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PET/CT in diagnosing cardiovascular disease

by Juhani Knuuti, M.D.

LEARNING OBJECTIVES

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

1. Identify generally the advantages and limitations of multislice CT and PET in cardiac imaging
2. Explain the advantages and limitations of hybrid PET/CT systems in cardiac imaging
3. Describe the common imaging protocols for cardiac PET/CT
4. Discuss the current and future applications of cardiac PET/CT

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Dr. Knuuti has no significant financial arrangement or affiliation with any manufacturer of any pharmaceutical or medical device and is not affiliated in any manner with any provider of any commercial medical or healthcare professional service.

Imaging the entire spectrum of cardiovascular diseases from diagnosis and prognosis of coronary artery disease (CAD) to evaluation of ischemic cardiomyopathy is challenging. The development of noninvasive cardiac imaging methods has provided new tools for this target. Obviously, the well-established techniques such as echocardiography and SPECT will continue to play an essential role in clinical practice for patient diagnosis and stratification. However, newer techniques such as PET, cardiovascular magnetic resonance, and multislice computed tomography are demonstrating increasing potential in clinical cardiology. Hybrid imaging devices, the newest development, have matured to the level that they can also be successfully used for cardiovascular imaging. The most promising combination is a hybrid system with multislice CT (MSCT) and PET. Recently, hybrid devices with 64-slice CT aimed specifically at cardiac imaging have become available.

MSCT for noninvasive imaging of the coronary arteries has developed rapidly. Accuracy of the technique for assessing coronary artery disease has improved with increased detector rows. But, more important, the percentage of nonassessable segments has decreased significantly. The modality's consistently high negative predictive value underlines the potential of the technique to exclude CAD.[1] The major shortcoming of the modality is that estimating the hemodynamic significance of the detected stenoses is challenging, especially for severely calcified plaques, which are difficult to assess reliably. And there is a tendency for MSCT to overestimate the degree of stenosis. An additional drawback is that very limited information about the myocardium itself is gained. Nor does it provide functional information on myocardial perfusion and metabolic processes.

PET allows noninvasive quantification of myocardial blood flow (MBF) and metabolism. Measurement of MBF and coronary flow reserve provides information on both macro- and microcirculation. The three main tracers used for this assessment are oxygen-15-labeled water and nitrogen-13-labeled ammonia and generator-produced rubidium-82. Each of these tracers has specific advantages and limitations. The first two allow absolute quantification of myocardial perfusion but their production also requires an onsite cyclotron.

PET stress-rest perfusion imaging has been used for diagnosis and prognosis in CAD. Based on pooled analysis of seven studies with 633 patients, the sensitivity and specificity of PET for detection of CAD were 89% and 86% respectively.[2] Patients with a normal PET perfusion scan have an excellent prognosis; patients with extensive abnormalities have an event rate of 24%.[3]

FDG-PET has been used extensively to identify jeopardized but viable myocardium and predict improvement in left ventricular (LV) function after revascularization. Pooled analysis of 20 studies with 598 patients revealed a sensitivity of 93% for prediction of functional

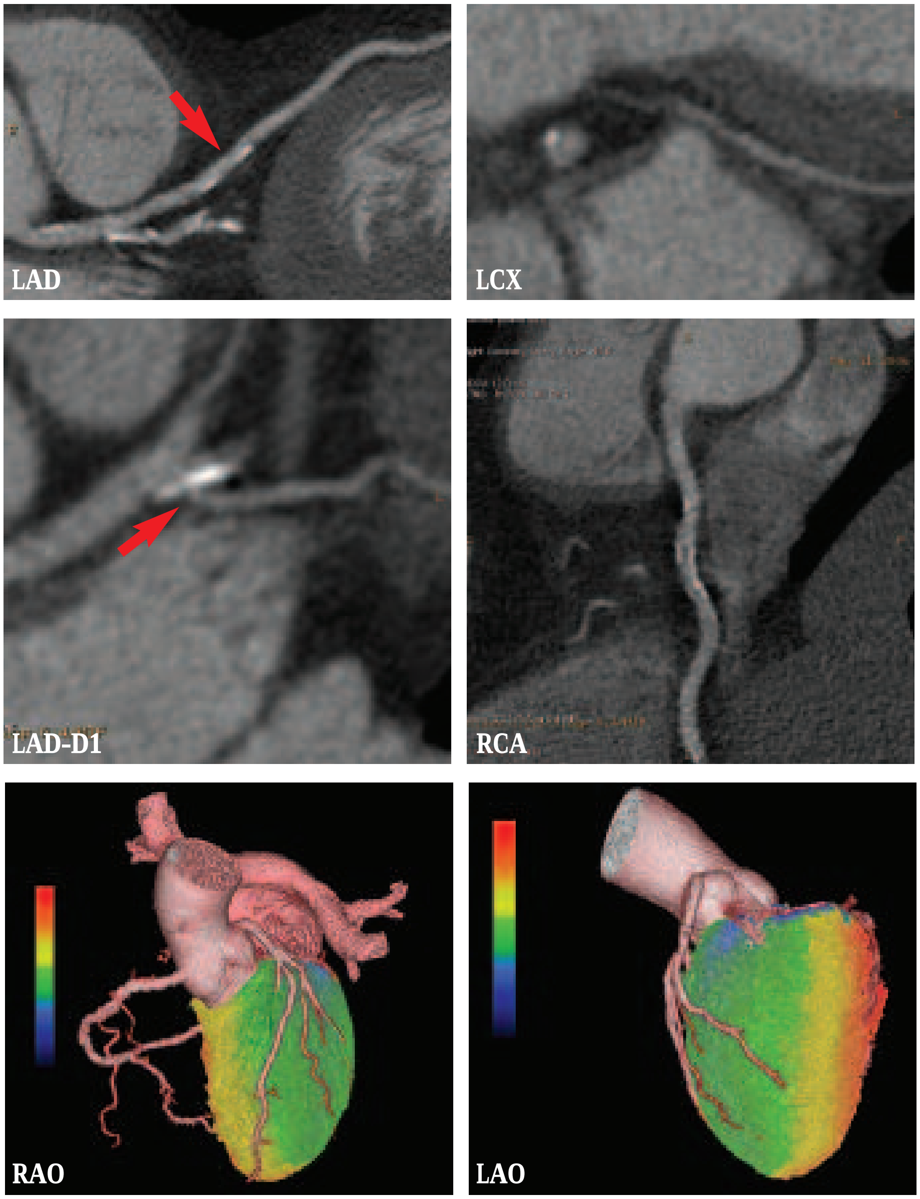

Figure 1. 63-year-old male with chest pain and shortness of breath during exercise underwent PET/CT study using O-15 water. A (top four): Contrast-enhanced 64-slice CT angiography revealed calcifications and suspicious calcified stenoses in the mid-left anterior descending coronary artery and significant-looking stenosis in D1. Left circumflex artery origin was anomalous (from right coronary artery) and the vessel was very thin. Right coronary artery was large with many calcified plaques but no clearly significant stenoses. B (bottom two): Right and left anterior oblique views of hybrid PET/CT display. The resting perfusion (not shown) in PET studies was normal but stress perfusion was reduced (2 ml/min/g) in large anterolateral region associated with LAD. The stress perfusion in RCA region was normal (4 ml/min/g).

recovery, which was higher than that for SPECT imaging with thallium-201- or technetium-99m-labelled agents or dobutamine stress echocardiography.[4]

According to the American College of Cardiology/American Hospital Association/American Society of Nuclear Cardiology guidelines, ischemic cardiomyopathy is considered a class I indication for assessment of viability using FDG-PET.[2] FDG also can be used in combination with a perfusion tracer, making distinctions between (repetitive) stunning, hibernation, and (non-)transmural scar tissue possible.[5] Available studies on long-term outcomes consistently demonstrate that viability on FDG-PET was associated with a high event rate if patients were treated medically but also that delayed revascularization resulted in worse outcomes.[6]

THE ADVANTAGES AND LIMITATIONS OF PET/CT

The benefits of coregistration. From a computational perspective, one of the major benefits of hardware-based image fusion is that it permits the acquisition of coregistered anatomical and functional images. Despite significant advances in software-based coregistration techniques, issues concerning accuracy and user interaction have limited their routine clinical use. The real benefit of fusing different imaging modalities, however, is that anatomical information acquired in situ may be used to improve scan efficiency and that CT images can be used for attenuation correction of the PET scan. That detected perfusion abnormalities can be immediately and accurately associated with the individual's coronary anatomy is also important. This helps to identify and correctly register subtle irregularities in myocardial PET perfusion. Last but not least, a clear benefit for patients is that a comprehensive study can be performed in short single sessions. The drawback is that the sequential procedure requires careful logistical planning for efficient patient throughput.

Functional assessment of coronary stenosis. To optimally evaluate the hemodynamic significance of coronary artery lesions (to guide therapy) integration of anatomic information and data on the hemodynamic consequences is needed. The new generation of PET/CT scanners makes integration of CT angiography with stress-rest perfusion PET possible. Preliminary results are encouraging. The concept was evaluated in patients with suspected CAD in a study by Namdar and colleagues,[7] yielding a sensitivity and specificity of 90% and 98% respectively for the detection of hemodynamically important coronary lesions. A recent study using PET/CT systems with a 64-slice CT scanner found that CT's positive predictive value for stenosis was lower than PET's for predicting stress-inducible perfusion abnormalities but that the negative predictive value was high.[8] This indicates that assessing functional consequences of coronary stenoses is difficult with CT, and that perfusion imaging provides useful complementary information.

As mentioned above, O-15 water and N-13 ammonia offer unique possibilities for measuring myocardial perfusion quantitatively. This is useful in patients with diffuse CAD or balanced disease where relative assessment of myocardial perfusion cannot uncover global reduction in perfusion. Typically, in relative analysis of perfusion only the regions with the most severe stenosis are detected. Quantification of myocardial perfusion using dynamic PET is high for the detection and localization of CAD.[9] Recent studies have found that the accuracy of PET was further improved by quantitative analysis.[10,11]

Assessment of viability using PET/CT. Although assessment of myocardial viability using stand-alone PET systems is well established, hybrid imaging provides clear benefits. Detected dysfunctional but viable or scar regions can be directly linked with the individual's coronary anatomy and with coronary stenoses. The limitation of a hybrid approach is that a substantial number of patients have other diseases that prevent the use of iodinated contrast agents.

Radiation safety aspects. The patient radiation dose for CT angiography has been reported to be in the range of 6 to 20 mSv, depending on the system and protocol used. Recently, techniques that reduce patient dose have been developed, although it is still higher than that from invasive coronary angiography. Patient dose will further increase with hybrid imaging since PET also uses ionizing radiation. However, the radiation dose from PET perfusion studies is clearly smaller than that from CT (dose from two PET perfusion studies using O-15 water is 1.7 mSv).

PRACTICE AND TECHNICAL ASPECTS

Protocols for angiography and perfusion using PET/CT. Patient preparation for the hybrid study is very similar to that for the individual scans.

It is important that the patient's heart rate is controlled for CT and that caffeinated drinks are avoided during the preceding 12 hours. The protocol can start with either study.

The high negative predictive value of CT means that only that fraction of patients with suspicious findings on CT will need PET perfusion imaging. Depending on the selected patient population, this fraction is 25% to 50%, thus, only one PET perfusion session is needed for each three patients, on average.

The positioning of the patient on the scanner bed is critical to prevent any motion artifacts. It is strongly recommended that the patient's hands be supported upright and not within the field-of-view. The calcium score study can be performed first, followed by the CT angiography study. The detailed protocol of CT angiography depends on the system used.

Thereafter, low-dose CT for attenuation correction of PET is performed if needed (in some systems the calcium score study can be used for this). The PET tracer injection (1100 to 2200 MBq of Rb-82, 340 to 740 MBq of N-13 ammonia, or 700 to 1500 MBq of O-15 water) is given and a resting PET perfusion study performed. The scan protocol depends on the tracer used.[12] With Rb-82 the static scan is started 90 to 120 sec after injection and lasts for five minutes. With O-15 water and N-13 ammonia the dynamic scan is started immediately after tracer injection and lasts for five and 20 minutes, respectively.

A dynamic PET scan is required for quantitative perfusion measurement. After decay of the tracer, the stress study follows using a pharmacologic stressor such as adenosine, dipyridamole, or dobutamine. The tracer injection and PET scan are repeated during peak stress. With studies using Rb-82 and O-15 water, which have half-lives of 76 s and 112 s, respectively, the stress study can be performed practically without delay after the rest study. With N-13 ammonia stress testing is delayed for about 30 min to allow for tracer decay. If a method of correcting for patient motion between stress and rest studies is not

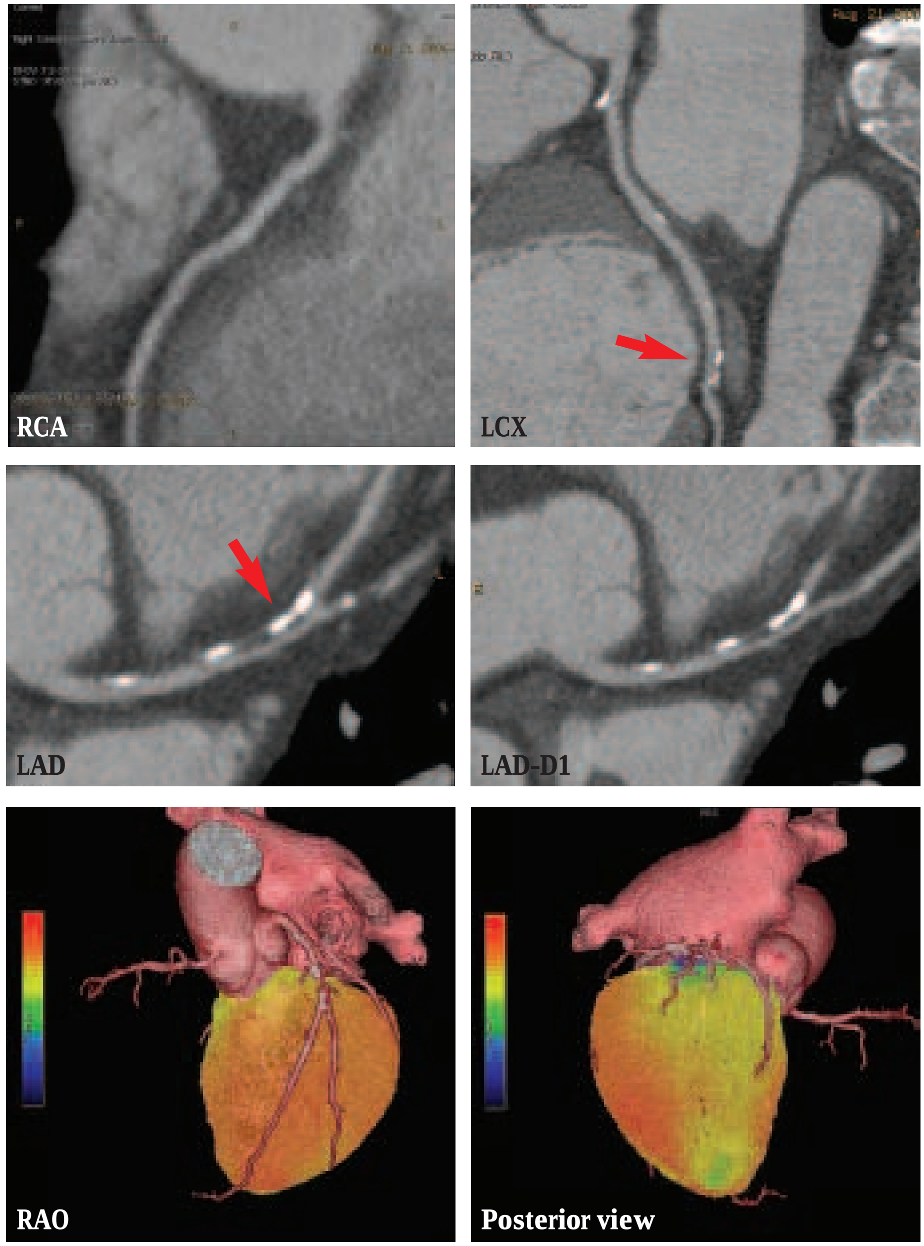

Figure 2. 58-year-old male with atrial fibrillation attacks and reduced exercise capacity underwent stress testing that induced no symptoms but 3 mm ST-depression. PET/CT study using O-15 water was performed. A (top four): Contrast enhanced 64-slice CT angiography revealed calcified and mixed plaques in LAD (arrow). Stenosis degree was estimated to be about 50%. In distal LCX significant stenosis (~50%) was detected (arrow). RCA was normal. B (bottom two): RAO and posterior views of hybrid PET/CT display. The resting perfusion (not shown) in PET studies was normal but stress perfusion was mildly reduced in posterior wall (2.5 ml/g/min) but was normal in other walls (3.5 to 4.2 ml/g/min).

available, a second low-dose CT scan for attenuation correction is needed.

If the PET system is capable of listing mode acquisition, the data can be collected as ECG-gated mode, which allows the simultaneous assessment of regional and global LV wall motion from the same scan data. This is particularly practical in Rb-82 studies.

The total time required for the session depends on the tracer used. With O-15 water and Rb-82 the whole session can be finished in 30 minutes; with N-13 ammonia it can be finished in 80 minutes.

Protocols for assessment of viability using PET/CT. For viability testing it is important that patients have fasted a minimum of 10 hours (usually overnight). Alternatives for patient preparation are oral glucose loading, insulin clamping, and nicotinic acid derivatives. In diabetic patients monitoring of plasma glucose is especially necessary to ensure good image quality.[12] Imaging is started 45 to 60 min after FDG injection (200 to 350 MBq) and image duration is 10 to 30 min (depending on count rate and dose). Gated acquisition is preferred.

Analyzing CT angiography includes the standard processes and techniques such as visual assessment of original transaxial slices, multiplanar reconstructions, and utilization of quantitative tools available. Analysis of PET studies also follows standard procedures, which have been explained in detail in various guidelines.[12-14] However, to realize the true power of hybrid imaging, an analysis system that is able to handle fused images and data should also be used. This enables accurate association between coronary anatomy and perfusion.

FUTURE PERSPECTIVES

The position of PET in cardiovascular research and patient care is based on its capacity to image perfusion and glucose metabolism. However, because PET also allows for imaging and quantification of molecular interactions and pathways with picomolar sensitivity, a number of cellular processes can be studied; e.g., receptor density, enzyme activity, inflammatory processes, and gene expression.

In particular, a number of positron-labelled tracers for imaging cardiac sympathetic and parasympathetic receptors with PET have been developed and validated. These include the catecholamine analogue C11-hydroxyephedrine and tracers for the measurement of beta adrenoceptor and muscarinic receptors. These ligands allow the demonstration of abnormal autonomic function in different cardiac diseases including dilated and hypertrophic cardiomyopathy and such idiopathic arrhythmogenic diseases as the Brugada syndrome.[15,16]

Rupture of vulnerable coronary atherosclerotic lesions accounts for one-third of all deaths worldwide and constitute a major source of disability and healthcare costs. Therefore, identifying individual patients at high risk for plaque rupture is an important challenge in clinical medicine. Noninvasive techniques such as multislice CT can characterize morphologic criteria associated with this risk. In contrast, the radiolabeled molecules used by PET are designed to specifically target individual inflammatory activities in atherosclerotic plaques. Plaque rupture is usually a consequence of such inflammatory cell activity. Techniques that illustrate plaque anatomy and composition do not provide information on plaque inflammation. In patients with symptomatic carotid atherosclerosis, FDG PET/CT has been used to identify inflammation within plaques.[17] A variety of cellular molecular characteristics involved in the progression and potential rupture of vulnerable plaques have been identified, including macrophage density, apoptosis, and protease activity. Ligands for these targets are currently under development. This approach is possible only with high-resolution morphological imaging of the coronary arteries using PET/CT. Methods that are able to correct for patient movement and cardiac and respiratory motion are needed and are under development.

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M+W06JS008NOV • Release: Nov 2006 • Expiration: Nov 2009
Reviews Scheduled: Nov 2007 and Nov 2008

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