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PET/CT Myocardial Perfusion Imaging

By Kevin L. Berger, M.D.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe how to perform a cardiac PET/CT myocardial perfusion exam.
- List the properties and availability of the two most commonly used cardiac radiotracers.
- Summarize the advantages of cardiac PET/CT myocardial perfusion imaging relative to SPECT.
- Explain the benefits of quantitative analysis in cardiac PET.

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SPPECT myocardial perfusion imaging has a well-documented record of success in imaging patients with suspected coronary artery disease. Since CAD is a leading cause of death in the U.S., the proven utility of myocardial perfusion imaging has led to continued growth in its use.¹

SPECT myocardial perfusion imaging has limitations. Artifacts related to nonuniform attenuation, for example, decrease accuracy and increase diagnostic uncertainty. Balanced ischemia may prevent detection of significant CAD. Given the relatively long half-life of current radioisotopes and reasonable limits on the maximal dose of injected radiotracer, patients may spend hours undergoing combined rest and stress imaging protocols.

Advances in cardiac PET/CT offer the opportunity to overcome these limitations. With clear clinical needs and comparative advantages, cardiac PET/CT utilization can grow by proving the combined modality's availability, efficiency, accuracy, and cost-effectiveness.

AVAILABILITY

In 2005, more than 1200 PET scanners were operating in the U.S., and the average number of procedures per scanner was about 3.7 per day. Clearly, the potential capacity available on these scanners is significant. The Centers for Medicare and Medicaid Services and most third-party payers currently reimburse for cardiac PET procedures. Recently, CMS released proposed rule changes to the Hospital Outpatient Prospective Payment System (HOPPS) for cardiac PET that may dramatically reduce reimbursement for and discourage adoption of this technology. In 2004, probably

fewer than 60 sites were performing cardiac PET.

Two cardiac PET radiotracers, nitrogen-13 ammonia and rubidium-82, have been approved for reimbursement. The table compares these two most commonly used PET cardiac myocardial perfusion tracers.

N-13 ammonia is a cyclotron-produced radiopharmaceutical with a half-life of approximately 10 minutes. Its production has been limited to facilities that have an onsite cyclotron with unused capacity. N-13 ammonia exists in equilibrium with a charged ammonium ion. The neutral ammonia molecule can diffuse across cell membranes and be trapped in glutamine by the enzyme glutamine synthase. The high first-pass extraction of about 80% decreases with higher blood flow rates.

Rb-82 is a generator-produced radiopharmaceutical. Like thallium-201, Rb-82 is a cation and analog of potassium extracted by myocardial cells via the sodium/potassium ATPase pump. Its myocardial extraction fraction is similar to Th-201 and less than ammonia (approximately 50% to 60%). Given its short half-life of 75 seconds, background contamination is not an issue for rapid rest-stress protocols, and patient radiation dosimetry is favorable even in the setting of repeat injections. Mobile Rb-82 generators are available throughout most of the U.S., and PET centers may even contract for services for one day or more per week.

The mean positron range of N-13 ammonia is lower than that of Rb-82, which improves the resolution of its studies. In conjunction with additional counts acquired during N-13 ammonia's longer half-life, these factors can improve the overall image quality. To minimize background conta-

CARDIAC PET TRACERS

Agent	Physical half-life	Mean positron range (mm)	Production	Extraction	Activity (mCi)	EDE (rem)	Critical organ	Organ dose (rem)
N-13	9.96 min	0.166	Cyclotron	80%	20	0.166	Bladder	0.52
Rb-82	75 sec	2.6	Generator	50 % to 60%	60	0.096	Kidneys	1.98

mination in stress images, the examiner can stagger patients, escalate injection doses, or prolong the interval between injections.

In the example protocol below, background contamination is less than 20%, similar to same-day rest and stress technetium protocols. Performing N-13 ammonia imaging requires careful coordination of cyclotron production, stress testing, and PET camera operation, and this involves synchronization by numerous staff. The logistical burden of coordination and the requirement of an onsite cyclotron can limit N-13 ammonia use.

EFFICIENT PATIENT THROUGHPUT AND PROCESSING

Patient preparation for a cardiac PET/CT perfusion examination is identical to that for a SPECT procedure. Patients are instructed to avoid caffeine or theophylline use, and they have typically fasted for six or more hours. Patients are usually imaged with pharmacologic stress for ease of use logistically, although both N-13 ammonia and Rb-82 have

been successfully performed with exercise. Chow and colleagues showed that treadmill exercise produces larger perfusion defects than dipyridamole stress PET.²

In our laboratory, we use 0.568 mg/kg of dipyridamole administered over four minutes. Other labs use adenosine 140 µg/kg/min for six minutes. We routinely reverse all our patients with aminophylline. In asthmatic patients, we use an accelerated dobutamine stress protocol supplemented with atropine if necessary. Patients are reversed with metoprolol if necessary.

PET/CT myocardial perfusion imaging primarily derives its efficiency from the short half-life of the cardiac PET radiotracers. Rapid imaging protocols are feasible with both N-13 ammonia and Rb-82, as illustrated in the example protocols shown in Figure 1.

Cardiac PET imaging places severe demands on scanner performance beyond those normally encountered in clinical PET studies for oncology or neurology. Dynamic imaging, with five to 10-second sampling intervals of

high injected doses over the initial uptake period, is required to perform myocardial blood flow quantitation. Myocardial and blood pool time activity curves are generated and corrected for decay, partial volume effect, and tissue cross-talk, then a compartmental model is applied to solve for blood flow.³

DeKemp with Rb-82 and Yoshida with N-13 ammonia have developed simplified models that have been validated in animal experiments with good correlation to microsphere flow measurements.^{4,5} Gated images can be obtained for assessment of wall motion. Both gated Rb-82 and gated N-13 ammonia imaging have shown regional wall motion abnormalities and left ventricular ejection fractions that correlate well with gated SPECT.

A segmented imaging approach can work well with N-13 ammonia studies that demonstrate relatively good first-pass extraction and sufficient counts to allow early dynamic imaging and later gated images. Variation in the myocardial uptake in settings of low cardiac output or poor bolus quality can occur, and a

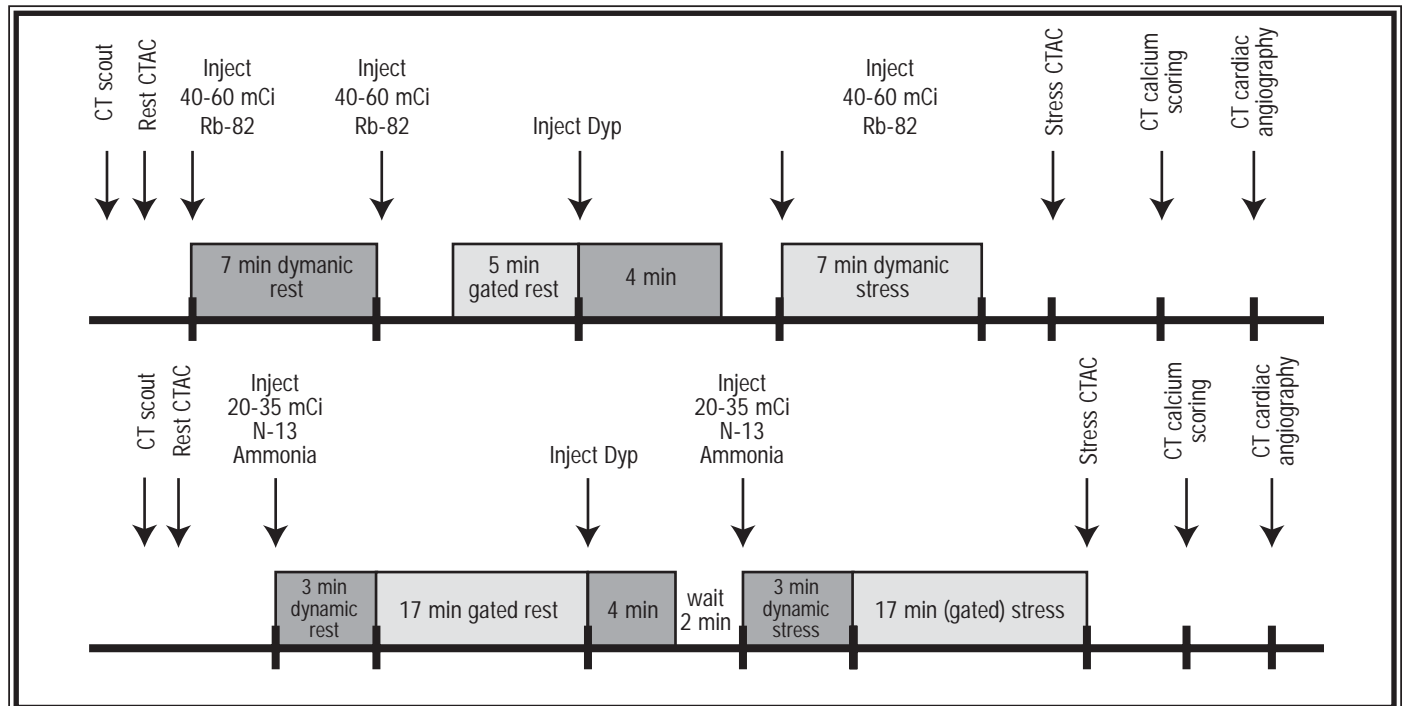


Figure 1. Myocardial perfusion PET/CT acquisition protocols for Rb-82 (top row) and N-13 ammonia (bottom row).

retrospective selection of the onset of the myocardial phase can be preferable in some instances. For this reason, separate injections are sometimes used with rubidium imaging to acquire dynamic and gated data.

List mode acquisition allows maximal use of information acquired from a single injection and works best with PET console systems that can handle large file sizes and variable retrospective reconstruction parameters to maintain adequate workflow. Advances in PET camera systems that allow simultaneous cardiac and respiratory gating should help to offset loss of image resolution secondary to physiologic patient motion. Console capabilities to handle large file structures and ease multiple retrospective reconstruction parameters should be emphasized in selection of a PET/CT camera system for cardiac imaging.

TRADE-OFFS

An important trade-off in cardiac PET imaging is the choice between 2D and 3D acquisition modes. Knesaurek and colleagues, using a bismuth germanate oxide crystal scanner, demonstrated similar image quality and resolution in phantom models of lean individuals and better results with 2D imaging in obese individuals. They also noted that 3D image quantification may be limited by significant axial nonuniformity.⁶

Moser and colleagues, using a lutetium oxyorthosilicate crystal scanner, performed a quantitative comparison that showed similar results on 2D and 3D rest images but significant differences with stress imaging. These did not appear to affect accuracy, however.⁷ When 3D imaging and 2D imaging have comparable image quality, 3D imaging would minimize patient radiation dose and prove more cost-effective with the development of less expensive low-dose Rb-82 generators.⁸

For rest and stress perfusion images, Machac and colleagues found that filter back projection and measured attenuation correction produce better myocardial image uniformity than iterative reconstruction methods. They use iterative reconstruction methods with segmentation attenuation correction in wall motion studies to suppress the higher noise level.⁹ We typically use filter back projection with a Hanning transaxial filter for our perfusion images. We reconstruct images in a 128 x 128 matrix in a targeted reconstructed

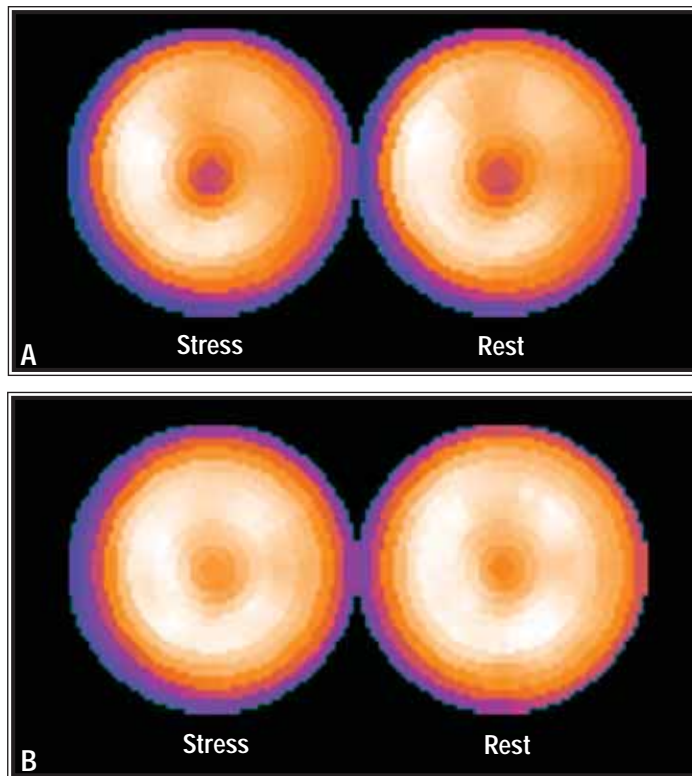


Figure 2. Normal polar distribution maps for N-13 ammonia (A) and Rb-82 (B).

field-of-view of 41.9 cm with a left shift of 4 cm. We also use measured attenuation and random correction by singles. Applying a 3D post filter such as a Butterworth for smoothing can also be of value.

Hybrid PET/CT scanners may improve efficiency by allowing more rapid positioning, decreasing the time to acquire attenuation information, and potentially providing alternative images of diagnostic value. CT scout images allow internal anatomic landmarks to be used to delineate the acquired field-of-view. CT offers a rapid method of providing high-quality, low-noise attenuation correction. Compared with transmission scanning with a germanium-68 pin source, which takes about three to five minutes, CT-based attenuation correction (CTAC) using a 16-slice detector takes 3.4 seconds to cover the same field-of-view and may be obtained at relatively low mA levels to reduce patient radiation exposure.

Alternatively, gated CTAC images take approximately 16 seconds to acquire and may also be used for coronary calcium scoring. While coronary calcium scoring may add sensitivity to the detection of preclinical coronary artery disease, its role in clinical practice is not established. Even low-dose CT attenuation scans contain diagnostic value. We have seen unsuspected pericardial effusions, pleural effusions, aortic aneurysms, thoracic spine com-

pression deformities, and pulmonary masses that have had significant impact on clinical management. Many of the patients imaged for CAD are smokers, and the detection of pulmonary lesions on scout CT images and through the visualized lower lung is not uncommon.

With CT's speed advantage also comes potential for PET and CT image misregistration. Transmission images acquired with a point source are temporally averaged over the respiratory and cardiac cycle and more closely simulate the average cardiac position during emission imaging. Loghin and colleagues, however, found 21% of subjects had transmission-emission misregistration, which produced artifactual defects.¹⁰ The apparent PET perfusion defects result from underestimation of the attenuation values of myocardium that had been misregistered into adjacent lung, for example. In our experience, this is most commonly seen in the anterolateral

wall near the base. The degree of misregistration is greatest in transmission scans performed early in the imaging protocol. This may be a result of delayed displacement of the diaphragm after positioning secondary to shifting abdominal contents.

Misregistration can be reduced by performing CT imaging in the expiratory phase. Manual alignment methods have been developed that allow shifting of the CTAC scan, and we have successfully implemented automated PET and CT alignment programs to correct for image misregistration.¹¹

ACCURACY

Cardiac PET has a proven track record for diagnostic accuracy in imaging patients for CAD when compared with the gold standard of invasive coronary angiography. Machac summarized data from eight different studies using N-13 ammonia and Rb-82 to demonstrate an overall sensitivity of 93% and specificity 92% in 791 patients.¹²

The largest comparison study of PET and SPECT by Go and colleagues showed 95% sensitivity, 82% specificity, and 92% accuracy for Rb-82 PET compared with 79% sensitivity, 76% specificity, and 78% accuracy for thallium SPECT.¹³ In a later study in 2006, Bateman and colleagues demonstrated a similar significant improvement for Rb-82 PET compared with technetium SPECT.¹⁴

Nonuniform attenuation of gamma photons in the chest is the major challenge in cardiac perfusion imaging. SPECT imaging in women can be limited by breast attenuation and a smaller heart size.¹⁵ PET/CT holds the advantages of superior resolution (5 to 7 mm compared with 15 mm for SPECT) and measured attenuation correction; therefore, it may be of particular value in this patient group.¹⁶

Patterson and colleagues showed PET was equally sensitive and specific for the detection of CAD in men and women.¹⁷ In PET, the probability of attenuation of photons is uniform along a line between any two detectors. Attenuation is rapidly and easily measured and corrected with either transmission sources or CT. With gamma cameras, image resolution and attenuation vary with distance from the gamma camera and depth within the patient.

Normal maps of distribution of radiotracer vary by gender in SPECT but are identical in PET. While polar maps of Rb-82 are similar to SPECT, N-13 ammonia has a different normal distribution. Beanlands and colleagues demonstrated decreased uptake of ammonia in the lateral wall in normal volunteers.¹⁸ The mechanism is not known. This differential distribution must be recognized in image interpretation.

Figure 2 displays normal polar distribution maps for N-13 ammonia and Rb-82. Statistical display of patient specific data with reference to these normal maps can greatly assist image interpretation.

PET offers the ability to quantify myocar-

dial blood flow and coronary flow reserve (CFR), which has many potential advantages. Muzik and colleagues showed that absolute N-13 myocardial blood flow was sensitive and accurate for the detection of CAD,¹⁹ and Parkash and colleagues demonstrated that it can improve the differentiation of three-vessel and one-vessel disease.²⁰ Demonstration of an adequate response to a vasodilator (increase of CFR greater than 2) would document adequacy of the stress pharmacologic challenge.

Patients with hyperlipidemia, diabetes, end-stage liver disease, or unrecognized caffeine ingestion may all have inadequate responses to pharmacologic challenge, and the decreased sensitivity of the test would go unrecognized. Patients who present with balanced ischemia may show only minimal or no regional mismatch, severely underestimating the extent of underlying CAD.

Coronary flow reserve quantification offers an objective method of characterizing the significance of a stenosis and noninvasively monitoring disease progression or response to therapy.^{21,22} In patients with an equivocal stenosis detected by CT angiography or diffuse long segmental disease, quantification of myocardial blood flow allows an objective physiologic assessment of disease severity.

New software applications that fuse the display information of CT angiography data and myocardial perfusion allow 3D interactive manipulation of data that can help assess which vessel is responsible for a perfusion defect and the extent of myocardium at risk.

COST-EFFECTIVENESS

Gould and coworkers documented that PET perfusion imaging is cost-effective when the pretest probability of disease is less than 70%, and PET is more cost-effective than SPECT when the pretest probability of disease is less than 60%.²³ In clinical practice, Merhige found the use of PET decreased the false-positive rate, resulting in a reduction in catheter angiography. His outcomes data show that the rate of heart attack and cardiac catheterization is significantly lower after one year in patients managed by PET. PET decreased the number of angiograms, balloon angioplasty with stenting procedures, and coronary artery bypass grafts.²⁴ The average cost to manage a patient with CAD was 25% lower in the PET group.

CONCLUSION

As availability of underutilized PET scanners and access to cardiac radiotracers become widespread, cardiac PET/CT has the opportunity to be a first-line modality in the evaluation of patients with suspected CAD. PET/CT offers accurate measured attenuation correction, high-resolution imaging, and myocardial blood flow and coronary flow reserve quantification. Its short half-life radiotracers can overcome the attenuation artifacts, diminished sensitivity in specific clinical scenarios, and long patient days that are often associated with conventional SPECT imaging. The well-documented accuracy of PET in the literature and its cost-effective application should grow this modality in an appropriately encouraging reimbursement environment.

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