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Noninvasive Assessment of Coronary Artery Disease with CT and PET/CT

By Marcelo F. Di Carli, M.D.

LEARNING OBJECTIVES

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

- Describe the advantages and disadvantages of positron-emitting radiopharmaceuticals used for clinical PET imaging.
- Compare PET and SPECT for assessing regional myocardial perfusion.
- Discuss the value of CT for evaluating patients with known or suspected coronary artery disease.
- Explain the complementary value of PET and CT for detecting coronary artery stenoses.

Dr. Di Carli is chief of nuclear medicine at Brigham and Women's Hospital in Boston and an associate professor of radiology at Harvard.

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Coronary stenoses may be located and diagnosed through PET myocardial perfusion imaging in patients with suspected ischemic heart disease. In addition, the physiological severity of known coronary stenoses may be precisely characterized, since PET enables absolute quantification of coronary flow reserve. This important clinical role is expected to grow with the availability of PET/CT scanners that enable a true integration of structure and function.[1]

PET FLOW IMAGING AGENTS

While several tracers have been used for evaluating myocardial perfusion with PET, the most widely used for clinical imaging are nitrogen-13 ammonia and rubidium-82. The advantages of N-13 ammonia are its slightly higher first-pass tissue extraction (65% to 70%) compared to Rb-82 (60% to 65%) and a longer half-life that allows longer imaging times, better count statistics, and injection during treadmill exercise. Nonetheless, Rb-82 imaging using modern PET/CT scanners yields excellent-quality gated myocardial perfusion images for clinical use. The main disadvantage of N-13 ammonia vis-

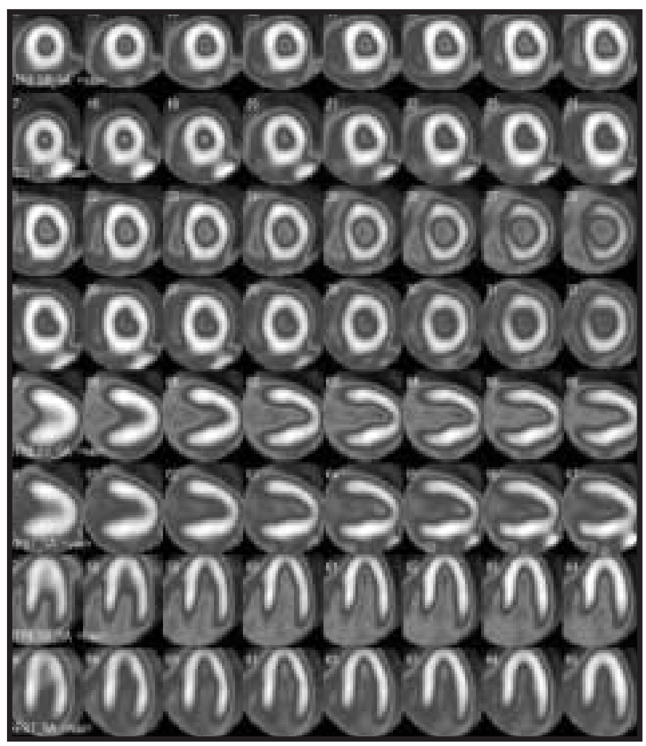


Figure 1. Normal myocardial perfusion images obtained with Rb-82 during vasodilator-stress and at rest.

à-vis Rb-82 is the need for an onsite cyclotron, which makes it costly and impractical. Also, its longer physical half-life makes rest-stress protocols less efficient than when Rb-82 is used (about 90 min versus about 25 min, respectively).

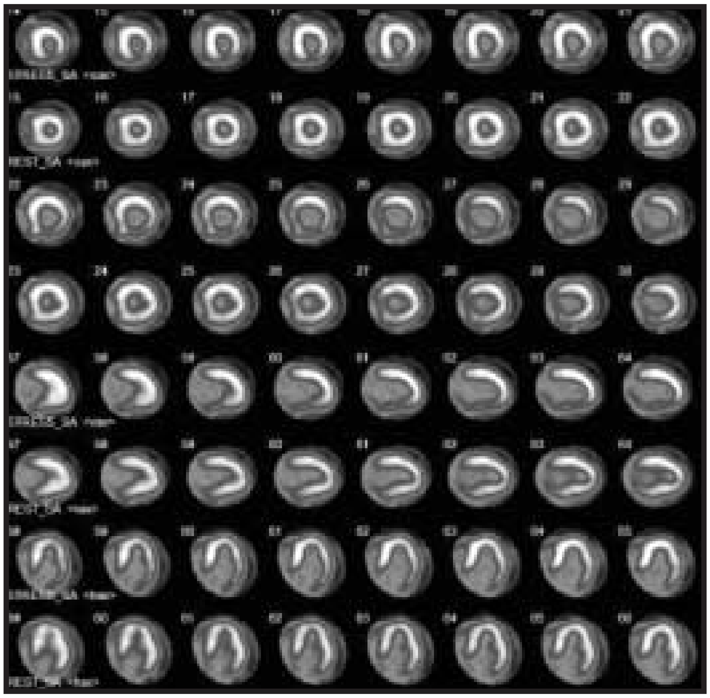


Figure 2. Abnormal myocardial perfusion images obtained with Rb-82 during vasodilator-stress and at rest. Images demonstrate a severe perfusion deficit in the right coronary and left circumflex/obtuse marginal territories.

ASSESSING MYOCARDIAL PERFUSION WITH PET

Image acquisition starts with careful positioning of the patient in the PET/CT gantry. Patients should be made as comfortable as possible to minimize movement during the study. After the patient is positioned, the precise location of the heart in the thorax should be determined. This is done using a CT scout image. Once the heart is localized, a CT-based transmission image (15 to 40 sec) is obtained to directly measure photon attenuation.

After the scout and transmission scans, Rb-82 (40 to 60 mCi) or N-13 ammonia (about 20 mCi) is injected at rest. Single-frame acquisition imaging begins 90 to 120 seconds after Rb-82 injection or three to five minutes after N-13 ammonia injection—to allow for clearance of radioactivity from the lungs and blood pool—and goes on for five or 20 minutes, respectively. For a multiframe or dynamic image sequence, imaging can begin with the infusion of Rb-82 or N-13 ammonia and continue for seven to eight minutes or 20 minutes, respectively. The latter approach is generally used for quantification of myocardial blood flow (in mL/min/g). After resting imaging, a pharmacologic stress is performed (e.g., vasodilator stress with adenosine or dipyridamole, or dobutamine), and at peak stress a second injection of Rb-82 (40 to 60 mCi) or N-13 ammonia (about 20 mCi) is administered.

Since all PET radiotracers decay by emitting photons with similar energy (511 keV), counts in the field-of-view should decrease to background levels before new images with a second radiotracer injection are obtained. For Rb-82 (physical half-life: 76 sec), stress testing can be performed without delay after completion of the resting study. For N-13 ammonia (physical half-life: 9.96 min), however, stress testing is delayed for approximately 30 minutes after completion of the resting study to allow for radioactive decay of the first dose of N-13 ammonia to background levels. Stress images are then obtained in the same manner as with the resting study.

Attenuation correction of the stress images is generally performed with a separate transmission image that is obtained after stress imaging is complete. This second transmission scan is important because the different breathing pattern during pharmacologic stress will tend to change the heart's position within the chest.

When studies are acquired with a single-frame format, image acquisition can be ECG-gated to allow assessment of regional and global left ventricular function. Due to its ultrashort half-life, Rb-82 permits peak stress gated imaging, which may be helpful in identifying patients with extensive coronary artery disease because left ventricular ejection fraction changes during pharmacologic stress have effects similar to those observed during exercise. However, when images are obtained using a multiframe sequence, a separate Rb-82 or N-13 ammonia injection is necessary to obtain ECG-gated images. The time required for completing a rest-and-stress myocardial perfusion study varies between 25 and 90 minutes depending on the radionuclide, imaging protocol, and scanner used.

ACCURACY OF PET IN OBSTRUCTIVE CAD

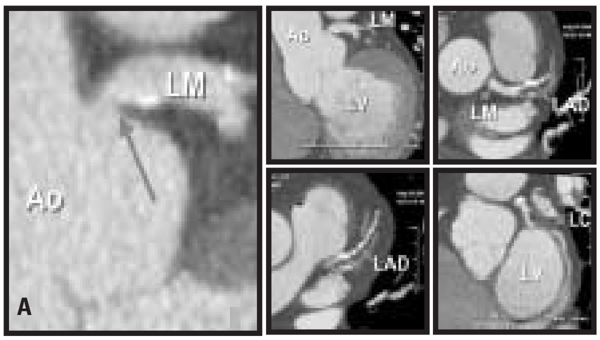
Experience with PET for detecting obstructive CAD, assessing regional myocardial perfusion with N-13 ammonia or Rb-82, has been extensively documented in seven studies that included 663 patients.[1] In these studies, the average sensitivity for detecting angiographic stenosis >50% was 89% (range, 83% to 100%), whereas the average specificity was 86% (range, 73% to 100%).

• *Comparative studies of PET versus SPECT*. Only two studies have performed a head-to-head comparison of the diagnostic accuracy of Rb-82 PET and thallium-201 SPECT in the same patient population.[1] Go and colleagues compared PET and SPECT in 202 patients.[2] Their results showed a higher sensitivity with PET (93% vs. 76%), and no significant changes for specificity (78% vs. 80% for PET and SPECT, respectively). In the other study, Stewart et al compared PET and SPECT in 81 patients.[3] They observed a higher specificity for PET (83% vs. 53%), and no significant differences in sensitivity (86% vs. 84% for PET and SPECT, respectively). Diagnostic accuracy was higher with PET (89% vs. 78%).

• *Assessing coronary flow reserve to evaluate the extent of CAD*. In patients with so-called "balanced" ischemia or diffuse CAD, measurements of coronary vasodilator reserve would uncover areas of myocardium at risk that would generally be missed by performing only relative assessments of myocardial perfusion. It is generally accepted that while the relative assessment of myocardial perfusion with SPECT remains a sensitive means for detecting CAD, the approach often uncovers only the territory supplied by the most severe stenosis. This is because in patients with CAD, coronary vasodilator reserve is often abnormal even in territories supplied by noncritical angiographic stenoses,[4,5] thereby reducing the heterogeneity of flow between "normal" and "abnormal" zones. Two recent reports demonstrate the improved accuracy of PET for delineating the extent of CAD using measurements of coronary flow reserve compared to the traditional semiquantitative assessments of regional myocardial perfusion.[5,6]

CORONARY ANATOMY AND MYOCARDIAL PERFUSION

In addition to the functional assessments obtained with PET (i.e., myocardial perfusion and metabolism), the new hybrid PET/multislice CT (MSCT) technology[7] allows detection and quantification of the burden of coronary atherosclerosis (i.e., extent of calcified and noncalcified plaques), quantification of vascular reactivity and endothelial health, identification of flow-limiting coronary stenoses, and, potentially, identification of high-risk plaques in the coronary and other arterial beds. Together, by revealing the degree and location of anatomic stenoses and their physiologic significance, and the plaque burden and its composition, PET/MSCT can provide unique information that may improve noninvasive detection of CAD and the prediction of cardiovascular risk. In addition, it may facilitate further study of atherothrombosis progression and its response to therapy and allow assessment of subclinical disease.



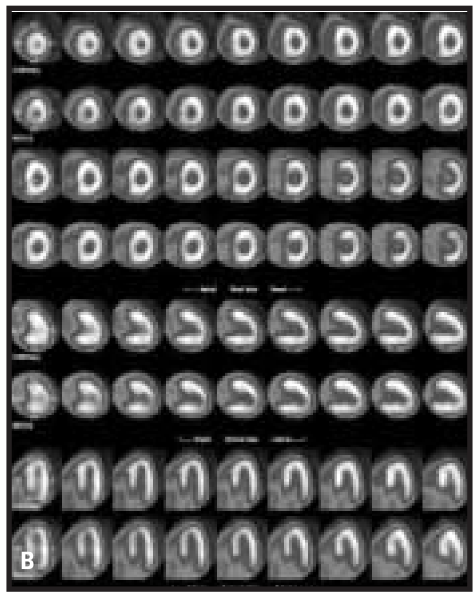


Figure 3. A: Contrast-enhanced MSCT coronary angiographic images in transverse and oblique maximum-intensity projection in a patient with ostial obstruction of the left main and moderate calcification of the distal LM and proximal left anterior descending artery. B: Stress and rest myocardial perfusion images obtained with Rb-82 demonstrate that the anatomic stenoses on MSCT are not flow-limiting. The functional PET data gave instant access to the functional significance of the anatomic MSCT data. This patient was counseled about the presence of coronary atherosclerosis and the benefits of risk factor modification, and treated with aggressive medical therapy. (Reproduced from reference 1, with permission)

ASSESSMENT OF CORONARY ATHEROSCLEROTIC BURDEN

Calcification of the arterial wall is associated with the majority of atherosclerotic lesions, although it is most frequently found in advanced atherosclerotic lesions. Conventional chest x-ray, cine fluoroscopy, coronary angiography, ultrasound, and MRI can identify calcium in blood vessels; however, only electron-beam CT and MSCT are able to accurately quantify the coronary calcium plaque burden. Because arterial calcification almost always represents atherosclerosis, detection of coronary artery calcium by means of CT is a sensitive, although not specific, marker for obstructive CAD.[8] Indeed, a recent study by Berman and colleagues reported that only 13% of patients with coronary artery calcium scores ≥400 (Agatston method) showed mild to moderate ischemic defects on stress SPECT.[9] This number was slightly higher (20%) among those with calcium scores ≥1000. Together, these data suggest that coronary calcium may provide an assessment of preclinical CAD. Recent data from Shaw et al show that coronary calcium may provide incremental information independent of that provided by traditional risk factors in the prediction of all-cause mortality.[10]

MSCT can also delineate the burden of noncalcified coronary plaques, even in arterial segments without significant luminal narrowing. Achenbach et al showed a sensitivity of 78% and a specificity of 87% for MSCT compared to intravascular ultrasound (IVUS) in this application.[11] The numbers were higher for plaques localized in proximal coronary segments (91% and 89%, respectively). However, MSCT systematically underestimates plaque volume per segment compared with IVUS.[11]

CT CORONARY ANGIOGRAPHY

Breath-hold cardiac CT with retrospective ECG gating can provide detailed information regarding angiographic stenoses of the coronary artery tree, especially its mid- and proximal portions. The overall diagnostic quality of noninvasive CT coronary angiography depends largely on the spatial resolution, patient heart rate during the examination, temporal resolution of the scanner, choice of the appropriate reconstruction time point within the cardiac cycle, and quality of contrast enhancement.[12] The coronary arteries and disease manifestation within these vessels are minute and difficult targets for imaging. Recent multislice (16- and now 64-slice) CT scanners provide high spatial and temporal resolution cardiac scans with submillimeter (0.5 to 0.75-mm) section collimation and an in-plane spatial resolution of up to 0.5 x 0.5 mm.

The accuracy of CT coronary angiography for noninvasive detection of coronary artery stenosis is an area of active research. The advent of faster CT scanners with added detector elements (e.g., 16- and 64-slice CT) increases the number of assessable coronary arteries and improves the overall accuracy of noninvasive CT coronary angiography for stenosis detection.[13,14] The majority of published studies agree with regard to the high negative predictive value of a negative CT coronary angiogram (as high as 97% with 16-slice CT).[15-19]

ASSESSMENT OF MYOCARDIAL ISCHEMIA

Because not all coronary stenoses are flow-limiting, however, the myocardial perfusion PET data complements the CT anatomic information by providing instant readings about the clinical significance (i.e., ischemic burden) of such stenoses, thereby facilitating decisions regarding revascularization in patients with anatomic evidence of atherosclerosis (Figure 1). Image fusion of the functional

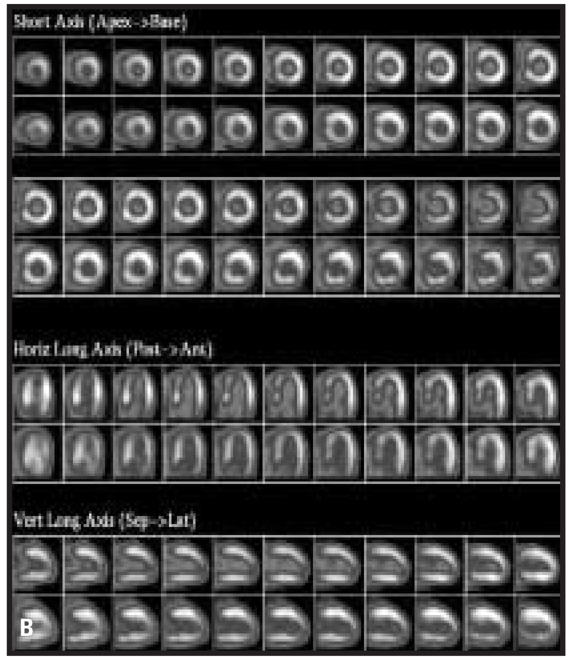


Figure 4. A: Contrast-enhanced MSCT coronary angiographic images in transverse and oblique maximum-intensity projection in a patient with established CAD. The images demonstrate extensive calcified (proximal left anterior descending artery) and noncalcified (proximal right coronary artery) plaque, as well as a stent in the mid portion of the LAD artery. The presence of coronary calcium and stents limits the ability of contrast-enhanced CT coronary angiography to determine the degree of luminal narrowing. B: Stress and rest myocardial perfusion images obtained with Rb-82 demonstrate a moderate perfusion deficit during stress with near complete reversibility throughout the midportion of the LAD territory, suggesting in-stent restenosis or progression of disease distal to the stent implantation. The functional PET information added diagnostic sensitivity to the MSCT data and provided the additional information needed for an appropriate management decision. (Reproduced from reference 1, with permission)

PET data with the structural information of coronary CT can also help identify the culprit stenosis in a patient presenting with chest pain. Presence of severe calcification limits the value of contrast-enhanced CT coronary angiography because beam-hardening artifacts and partial-volume effects can completely obscure the cross section of the vessel and prevent assessment of the degree of luminal narrowing. Owing to similar effects, metal objects such as stents, surgical clips, and sternal wires can also interfere with the evaluation of underlying coronary stenoses. Thus, the functional myocardial perfusion PET data are also very useful for sorting out the presence of flow-limiting stenoses within areas of heavy calcification or prior stenting (Figure 2).

CONCLUSION

PET provides accurate diagnosis of the extent, severity, and anatomic location of coronary artery disease. The high relative cost of PET requires careful patient selection. The great sensitivity and, above all, the high specificity of PET for diagnosing coronary heart disease make it a particularly useful tool for the assessment of obese patients and women with a low to intermediate probability of having coronary disease. This important clinical role is expected to grow with the availability of PET/CT scanners that truly integrate structural and functional images, providing a comprehensive examination of the heart's anatomy and function.[1,7]

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