Promising New ^{18}F-Labeled Tracers for PET Myocardial Perfusion Imaging

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Myocardial perfusion imaging with PET offers several advantages over SPECT for the detection and characterization of coronary artery disease. With PET, individual tissue-density measurements are routinely used to correct the emission images for photon attenuation and scatter by interposed tissue. And because PET scanners have higher spatial resolutions and count sensitivities than SPECT scanners, PET images can discriminate more readily between areas with normal and abnormal perfusion. As a result, PET imaging has a better diagnostic accuracy for coronary artery disease detection, with reported sensitivities approximately 4%–5% higher and specificities 3%–5% higher than for SPECT imaging (*1,2*). Moreover, left ventricular function can be assessed during vasodilator stress with PET imaging, permitting measurement of ventricular contractile reserve and identification of ischemia-related deterioration in regional function (*3,4*). It is also feasible to assess rest and hyperemic myocardial perfusion (in milliliters of blood flow/min/gram of tissue) and to derive myocardial perfusion reserve measurements from dynamic PET perfusion images using commercially available software (*5*).This assists in the detection of "balanced coronary artery disease" and in the identification of microvascular disease (*6*). On a practical level, patients are exposed to significantly less radiation with PET imaging than with SPECT imaging (typically less than 5 mSv for a rest and stress PET study (*7*)). Finally, a rest–vasodilator stress PET myocardial perfusion study can be completed in a quarter of the time required for a SPECT perfusion study with a ^{99m}Tc-labeled tracer.

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WHY PET IS NOT USED MORE OFTEN FOR CLINICAL IMAGING

Given the advantages of PET, why is it not used more frequently for clinical myocardial perfusion imaging? One reason is cost. PET/CT scanners are more expensive than SPECT or SPECT/CT scanners, both to purchase and to maintain. Currently, clinical PET myocardial perfusion imaging is performed using either ^{82}Rb or ^{13}N-NH_3. ^{82}Rb is eluted from a bedside generator, and there are periodic ongoing costs associated with generator replacement when the generator reaches the end of its service life (usually between 2 and 8 wk). Generator life is determined by its manufacturing characteristics, not its number of uses. As a result, costs per ^{82}Rb imaging procedure are reduced by maximizing the number of imaging studies performed during the useful life of the generator. ^{13}N-NH_3, the other tracer used for clinical PET perfusion imaging, is cyclotron-produced and has only a 10-min half-life. If this tracer is to be used for clinical perfusion imaging, the cyclotron has to be near the imaging center. In addition, close coordination between personnel at the imaging center and personnel at the cyclotron is required to ensure that the ^{13}N-NH_3 is available at the time it is needed for the stress injection.

Aside from the economic considerations, both ^{82}Rb and ^{13}N-NH_3 have other limitations. ^{82}Rb is impractical for exercise stress perfusion imaging because of its short 75-s half-life. Gastrointestinal background activity may be high, even in fasting patients. Images obtained with ^{13}N-NH_3 typically exhibit prominent background activity in the liver and may also show prominent pulmonary uptake in many cases. Moreover, some patients without coronary artery disease may exhibit relatively low tracer uptake in the inferolateral region of the ventricle on ^{13}N-NH_3 images, possibly because of genetic differences in tracer retention (*8,9*).

ADVANTAGES OF AN ^{18}F-LABELED PERFUSION TRACER

Because of the limitations of ^{82}Rb and ^{13}N-NH_3, a perfusion tracer labeled with ^{18}F for PET imaging is attractive clinically. The half-life of ^{18}F is almost 110 min, which is long enough to permit the transport of unit doses of ^{18}F-labeled perfusion tracers from a regional cyclotron to a PET imaging center. Therefore, either exercise or vasodilator stress myocardial perfusion imaging could be performed at centers that are presently performing only ^{18}F-FDG PET/CT imaging for oncology patients. The extra cost of adding myocardial perfusion imaging to the case mix for such a center would likely be modest if unit doses of an ^{18}F-labeled perfusion tracer were available at a reasonable price. If ^{18}F-labeled perfusion tracers were available as unit doses, more PET imaging centers could perform cardiac perfusion studies. These studies could be performed with or without ^{18}F-FDG for the assessment of myocardial viability (e.g., as part of a 2-d imaging protocol), thereby increasing the numbers of patients with access to PET myocardial imaging studies.

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Because the positron emitted by ^{18}F is relatively low-energy, travel distances in tissue before annihilation are significantly shorter than with ^{82}Rb and somewhat shorter than with ^{13}N-NH_3. The result is myocardial images that are more sharply defined than those obtained with the other perfusion tracers. Moreover, as initial experience with ^{18}F-flurpiridaz suggests, ^{18}F-labeled tracers may offer better target-to-background ratios than the present tracers, yielding higher-quality images (*10*).

^{18}F-LABELED FLUOROALKYLPHOSPHONIUM SALTS FOR PERFUSION IMAGING

In a preclinical study appearing in this issue of *The Journal of Nuclear Medicine,* Kim and colleagues assess the suitability of 3 ^{18}F-labeled fluoroalkylphosphonium salts for PET myocardial perfusion imaging (*11*). Similar to ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin, these moieties depend on high mitochondrial membrane potentials for retention in cardiac myocytes. In the current study, (5-^{18}F-fluoropentyl)triphenylphosphonium cation (^{18}F-FPTP), (6-^{18}F-fluorohexyl) triphenylphosphonium cation (^{18}F-FHTP), and (2-(2-^{18}F-fluoroethoxy)triphenylphosphonium cation (or ^{18}F-FETP) were compared with ^{13}N-NH_3 in Sprague–Dawley rat hearts.

In studies on isolated Langendorff perfused hearts, the authors found higher first-pass extraction fractions for all 3 ^{18}F-labeled tracers than for ^{13}N-NH_3 at flow velocities exceeding 4.0 mL/min. A higher first-pass extraction fraction indicates that net myocardial uptake of the tracer will more closely parallel tissue perfusion at high flow rates. On perfusion images, therefore, slight differences in hyperemic flow rate should be more readily detectable than on ^{13}N-NH_3 images, suggesting that PET imaging with the new perfusion tracers will prove more sensitive for detecting moderate coronary stenoses. The authors also performed dynamic PET imaging on normal rats and rats with infarctions using a small-animal PET/CT tomograph. Areas of infarction were well defined on the ^{18}F-labeled perfusion images. Moreover, at 10 min after tracer injection, myocardium-to-liver ratios were 3–5 times higher for the ^{18}F-labeled images than the ^{13}N-NH_3 images, and myocardium-to-lung ratios were approximately 2–3 times higher. Target-to-background ratios were therefore considerably better with the newer tracers, resulting in better image quality. These preclinical studies thus indicate that the ^{18}F-labeled phosphonium cations are promising PET myocardial perfusion tracers.

CHALLENGES AHEAD

Several major hurdles must of course be overcome to transfer the findings of a promising preclinical study into daily practice. Safety and biodistribution studies are a prerequisite to use in humans, and a well-designed hierarchy of clinical trials using appropriately constructed imaging protocols is necessary to confirm efficacy and secure Food and Drug Administration approval for clinical use. ^{18}F-flurpiridaz, another tracer of myocardial perfusion, is in stage III clinical trials and may be the first ^{18}F-labeled PET perfusion tracer to be approved by the Food and Drug Administration for clinical practice. Nevertheless, the new ^{18}F-labeled fluoroalkylphosphonium tracers may also one day prove useful for human studies and could provide an additional option for clinical PET perfusion imaging. Ultimately, it is hoped that cardiac care will benefit from access of greater numbers of patients to PET myocardial perfusion imaging.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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