaging
**Patient With Coronary Artery Disease**

**Angiography**
- 71 year old male
- LAD: 48%
- LCX: 77%
- RCA 100%

**Flurpiridaz**
- Improves sensitivity and detects multi-vessel disease

**Flurpiridaz Reader:**
- **Definitely abnormal**

**SPECT Reader:**
- **Probably normal**

**Flurpiridaz**
- Short Axis
  - Apical
  - Mid
  - Basal
- Vertical Axis
- Horizontal Axis

**SPECT**
- Stress MIBI
- Rest MIBI
- Stress FLUR
- Rest FLUR

**Phase 2**

*Courtesy, Cesare Orlandi, MD Lantheus Medical Imaging*
BF PET Fluoropharma

- Blood flow agent
- Phase 1 complete
- Phase 2 in development
Second Agent 18F-TTP (BFPET) in Phase 2 Trial

JACC Imaging 2012;5:285-92
BFPET Phase Ia completed

- 12 healthy volunteers ages 20-85
- No adverse events
- No clinically significant changes noted in follow-up clinical and laboratory testing

Results show excellent perfusion imaging properties

- Rapid extraction from blood
- Stable heart uptake over time
- High target to background ratios
- Convenient imaging window
- Whole body effective dose: 73.5 ± 17.59 mrem/mCi

Cardiac PET Images in NHV

Source: FluoroPharma Medical, Inc.
Source: Results of investigator-sponsored trial at PLA 301 Hospital in Beijing, China.
Ischemic Memory Imaging

- Two approaches: FFA or glucose
- BMIPP a FFA SPECT agent, used in Japan, not approved USA
- CardioPET, F-18 FFA agent, Fluoropharma, Phase 2 evaluation
**18-F FCPHA (CardioPET) Phase I Results**

**PHASE I TRIAL COMPLETED**
(15 NHV and 6 CAD patients)

- CardioPET promising safety with no AEs detected
- Clinical findings consistent with MPI SPECT
- Quality of CardioPET images substantially superior to MPI SPECT

**Infarcted region of the heart**
F-18 FCPHA Phase II Case Example
MIBI SPECT Stress-rest (without attenuation correction)
F-18 FCPHA Phase II
Case Example rest (55-60 min.)
New Developments PET

• Two perfusion agents, F-18 in FDA trial
• Free fatty acid F-18 agent in FDA trial
• Neuronal Imaging agent: phase 1
• Several others on the horizon
PET: Will It Change the Future? Which is Favored, PET or SPECT?

- Diagnostic differences between PET and SPECT: PET
- Unique aspects to perfusion: PET
- Myocardial flow: PET
- New perfusion tracers: PET
- Radiation exposure, protocol: PET
- Applications beyond CAD: PET
May 12, 2014 Washington DC

ASNC PET Summit
Exploring the Evolution of Nuclear Cardiology and Paving the Road Forward

E. Gordon DePuey, MD, Kathy Flood CEO