A Welcomed New Myocardial Perfusion Imaging Agent for Positron Emission Tomography

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It has been quite some time since a new myocardial perfusion agent for radionuclide imaging was introduced into clinical practice. For more than 30 years, rest and stress myocardial perfusion imaging (MPI), employing first planar and then single photon emission computed tomography (SPECT) technology, have been performed with thallium-201, Tc-99m sestamibi and Tc-99m tetrofosmin. MPI with these agents has provided useful diagnostic and prognostic information superior to that attained with exercise electrocardiography alone in patients with suspected or known coronary artery disease (CAD).1 With the exception of diabetic patients1 and patients with advanced chronic kidney disease,2 subjects with normal exercise perfusion scans have a <1.0% death or nonfatal infarction rate per year, whereas patients with abnormal scans have an ≈6% yearly hard event rate.3 Patients with normal pharmacological stress scans have a slightly higher annual event rate4 because patients who are unable to exercise are at higher clinical risk for CAD. For positron emission tomography (PET) imaging, the dominant perfusion tracers used in the clinical setting are N-13 ammonia and Rb-82, the latter eluted from a generator.5 The short-lived cyclotron-produced radionuclide Oxygen-15 water is another PET perfusion agent that has predominantly been used in the research setting. Sensitivity and specificity of PET myocardial perfusion imaging appear to be higher compared with that reported for SPECT;6,7 One potential advantage of PET over SPECT MPI is the ability to quantitate myocardial blood flow in mL·min⁻¹·g⁻¹ and measure coronary flow reserve using dynamic imaging and tracer kinetic models.8,9

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All the existing myocardial perfusion agents for SPECT and PET have some limitations that affect accuracy in detecting CAD or detecting its extent and functional significance. With conventional SPECT imaging, 1 primary limitation is the nonlinear relation of extracted tracer to myocardial blood flow imposed by lower first-pass myocardial extraction.10 If the tracer is incompletely extracted during a single pass through the coronary capillary bed, then the amount of extracted tracer will decrease as the blood flow increases. This causes a significant underestimation of exercise or vasodilator-induced increased blood flow and underestimation of flow reduction caused by a flow-limiting stenosis.11,12 The first-pass myocardial extraction fractions for Tc-99m sestamibi and Tc-99m-tetrofosmin are in the 0.5 to 0.6 range, whereas for Tl-201 it is ≈0.8. This is why the extraction of Tl-201 plateaus at a higher flow than the Tc-99m-labeled tracers. A second limitation of SPECT imaging is the difficulty in detecting blood flow abnormalities in any physiological condition that results in myocardial blood flow reserve being uniformly diminished throughout the myocardium. In some patients with left main or 3-vessel CAD or in the instance of diffuse endothelial or microvascular dysfunction (or both), uniform tracer uptake during stress may occur because of “balanced ischemia” or a diffuse abnormality in flow reserve.13 Some of these patients with balanced ischemia and uniform uptake of a perfusion tracer exhibit diffuse abnormal myocardial metabolism on poststress 18F-FDG scans.14 At present in state-of-the-art SPECT imaging, it is not possible to quantify absolute myocardial blood flow or even the relative increase in global myocardial blood flow caused by exercise or vasodilator stress. The semi-quantitation that is currently performed with SPECT, although an improvement over visual assessment alone, can only evaluate relative differences in regional tracer uptake.15 ECG gating of SPECT images with evaluation of regional and global left ventricular function, has enhanced somewhat the accuracy for CAD detection and the identification of patients with multivessel CAD.16 Other problems with SPECT are low spatial resolution, soft tissue attenuation artifacts that may be interpreted as perfusion defects, high visceral activity with vasodilator stress, and rather long rest/stress imaging protocols. The most commonly employed PET perfusion imaging tracer is Rb-82 which is eluted from a generator and has a short half-life of 78 seconds. The short half-life permits a fast throughput of patients for clinical stress/rest MPI. Like the SPECT tracers, Rb-82 also shows a plateau in myocardial extraction at hyperemic flows.17 One advantage of Rb-82 is that an in-house cyclotron is not required for production. Currently, most clinical nuclear cardiology laboratories analyze Rb-82 tomograms similar to that for SPECT, in which only relative differences in tracer uptake are determined. When absolute quantitation of blood flow is undertaken with rapid dynamic imaging of tracer kinetics, the identification of multivessel stenoses is enhanced.18 Quantitation of blood flow with any of the PET perfusion tracers involves corrections for the partial volume effect, activity spillover from the blood pool to the myocardium, correction for attenuation, and...
correction for physical decay. PET MPI with quantitation of coronary flow reserve (stress minus rest perfusion) can be used to assess myocardial blood flow abnormalities in patients who may have endothelial and microvascular dysfunction without significant epicardial coronary stenoses. Abnormal flow reserve has been measured in patients with dyslipidemia and hypertension and in smokers and diabetic patients. PET also has higher spatial and contrast resolution than SPECT, and depth-independent attenuation correction is more easily performed and is intrinsic to the PET methodology. When CT is used for attenuation correction, sensitivity for CAD detection is 93% without absolute quantitation of myocardial blood flow. Hybrid PET-CT cameras can now provide information pertaining to coronary anatomy and physiology in the same study. Limitations of PET MPI are limited availability in many institutions for routine clinical use, higher cost than SPECT, and inability to perform exercise stress imaging with Rb-82.

In this issue of Circulation, Nekolla et al evaluate the properties of a new 18F-labeled perfusion agent, 18F-BMS-747158-02 (18F-BMS) in a porcine transient ischemia model with comparisons to myocardial uptake with N-13 ammonia and radioactive microspheres. This tracer is an analog of the insecticide pyridaben that appears to bind to the mitochondrial complex 1, MTC 1 of the electron transport chain, with a very high affinity. In the isolated perfused rat heart, 18F-BMS has a high first-pass extraction (above 90%) and does not show delayed redistribution like Tl-201. In the isolated rabbit heart, uptake of the tracer increased with hyperemic flows to a greater extent than seen with Tl-201 or Tc-99m sestamibi. Nekolla et al confirm that extraction remains high in the pig model (21). This is reflected by the more nearly linear tracking of the extracted tracer with microsphere-determined blood flow (r=0.88) over a fairly wide range of myocardial blood flows. The data in this article indicate a tracer extraction of about 1.5 times resting extraction at a flow rate of 2.0 times resting flow. This degree of underestimation is typical of Tl-201 and suggests that 18F-BMS would have about the same first-pass myocardial extraction fraction as Tl-201, which would make it a good but not perfect flow indicator. Image quality was rated superior to that of the 13N-ammonia images by blinded observers. Contrast ratios of myocardium to blood activity, myocardium-to-lung, and blood-to-liver were higher for 18F-BMS than for 13N-ammonia. These results in the pig model of transient left anterior descending coronary artery occlusion are most encouraging for the further development of this tracer for human use. From its flow-extraction properties, it should permit a good sensitivity to detect flow-limiting coronary stenoses.

One potential of 18F-BMS PET is the ability to quantify myocardial flow reserve, which would be a great contribution to clinical MPI. Nekolla et al have used a compartmental model from which to extract myocardial blood flow from a bolus injection of 18F-BMS with favorable comparisons to flow determined by N-13 ammonia and radiolabeled microspheres. The possibility of its use for quantitative flow imaging is encouraging. Quantification of absolute myocardial perfusion from tracers that are introduced peripherally, only partially extracted and bound, can be quite complicated. Simply measuring the fraction of tracer extracted by the heart is not sufficient: It can only indicate the fraction of total cardiac output distributed to the heart. The fractional distribution of cardiac output to the heart does not relate in any simple way to absolute flow or the actual myocardial flow reserve. In this study, the authors have used a compartmental model sampling the arterial input function of an injected bolus of tracer and estimating flow from the time-activity curve of the tracer concentration sampled in myocardial tissue. This approach has the potential to estimate actual myocardial blood flow, but the technique is mathematically challenging. It requires dynamic sampling, corrections for blood pool spillover into tissue samples, corrections for motion and partial volume effects, and the strategic choice of model parameters. The technique also requires an intact bolus arrival into the left ventricle starting from a peripheral venous injection. This technique is usually easier in the laboratory setting where variables are more easily controlled. Nevertheless, the importance of absolute flow or coronary flow reserve estimation and the success in the pig model should lead to sustained and significant efforts to develop the quantitative potential of this new tracer so that it has sufficient reproducibility and accuracy to become a clinically useful tool for human imaging. Advantages of having a well validated 18F-labeled perfusion agent with a good signal-to-noise ratio and with a longer half-life that N-13 ammonia or Rb-82 are substantially. The agent could be injected during exercise stress, with rest and stress studies performed on different days, or a methodology, as related by Nekolla et al, could be developed to perform same-day rest-stress studies. Because of the 100-minute half-life, 18F can be distributed to imaging centers from a central cyclotron facility as is presently undertaken for oncology imaging with 18FDG. An on-site cyclotron is not necessary for production. The problem with the Rb-82 generator is the requirement that the imaging laboratory commit to its use for an entire month. In order for it to be cost-effective, a high patient throughput is necessary.

The emergence of a new longer-half-life PET myocardial perfusion imaging agent with the potential for myocardial blood flow and flow reserve quantitation over a wide range of flows, which has the potential to be performed with exercise stress and hopefully to yield high quality images in patients, is most welcome. We certainly look forward to further validation in the clinical setting.

Disclosures
None.

References


**Key Words:** Editorials Imaging Regional blood flow Perfusion
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Circulation. 2009;119:2299-2301
doi: 10.1161/CIRCULATIONAHA.109.854919
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/119/17/2299

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