Cardiac Positron Emission Tomography Imaging—State of the Art

a report by

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Positron emission tomography (PET) has contributed significantly to advancing our understanding of heart physiology and pathophysiology for more than 25 years. Despite its clear success in research applications, the restricted availability of this technology, its increased cost, and limited data supporting its use and reimbursement have all contributed to the relatively limited clinical acceptance of it. However, the rapid dissemination of PET/computed tomography (CT) systems initially dedicated to oncology imaging, along with increasing evidence of PET’s clinical efficacy in cardiology and changes in reimbursement, are all contributing to help advance its clinical role in cardiovascular medicine. Additionally, the emergence of integrated PET/CT technology as the dominant configuration of clinical PET scanners also holds great promise for cardiac imaging as it provides a potential opportunity to delineate the anatomical extent and physiological severity of coronary atherosclerosis in a single setting. The objective of this review is to provide the reader with an update on the applications and promises of PET and PET/CT in cardiovascular medicine.

Myocardial Perfusion Imaging Agents for PET

Several myocardial perfusion tracers are approved by the US Food and Drug Administration (FDA) and are available for clinical use, including cyclotron-produced radiopharmaceuticals (N-13-ammonia) and generator-produced rubidium-82. Rb-82 is a potassium analog with a physical half-life of 76 seconds and kinetic properties similar to those of thallium-201.1 Due to the distinct advantage of not requiring an on-site cyclotron, Rb-82 is the most widely used radionuclide for the assessment of myocardial perfusion with PET. Its parent radionuclide is strontium-82, which has a physical half-life of 26 days. Consequently, the Sr-82/Rb-82 generator is replaced every four weeks. N-13 ammonia is a cyclotron product and has a physical half-life of 9.96 minutes. After injection, 13N-ammonia rapidly disappears from the circulation, permitting the acquisition of images of excellent quality. The main disadvantage of PET is the need of an on-site cyclotron, which adds cost and is logistically demanding. The recent development of a fluorine-18-labeled (two-hour half-life) myocardial perfusion imaging (MPI) agent with excellent physiological and imaging properties may facilitate the unit-dose distribution configuration of clinical PET scanners also holds great promise for cardiac imaging as it provides a potential opportunity to delineate the anatomical extent and physiological severity of coronary atherosclerosis in a single setting. The objective of this review is to provide the reader with an update on the applications and promises of PET and PET/CT in cardiovascular medicine.

Technical Advantages of PET over SPECT

Several technical advantages account for the improved image quality and diagnostic ability of PET compared with single photon emission computed tomography (SPECT), including: routine measured (depth-independent) attenuation correction, which decreases false-positives and, thus, increases specificity; high spatial and contrast resolution (heart–background ratio), which allows improved detection of small perfusion defects, thereby decreasing false-negatives and increasing sensitivity; high temporal resolution, which allows fast dynamic imaging of tracer kinetics, which makes absolute quantification of myocardial perfusion (in ml/minute/g of tissue) possible; and the use of short-lived radiopharmaceuticals, which allows fast, sequential assessment of regional myocardial perfusion (e.g. rest and stress), thereby improving laboratory efficiency and patient throughput. Using Rb-82, a complete rest/stress myocardial perfusion PET study can be completed within 20 minutes.

Despite these advantages, SPECT scanners and imaging radiotracers (e.g. 99mTc agents and 201Thallium) are still more widely available and less expensive than PET scanners and positron-emitting radiotracers (e.g. Rubidium, 13N ammonia).

Diagnostic Accuracy of Myocardial Perfusion PET and PET/CT

Studies of PET versus SPECT

Three studies have performed a direct comparison of the diagnostic accuracy of 82Rubidium myocardial perfusion PET and 201Tlthallium or technetium-99m (99mTc) SPECT imaging in the same or matched patient populations. Go and colleagues compared PET with SPECT in 202 patients.4 Their results showed a higher sensitivity with PET than with SPECT (93 versus 76%, respectively) without significant changes in specificity (78 versus 80%, respectively). In another study, Stewart et al. compared PET with SPECT in 81 patients.5 They observed a higher specificity for PET than with SPECT (83 versus 53%, respectively) without significant differences in sensitivity (86 versus 84%, respectively). Diagnostic accuracy was higher with PET than with SPECT (89 versus 78%, respectively). More recently, Bateman et al. compared 82Rubidium PET with...
laboratory suggest that in normal subjects, LV ejection fraction (LVEF) increases peak stress (as opposed to post-stress with gated SPECT). Recent data from our laboratory also indicates pharmacological-stress perfusion imaging using contemporary technology for both SPECT and PET.6 Overall diagnostic accuracy using either a 50% (87 versus 71%) or a 70% (89 versus 79%) angiographic threshold was higher for PET than for SPECT. Differences in diagnostic accuracy primarily reflected the increased specificity (with a marginal advantage in sensitivity) of PET versus SPECT, and applied to both men and women and obese and non-obese individuals.

Diagnosing Multivessel CAD with Myocardial Perfusion PET/CT

As depicted in Table 1, the relative assessment of myocardial perfusion with PET remains a sensitive means for diagnosing or ruling out the presence of obstructive CAD. However, as with SPECT, PET often uncovers only that territory supplied by the most severe stenosis, and thus it often underestimates the extent of underlying CAD. PET’s unique ability to enable non-invasive measurements of myocardial blood flow (in ml/minute/g of myocardium) and coronary vasodilator reserve offers a powerful approach to improve the detection of multivessel CAD. This is based on the fact that non-invasive measurements of myocardial blood flow (in ml/minute/g of tissue) and coronary vasodilator reserve (the ratio between peak and rest myocardial blood flow) by PET are inversely and non-linearly related to stenosis severity, and can assess the physiological significance of stenoses of intermediate severity (see Figure 1). Preliminary evidence suggests that this approach is feasible and that it results in the improved quantification of at-risk myocardium and the identification of patients with multivessel CAD. Another advantage of PET is its distinct ability to assess left ventricular (LV) function at rest and during peak stress (as opposed to post-stress with gated SPECT). Recent data from our laboratory suggest that in normal subjects, LV ejection fraction (LVEF) increases during peak vasodilator stress. However, in patients with CAD, changes in LVEF (from baseline to peak stress) are inversely related to the magnitude of perfusion abnormalities during stress (reflecting ischemic myocardium). Indeed, patients with multivessel disease or left main disease show a frank drop in LVEF during peak stress even in the absence of apparent perfusion defects (see Figure 2). In contrast, patients without significant CAD or with one-vessel disease show a normal increase in LVEF. Consequently, the NPV of a delta LVEF less than 5% to 10% is 97%. Finally, the use of hybrid imaging also allows evaluation of coronary anatomy using computed tomography angiogram (CTA) in the same setting, thereby offering another opportunity for the detection of high-risk CAD (see Figure 3). Indeed, a CTA provides excellent diagnostic sensitivity for stenoses in the proximal and mid-segments (>1.5mm in diameter) of the main coronary arteries.

Risk Stratification with PET/CT

There is growing consistent evidence that, like for SPECT, an increased extent and severity of perfusion defects with stress PET is associated with increasing frequency of adverse events. Importantly, the hard event rate in patients with normal stress PET is low. The potential to acquire and quantify rest and stress myocardial perfusion and CT information from a single study using hybrid imaging opens the door to expanding the prognostic potential of stress imaging. Recent data from our laboratory suggest that quantification of coronary artery calcium (CAC) scores at the time of stress myocardial perfusion PET imaging using a hybrid approach can enhance risk predictions in patients with suspected CAD. In a consecutive series of 621 patients undergoing stress PET imaging and CAC scoring in the same clinical setting, risk-adjusted analysis demonstrated a stepwise increase in cardiac event rates with increasing levels of CAC score for any level of perfusion abnormality. Indeed, the annualized

**Table 1: Summary of Published Literature Regarding Diagnostic Accuracy of PET**

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Women</th>
<th>Prior CAD</th>
<th>PET Radiotracer</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
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<tr>
<td>Sampson*</td>
<td>102</td>
<td>0.42</td>
<td>0</td>
<td>Rb-82</td>
<td>0.93</td>
<td>0.83</td>
<td>0.80</td>
<td>0.94</td>
<td>0.87</td>
</tr>
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<td>Bateman*</td>
<td>112</td>
<td>0.46</td>
<td>0.25</td>
<td>Rb-82</td>
<td>0.87</td>
<td>0.93</td>
<td>0.95</td>
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<td>0.89</td>
</tr>
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<td>Marcicki*</td>
<td>74</td>
<td>0.19</td>
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<td>Rb-82</td>
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<td>1</td>
<td>0.36</td>
<td>0.91</td>
</tr>
<tr>
<td>Grover-McKay</td>
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<td>Rb-82</td>
<td>1</td>
<td>0.73</td>
<td>0.80</td>
<td>1</td>
<td>0.87</td>
</tr>
<tr>
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<td>81</td>
<td>0.36</td>
<td>0.42</td>
<td>Rb-82</td>
<td>0.83</td>
<td>0.86</td>
<td>0.94</td>
<td>0.64</td>
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</tr>
<tr>
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<td>0.47</td>
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<tr>
<td>Demaki</td>
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<td>0.26</td>
<td>0.34</td>
<td>Rb-82/13NH3</td>
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<td>0.98</td>
<td>0.60</td>
<td>0.85</td>
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</tr>
<tr>
<td>Tamaki</td>
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<td>Rb-82/13NH3</td>
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<td>1</td>
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<td>0.98</td>
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<tr>
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<td>1</td>
<td>1</td>
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<td>0.97</td>
</tr>
<tr>
<td>Stewart*</td>
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<td>0.35</td>
<td>0.90</td>
<td>0.89</td>
<td>0.94</td>
<td>0.73</td>
<td>0.90</td>
<td>0.90</td>
</tr>
</tbody>
</table>

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99mTc Sestamibi SPECT in two matched patient cohorts undergoing clinically indicated pharmacological-stress perfusion imaging using contemporary technology for both SPECT and PET: Overall diagnostic accuracy using either a 50% (87 versus 71%) or a 70% (89 versus 79%) angiographic threshold was higher for PET than for SPECT. Differences in diagnostic accuracy primarily reflected the increased specificity (with a marginal advantage in sensitivity) of PET versus SPECT, and applied to both men and women and obese and non-obese individuals.

**Figure 1: Relationship Between Coronary Vascular Resistance Measured by Rubidium-82 PET and Stenosis Severity Assessed by Quantitative Coronary Angiography**

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% Coronary resistance (mmHg/ml/min/g)

- Minimal coronary resistance (mmHg/ml/min/g)
- Minimal luminal diameter (mm)
- Percentage diameter stenosis

- Ln y=3.496 + 0.013x
- r²=0.7
- p<0.001

- Ln y=4.649 + 0.371x
- r²=0.69
- p<0.001

- Minimal luminal diameter (mm)
- Percentage diameter stenosis
- p<0.001

- 25 50 75 100 125 150 175
- 0 20 30 40 50 60 70 80 90 100
- Ln y=3.496 + 0.013x
- r²=0.7
- p<0.001
event rate in patients with normal PET MPI and no CAC score was substantially lower than among those with normal PET MPI and a CAC score ≥1,000 (see Figure 4). Likewise, the annualized event rate in patients with ischemia on PET MPI and no CAC score was lower than among those with ischemia and a CAC score ≥1,000. These findings suggest incremental risk stratification by incorporating information regarding the anatomical extent of atherosclerosis to conventional models using myocardial perfusion alone, a finding that may serve as a more rational basis for personalizing the intensity and goals of medical therapy in a more cost-effective manner.

Conclusions

Innovation in non-invasive cardiovascular imaging is rapidly advancing our ability to image in great detail the structure and function of the heart and vasculature, and hybrid PET/CT and SPECT/CT represent clear examples of this innovation. By providing concurrent quantitative information about myocardial perfusion and metabolism with coronary and cardiac anatomy, hybrid imaging offers the opportunity for a comprehensive non-invasive evaluation of the burden of atherosclerosis and its physiological consequences in the coronary arteries and the myocardium. This integrated platform for assessing anatomy and biology offers great potential for translating advances in molecularly targeted imaging into humans. The goals of future investigations will be to refine these technologies, establish standard protocols for image acquisition and interpretation, address the issue of cost-effectiveness, and validate a range of clinical applications in large-scale clinical trials.

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