Comparing Novel Positron Emission Tomography Myocardial Perfusion Imaging with Conventional Single-Photon Emission Computed Tomography

Evangelia Vlontzou, MD

ABSTRACT

For myocardial perfusion imaging, single-photon emission computed tomography (SPECT) technology is widely accepted by the cardiological community. It is supported by rich literature and has acceptable diagnostic accuracy. However, it does have limitations with false positive studies especially in women and obese patients and underestimates multivessel coronary artery disease. Positron emission tomography (PET) technology appears to be able to improve the diagnostic accuracy in detecting coronary artery disease. It offers qualitatively better images with shorter acquisition times and lower radiation burden on patients and personnel. It has the advantage of absolute quantification of myocardial blood flow for multivessel coronary disease diagnosis and is superior in the assessment of myocardial viability. In absolute terms it is an expensive method but avoiding the cost of additional diagnostic tests in equivocal studies makes it cost effective. Its availability is improving and it is expected to help in advancing nuclear cardiology.

INTRODUCTION

Radioisotope imaging of myocardial perfusion started in 1970 and peaked in the 1990's with advanced single-photon emission computed tomography (SPECT) systems and new radiopharmaceuticals. Almost in parallel, positron emission tomography (PET) technology became possible but only recently won support and is recognized for use in the imaging of myocardial perfusion. The main limitations delaying its timely use were the high cost of PET cameras hampering its availability, the cost and availability of radiopharmaceuticals for PET and the limited scientific literature. The increasing use of PET in clinical oncology over the last decade led to a reassessment of PET technology in clinical cardiology. The position of SPECT imaging of myocardial perfusion is widely accepted, evidenced by a wealth of literature, familiar to physicians, with clear guidelines for managing patients. Despite that, it has disadvantages that lead to inconclusive results and necessitate further patient examinations. The insufficiency of attenuation correction and tracer activity in the liver and intestine with technetium-based radiopharmaceuticals, despite the experience of physicians, use of gated SPECT...
and image acquisition in prone position, SPECT still leads to non-diagnostic tests particularly in obese patients and women. The inability to absolutely quantify myocardial blood flow (MBF) with SPECT underestimates the degree of ischemia and presence of multivessel coronary artery disease (CAD).6,7

PET AND RADIOPHARMACEUTICALS

A growing literature shows that PET can be an alternative solution to SPECT limitations. The radiopharmaceuticals and their characteristics8 for the two technologies are shown in Table 1. The radiopharmaceuticals for PET have better extraction fraction than SPECT tracers and more linear uptake at higher flow rates. The short half time of PET radiopharmaceuticals results in short-time protocols. The rest/stress study with 82Rb can be completed in 20-30 minutes while the corresponding SPECT process requires more time from the patient as well as a busy laboratory,9,10 since it takes 3-5 hours. The available improvements in SPECT hardware and software offer faster acquisition with lower dosimetry and qualitatively better imaging but they increase cost and are being introduced at a time of declining reimbursement and utilization.10 A limitation resulting from the short half-life of PET radiopharmaceuticals is the inability to perform regular stress test with only alternative the pharmaceutical stress.

13N-NH3 offers high quality images and the capability of absolute quantitative assessment of MBF. However, it suffers from an availability standpoint. Its production requires on-site cyclotron which increases the cost.11 15O-H2O has the ability to diffuse freely across capillary and cell membranes and this makes the tracer almost ideal for quantitative assessment of myocardial blood flow. But the images are non-satisfactory and its use is restricted to sites with a cyclotron. 82Rb can be produced from a 82Sr/82Rb generator and has better availability compared to the previous radiopharmaceuticals since the existence of the generator with proper patient handling makes it cost effective. 82Rb is analogous to potassium and the 78 seconds of its half-life (t1/2) reduce the time between examinations and allow their repetition after 15 min if technical problems arise. However, the relative rather than the absolute myocardial flow is estimated and for this reason it does not solve the SPECT problem of low sensitivity in patients with diffuse microvascular or balanced disease.12 Programs for absolute blood flow measurements with 82Rb exist but this is not in wide use.

New radiopharmaceuticals like fluridipaz-F18 based on 18F labeling are being developed and evaluated in order to overcome the existing limitations. These do not require on-site cyclotron, are produced with the technology and availability of radiopharmaceuticals for oncologic patients, have longer half life and allow stress tests and possibly have lower cost since they allow single patient doses.13,14 In general, the PET radiopharmaceuticals have higher cost and limited availability with 82Rb being the most commonly used. Because of the short half life, higher doses can be administered resulting in shorter duration studies.

RADIATION

It has been estimated that in the US population, 20% of the yearly collective radiation dose received is from radioisotope studies of myocardial perfusion and in a recent publication it was estimated that 7400 more cancers may occur based on myocardial perfusion testing frequencies in the US in 2008.15 However, the relationship between this level of radiation exposure and cancer risk is disputed and physicians should follow the relevant recommendations in order to achieve the desired result with minimum risk.

The radiation burden for patients is lower with PET radiopharmaceuticals compared to SPECT because of the short half life despite the larger administered doses (Table 2).16 For the laboratory personnel, despite PET radiopharmaceuticals

<p>| TABLE 1. Radiopharmaceuticals and Their Characteristics for the Two Technologies of PET and SPECT |
|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-life</th>
<th>Production</th>
<th>Extraction</th>
<th>Myocardial Uptake-Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>82Rb</td>
<td>78 sec</td>
<td>Generator</td>
<td>50-60%</td>
<td>Na/K-ATPase (perfusion)</td>
</tr>
<tr>
<td>13N-NH3</td>
<td>10min</td>
<td>Cyclotron</td>
<td>80%</td>
<td>Diffusion/metabolic trapping (perfusion)</td>
</tr>
<tr>
<td>15O-H2O</td>
<td>2min</td>
<td>Cyclotron</td>
<td>Diffusible</td>
<td>Free diffusion</td>
</tr>
<tr>
<td>18F-FDG</td>
<td>110min</td>
<td>Cyclotron</td>
<td>1-3%</td>
<td>Glucose transport/hexokinase (viability)</td>
</tr>
<tr>
<td>SPECT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>201TI</td>
<td>73h</td>
<td>Cyclotron</td>
<td>73%</td>
<td>Potassium analog</td>
</tr>
<tr>
<td>99mTc-Sestamibi/Tetrafosmin</td>
<td>6h Generator</td>
<td>50-60%</td>
<td>Mitochondrial uptake</td>
<td></td>
</tr>
</tbody>
</table>

FDG = fluorodeoxyglucose; PET = positron emission tomography; SPECT = single photon emission computed tomography.
having high energy photons that could theoretically represent greater radiation burden, this is not confirmed because of differences in radiotracer administration, in various acquisition and stress-testing tasks.\(^{17}\)

**IMAGE RESOLUTION**

Imaging with PET provides higher spatial and temporal resolution compared to SPECT, and robust and common use of attenuation correction.\(^8\) The higher temporal resolution permits dynamic imaging and the higher spatial resolution and the attenuation correction offers better sensitivity and specificity for CAD detection than SPECT. The correction of attenuation with PET is more accurate than in SPECT because of the uniform attenuation of high energy photons (511 vs 140 KeV for \(^{99}\)Tc). As a result of attenuation correction we have better image quality, especially in sub-populations like women where breast attenuation is frequent and in obese patients where the direct result compared to SPECT is an increase in specificity and normalcy rate leading to fewer inconclusive studies.\(^{14}\)

Yoshinaga et al\(^{19}\) showed that in patients with equivocal SPECT, the quality of scans was rated as good in only 20% of SPECT vs 90% of PET. Bateman et al reached similar conclusions in matched patients.\(^{20}\) The attenuation artifacts of PET are a lot fewer because of the higher imaging activity of the radiopharmaceutical tracer and the attenuation correction. The artifacts because of liver and intestine activity are more in SPECT studies than PET (41% vs 5%) and consequently the reader certainty was greater with PET than SPECT (96% vs 82%) independent of gender or body mass index, with 4% equivocal studies with PET and 18% with SPECT. Examples of PET myocardial perfusion images are displayed in Fig. 1-3.

**TABLE 2. Patient Radiation Exposure by the Most Frequent Diagnostic Nuclear Imaging Procedures\(^{16}\)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Body Effective Dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{201})TI stress and re-injection (110+37 MBq)</td>
<td>25.1</td>
</tr>
<tr>
<td>(^{99})Tc-sestamibi 1 day (370+1,100 MBq)</td>
<td>10.7</td>
</tr>
<tr>
<td>(^{99})Tc-sestamibi 2 days (1100+1,100 MBq)</td>
<td>16.0</td>
</tr>
<tr>
<td>(^{201})TI/(^{99})TcDual isotope (110+1,100 MBq)</td>
<td>27.3</td>
</tr>
<tr>
<td>(^{82})Rb stress-rest PET (1100+1,100 MBq)</td>
<td>7.5</td>
</tr>
<tr>
<td>(^{13})NH3 stress-rest PET (500+500 MBq)</td>
<td>2.0</td>
</tr>
<tr>
<td>(^{15})O stress-rest PET (900+900 MBq)</td>
<td>1.7</td>
</tr>
<tr>
<td>(^{18})F-FDG PET viability (259 MBq)</td>
<td>4.9</td>
</tr>
</tbody>
</table>

**DIAGNOSTIC CAPABILITY**

The diagnostic accuracy of PET for CAD diagnosis has been verified in many studies. In Di Carli’s meta-analysis,\(^{21}\) 90% sensitivity and 89% specificity is reported from 9 studies, most with use of \(^{82}\)Rb-PET. In direct comparison with \(^{201}\)TI-SPECT and \(^{82}\)Rb or \(^{13}\)N-NH3-PET in three studies, sensitivity was 91% for PET and 81% for SPECT, while specificity was 93% vs 85% in CAD diagnosis.\(^8\) Even with technetium-based radiopharmaceuticals and gated acquisition, specificity was 93% for PET vs 73% for SPECT in Bateman’s study and especially in the female population 86% vs 64%.\(^{20}\) Using as a threshold luminal stenosis of 70%, the overall diagnostic accuracy for PET was 89% vs 79% for SPECT and this was due to the improved specificity of PET, while sensitivity was marginally greater at 87% vs 82%.

In the same study, recognized as the most notable, it was shown that PET was better than SPECT (71% vs 48%) in the diagnosis of multivessel CAD, probably related to differences in tracer kinetics between \(^{82}\)Rb and \(^{99}\)Tc-sestamibi. The extraction fraction of radiopharmaceuticals for SPECT is limited to higher flow rates resulting in limited usefulness in patients with incipient coronary artery disease.\(^ {6,7}\)

\(^{82}\)Rb has relative higher extraction of the \(^{99}\)Tc-sestamibi at high flow rates and this could explain in part the improved ability of PET to recognize better multivessel CAD.\(^3\) However, PET, at a 30% rate, misclassifies patients with multivessel disease as having one vessel disease or even misses some patients with balanced ischemia.\(^3\)

One additional PET advantage is the capability of assessment of left ventricular ejection fraction (LVEF) at the peak of pharmacological stress and of course the change from rest, offering prognostic information which is additive to that determined by the extent and severity of perfusion abnormality alone.\(^2\) Peak-stress myocardial function cannot be assessed with typical SPECT protocols. In Dorbala’s study,\(^23\) it is stated that by assessing the LVEF change, the diagnostic sensitivity for multivessel disease increases from 50% to 79%.

In general, PET appears more important because the number of false positive studies is reduced and offers high specificity compared to SPECT. The higher sensitivity of PET can be explained by the better spatial resolution and the better tracer extraction. Regarding the prognostic value for SPECT, there are a lot of data, while for PET only a few studies exist,\(^ {24-26}\) therefore the prognostic value of PET is not as well documented as SPECT.

**MYOCARDIAL BLOOD FLOW**

The capability of absolute quantification of myocardial blood flow (MBF) at rest and during stress and coronary flow...
FIGURE 1. Myocardial perfusion PET images using $^{82}$Rb in a patient with severe angina. PET shows reversibility in the inferior wall region.

FIGURE 2. Myocardial perfusion PET images using $^{82}$Rb in a patient with four months history of angina and positive stress test at low work load. Moderate to severe anteroapical and septal inducible ischemia (LAD territory). LAD = left anterior descending (coronary artery).
reserve (CFR) by dynamic PET is an important PET advantage. The high temporal resolution of PET enables dynamic imaging providing robust and reproducible time activity data needed to quantify regional and global MBF in milliliters per minute per gram of tissue, thus PET is able to quantify absolute MBF and coronary flow reserve.\textsuperscript{27} \textsuperscript{15}N-NH\textsubscript{3} and \textsuperscript{15}O-H\textsubscript{2}O have been used for these measurements and constitute a non-invasive gold standard for the assessment of MBF and CFR.\textsuperscript{28,29} \textsuperscript{82}Rb has also been used but with limitations because it requires a correction for its lower extraction fraction.\textsuperscript{4} Several methods have been used with \textsuperscript{82}Rb to achieve sufficient accuracy for the evaluation of CFR and in quantification of MBF and it is expected that they will help in implementing flow quantification into clinical PET practice because \textsuperscript{82}Rb is the most frequently used radiopharmaceutical. However, it is accepted that the involvement of microcirculation plays a critical role in pathogenesis of many cardiac disorders and the quantitative flow measurement is useful in cases like widespread CAD with balanced ischemia, evaluation of collateral flow and identification of endothelial dysfunction in preclinical disease. Also CFR measurements with PET can provide prognostic information. Patients with normal perfusion but pathological CFR <2 were independently associated with higher annual event rate (1.4\% vs 6.3\%) and cardiac death rate (0.5\% vs 3.1\%) in the study of Herzog et al.\textsuperscript{30} The clinical value of flow quantification with PET is a promising method for patient risk stratification and an object of many studies because there is no credible technique in SPECT.

**Complementary Information**

The recent wide use of PET/computed tomography (CT) imaging systems offers complementary morphological and functional information like calcium scoring, increasing the prognostic value of the method and the negative prognostic value, especially in patients with low CAD prevalence.\textsuperscript{31} Recently, special pinhole collimators and arch arrangements of SPECT detectors have increased the SPECT count sensitivity but cost is also significantly increased and current availability is limited.\textsuperscript{32} Despite that, the count sensitivity of PET remains greater and its high quality images lead to high interpretive certainty and greater diagnostic accuracy.

**Myocardial Viability**

Positron emission tomography with \textsuperscript{18}F-FDG is considered...
by many the gold standard for the assessment of myocardial viability, based on the notion that the assessment of only the myocardial perfusion is not enough to predict function recovery after revascularization. $^{18}$F-FDG is the best known radiopharmaceutical for oncology but also for the assessment of myocardial viability. $^{18}$F-FDG uptake has been observed in areas of markedly reduced or absent radiopharmaceutical uptake in SPECT. Tillisch et al 10 compared the $^{18}$F-FDG uptake in patients with advanced CAD and affected regional and global function before and after revascularization and showed that imaging of viable myocardium was superior with $^{18}$F-FDG-PET compared to SPECT, in patients benefiting from revascularization. Approximately 30-50% of scarred tissue areas with $^{201}$TI showed FDG uptake and were characterized as viable. Later in 2007, Schinkel et al 34 in a comprehensive and systematic review, showed higher sensitivity of $^{18}$F-FDG-PET (92%) compared to $^{201}$TI and technetium based radiopharmaceuticals, including magnetic resonance imaging and dobutamine echocardiography. The specificity was highest for dobutamine echocardiography and the highest negative prognostic value was with $^{18}$F-FDG-PET. With $^{201}$TI reinjection the viability assessment was comparable to FDG but the weight of evidence favors the use of FDG. 35 Recent data from the Ottawa-Five substudy of PARR2 36 show that when $^{18}$F-FDG-PET is available and is used by experienced personnel it has the advantage in assessing patients who will benefit from revascularization. $^{18}$F-FDG-PET accurately predicts the improvement of global LVEF and of regional wall motion after revascularization, especially when blood flow is reduced by >50% and there is relatively high glucose uptake. Even in perfusion imaging with $^{82}$Rb, $^{18}$F-FDG-PET often shows additional viable tissue in patients with fixed $^{82}$Rb perfusion defects or in patients with only partial stress-inducible reversibility. 8

CONCLUSIONS

Positron emission tomography (PET) perfusion imaging offers better images with higher resolution and better attenuation correction than SPECT perfusion imaging. PET protocols are shorter and the patients are exposed to less radiation. All these lead to enhanced diagnostic certainty and accuracy and PET will enable nuclear cardiology to survive for years to come. However, at this time, SPECT myocardial perfusion imaging continues to be the main method, because this technique has been standardized for the protocols employed and has been tested in all patient populations.

REFERENCES

5. Cerquiera MD. Diagnosis and prognostic of coronary artery disease: PET is superior to SPECT: Con. J Nucl Cardiol 2010; 17:678-682.