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# IMAGING

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## LEARNING OBJECTIVES

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

- Explain the current status of PET/CT integration to radiation treatment planning.
- Describe the complementary role of morphologic and functional imaging in the workup of coronary artery disease.
- Identify methodological challenges and strengths of PET and CT as separate cardiac imaging modalities.
- Summarize the benefits of integrated PET/CT imaging systems over stand-alone scanners.
- Explain the future role of integrated imaging in clinical cardiology.

### Who will benefit:

Physicians, physician assistants, and radiologic technologists will benefit from the information in this educational activity and can receive Continuing Medical Education credit by completing the post test and evaluation provided.

## The role of integrated cardiac PET and coronary CTA

By Frank M. Bengel, M.D.

The present generation of positron emission tomography (PET) scanners is generally available in combination with an x-ray computed tomography (CT) component. PET/CT scanners now frequently incorporate multislice CT that is capable of contrast-enhanced electrocardiograph (ECG)-gated cardiac imaging. Thus, precise information about coronary and ventricular morphology, function, and scar can be added to the biologic/physiologic information derived from PET data.

This review focuses on the complementary role of PET-derived function and CT-derived morphology for cardiac imaging and highlights the potential of the latest generation of high-end PET/CT systems in clinical cardiology.

### ROLE OF PET IN CARDIAC IMAGING

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PET is an advanced nuclear imaging technique that combines superior detection sensitivity and higher spatial resolution with short-lived radiotracers whose biologic properties can be quantified in absolute terms. Following PET's introduction nearly 30 years ago, clinical applications for its use in cardiac imaging have emerged. For the functional assessment of coronary artery disease with regard to myocardial perfusion and viability, PET is widely regarded as the non-invasive gold standard. A major limitation for the use of PET has been the high cost, reflecting its sophisticated imaging technology, and the need of a cyclotron onsite or in close proximity for production of short-lived tracers.

These limitations have changed in recent years, however, due to the more widespread availability of PET systems through success in oncology and increasing independence of cyclotron units. The commercial distribution of the metabolic tracer fluorine-fluorodeoxyglucose (18

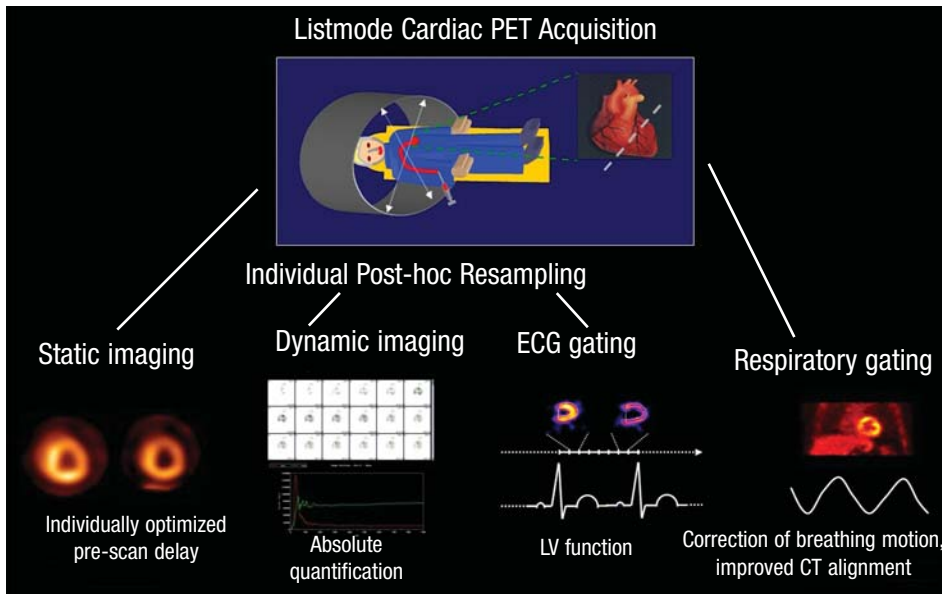


FIGURE 1. Schematic illustration of different options of image resampling after cardiac PET data acquisition in list mode.

FDG) and the availability of strontium-82/rubidium-82 (Rb-82) generator systems for myocardial perfusion assessment—both being FDA-approved and reimbursable in the U.S.—have contributed to an increasing acceptance of PET as a clinical cardiac imaging tool.

Today, PET systems are integrated into hybrid PET/CT scanners and are frequently equipped with more sensitive detectors that improve image quality, along with enhanced acquisition technology that offers list mode data recording. This is especially valuable for cardiac imaging because it allows for simultaneous creation of static images for qualitative perfusion analysis, dynamic data sets for kinetic modeling/absolute quantification, and gated data sets for analysis of left ventricular function (Figure 1). Most recently, techniques for respiratory gating have also been introduced.<sup>1</sup> These hold promise for further improvement of image quality and better coregistration with CT data.

- *PET perfusion imaging.* Myocardial perfusion PET imaging is accomplished using short-lived flow tracers such as oxygen-15 (O-15) water, nitrogen-13 (N-13) ammonia, or Rb-82—which have half-lives of two minutes, 10 minutes, and 75 seconds, respectively—at

rest and during pharmacologic stress.<sup>2,3</sup> Dipyridamole or adenosine is applied for pharmacologic vasodilation at doses commonly used for single photon emission computed tomography (SPECT) imaging. Physical exercise is not well accepted for stress flow measurements with PET due to the high likelihood of patient motion during imaging in the ring scanner, which needs to be started early after tracer injection due to the

short half-lives. Relative regional perfusion abnormalities are assessed from static images using N-13 ammonia and Rb-82 (Figure 2). The usefulness of O-15 water as a freely diffusible tracer in this regard is less well documented, because myocardial images are obtained only after application of factor analysis or blood-pool subtraction techniques.

In the clinical setting, the purpose of qualitative PET perfusion imaging is similar to that of SPECT; namely, to detect myocardial ischemia/regionally impaired flow reserve in patients with suspected or known coronary artery disease, to determine extent and severity of the disease, to determine individual risk for cardiac events, and to guide further workup.<sup>4,6</sup> The diagnostic accuracy for detection of computer aided detection (CAD) is higher compared with SPECT,<sup>7,8</sup> as the higher spatial resolution and higher extraction fraction of PET flow tracers contribute to higher sensitivity. The biggest gain comes from improved specificity due to absence of attenuation artifacts as a result of robust attenuation correction. Incremental prognostic value of qualitative perfusion PET over clinical variables for prediction of cardiac events has been demonstrated.<sup>9,10</sup> It has been shown that the more expen-

### IMAGING PARAMETERS DERIVED FROM CARDIAC CT AND PET

CT	PET
Valvular and vascular calcifications	
Coronary tree morphology	
Coronary artery plaques/stenosis	
Coronary bypass patency	
(Coronary stent patency)*	
Chamber geometry and function	LV function
(Myocardial perfusion)*	Myocardial perfusion
(Myocardial scar localization)*	Myocardial viability (metabolism)
	Absolute quantification of myocardial blood flow
	(Molecular imaging of the myocardium (innervation, integrins, stem cells . . .))*
(Atherosclerotic plaque composition and vascular remodeling)*	(Molecular imaging of plaque biology)*
* Clinical usefulness not yet proven	

sive PET perfusion imaging approach can still be cost-effective in a specific setting when compared with other strategies, including exercise ECG and SPECT.<sup>11</sup>

Another major advantage of PET perfusion studies is derived from the potential for noninvasive quantification of myocardial blood flow from dynamic imaging, allowing for studies of coronary microcirculatory regulation on the resistance level. Although potentially helpful in the clinical diagnosis of coronary artery disease,<sup>12,13</sup> absolute flow measurements by PET have mainly been applied in studies to understand the effects of CAD risk factors, such as hyperlipidemia, diabetes, and smoking, leading to an increased emphasis on preventive therapy.<sup>14-19</sup> With the ability to test specific components of microvascular function, such as endothelial-dependent and -independent vasodilation, PET serves increasingly as an endpoint to measure effects of risk factor manipulation, new drugs, and other therapeutic approaches in the prevention of clinical CAD.

- *PET viability imaging.* For assessment of myocardial viability in patients with advanced coronary artery disease and ischemic heart failure, F-18 FDG is combined with resting perfusion measurements using either a second PET tracer in the same session or, if performed at a place remote from a cyclotron and not equipped with a perfusion tracer generator, in combination with perfusion SPECT. PET viability imaging is obtained in patients with dysfunctional, hypoperfused myocardial regions to determine the likelihood of a benefit from revascularization. Residual metabolic activity is an indicator of myocardial viability and thus of reversibility of contractile dysfunction. Regional reduction of FDG uptake in proportion to perfusion (perfusion/metabolism match) reflects scar and thus irreversibility of contractile dysfunction, whereas increased regional FDG uptake relative to myocardial perfusion (perfusion/metabolism mismatch) indicates ischemically compromised but viable myocardium

(Figure 3).

Since introduction of the approach in 1986,<sup>20</sup> a variety of studies have shown that recovery of function after revascularization can be predicted by PET with high sensitivity of 85% to 90% and specificity of 75% to 85%.<sup>21</sup> The importance of identification of viable myocardium has increasingly been investigated beyond the prediction of functional recovery, which is only a surrogate endpoint for clinical and prognostic importance. It has been shown, for example, that recovery of function is coupled with improvement of heart failure symptoms.<sup>22</sup>

Patients benefit through reduced peri- and postoperative risk when PET criteria are used for selection for bypass surgery as compared with those selected without a PET study.<sup>23</sup> Increased preoperative mortality and limited functional recovery were observed when revascularization was delayed after detection of viable myocardium by PET, suggesting that the hibernating state is unstable and requires immediate attention.<sup>24,25</sup> PET viability studies have a significant impact on clinical decision-making in patients with coronary disease and left ventricular (LV) dysfunction.<sup>26</sup> Randomized trials based on PET are currently under way to further establish the clinical importance of viability imaging as an evidence-based approach.

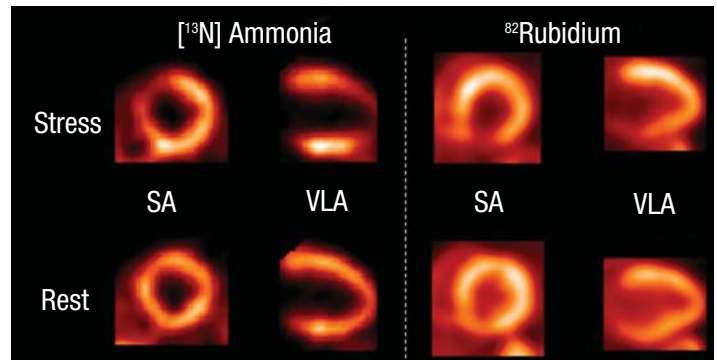


Figure 2. Representative short- (SA) and vertical long-axis (VLA) slices of PET perfusion studies in two different patients, using nitrogen-13 ammonia and rubidium-82 tracers. Both cases show reversible perfusion defects in anteroseptal/apical (left) and inferoseptal/basal myocardium (right).

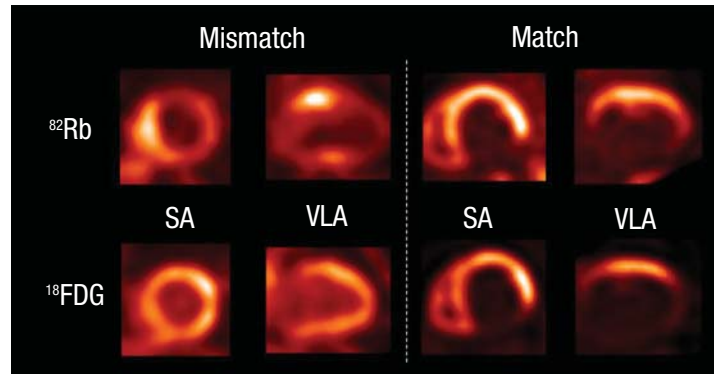


Figure 3. PET viability patterns in two different patients with ischemic cardiomyopathy. Perfusion/metabolism mismatch with reduced Rb-82 uptake (perfusion) but preserved F-18 FDG metabolism indicating hibernating myocardium in lateral and apical wall is shown on left. On right, a matched defect, indicating scar, is shown in inferior myocardium.

### ROLE OF CARDIAC CT

The introduction of multislice CT has enabled morphologic imaging of the heart as a moving target. Multiple detector rows permit high-resolution imaging with a short overall data acquisition time. Fast gantry rotation speed, together with dedicated ECG-gated image reconstruction algorithms, yields sufficiently high temporal resolution and offers the ability to obtain phase-correlated image data sets. Currently, 64-slice scanning is considered state of the art for cardiac CT imaging, although more recent developments include dual-source and 256-slice scanners.

Coronary artery visualization requires the acquisition of CT data with the highest temporal and spatial resolution. With current 64-slice systems, data acquisition

is performed within a single breath-hold. After acquisition of the raw data, thin-sliced retrospectively ECG-gated image data sets are generated. The effective radiation dose of a contrast-enhanced cardiac CT scan is approximately 5 to 20 mSv, although numerous factors influence radiation dose.<sup>27</sup> Reductions in dose can be achieved by obvious and straightforward measures, such as keeping the length of the scan volume as short and tube current as low as possible.

Another effective way of reducing radiation dose is the use of ECG-correlated tube current modulation, in which full tube current is limited to a short time period in diastole. This approach typically reduces radiation dose by 30% to 40%.<sup>28,29</sup> Recent developments by manufacturers include an extreme form of this tube current modulation that employs prospective gating to acquire CT data during only a certain phase of the cardiac cycle (step-and-shoot mode). This method will result in a significant further reduction of radiation exposure by 75% to 80%.

- *CT coronary angiography.* The opportunity to noninvasively visualize coronary anatomy is the major reason for current interest in cardiac CT. A recent meta-analysis demonstrated that 64-slice CT showed a significant improvement in accuracy for the detection of coronary artery stenoses as compared with previous scanner generations.<sup>30</sup> The weighted mean sensitivity for the detection of coronary artery stenoses increased from 84% for four-slice CT and 83% for 16-slice CT to 93% for 64-slice CT, with respective specificities of 93%, 96%, and 96%.

Studies that analyzed the accuracy of multislice computed tomography (MSCT) for the detection of coronary artery stenoses in patients with suspected CAD consistently showed high sensitivity and specificity and a very high negative predictive value of around 97%, when compared with invasive angiography as the reference.<sup>31</sup> This high negative predictive value indicates that the technique

may be most suitable as a noninvasive tool to rule out the presence of hemodynamically significant coronary stenoses and to avoid further imaging or invasive angiography.

CT used as a 3D volumetric tool allows for assessment of more than just

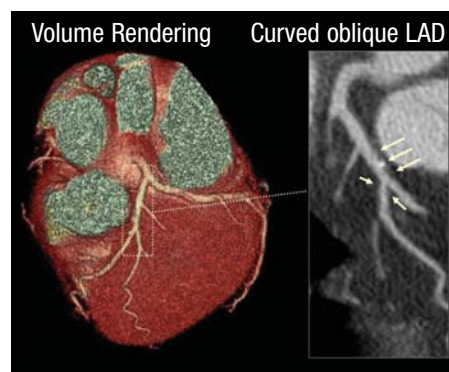


Figure 4. CT coronary angiography volume-rendered 3D view of left anterior descending artery (LAD) circulation (left), along with curved oblique view (right), shows vascular remodeling and mixed plaque with small amounts of calcification in LAD, close to branching of first diagonal (arrows). Plaque was judged to be nonobstructive.

luminal narrowing because the vessel wall itself, along with vascular thickening and remodeling, is visualized,<sup>32</sup> and calcified and noncalcified components of atherosclerotic lesions are identified (Figure 4). Thus, despite lower spatial resolution compared with invasive angiography, CT provides even more information with regard to characterization of nonobstructive stages of atherosclerosis, although the clinical relevance of these findings remains to be determined.

Patient selection may still heavily influence CT results, with substantially impaired image quality in patients with higher heart rates, high heart rate variability, or arrhythmia. Image quality may also be degraded in patients with severe CAD due to the presence of extensive calcifications, which potentially limit precise assessment of stenosis severity.<sup>33</sup> Thus, while 64-slice CT is a reliable tool to rule out functionally relevant CAD in a nonselected population with a low to intermediate pretest likelihood of disease, an abnormal coronary CT angiogram

does not necessarily predict ischemia or increased cardiovascular risk.<sup>34</sup> Thus, CT plays a complementary role as a morphologic technique that identifies coronary obstruction, while PET is the functional technique that identifies ischemia on the myocardial tissue level.

- *Other CT-derived imaging parameters.* Coronary calcium is a surrogate marker for the presence and amount of coronary atherosclerotic plaque that can be accurately quantified by CT at low radiation exposure.<sup>35</sup> In several trials, the absence of coronary calcium ruled out the presence of significant coronary artery stenoses with high predictive value.<sup>36</sup> Even pronounced coronary calcification, however, is not necessarily associated with hemodynamically relevant luminal narrowing. Therefore, even the detection of large amounts of calcium does not indicate the presence of significant stenoses, and it should not prompt invasive coronary angiography in otherwise asymptomatic individuals.

Numerous prospective trials have demonstrated that the presence of coronary calcium in asymptomatic individuals is a prognostic parameter with strong predictive power for future hard cardiac events.<sup>36</sup> At the same time, however, patient management approaches based on calcium assessment have not been prospectively investigated, and the relative role of calcium score versus other noninvasive predictors of risk remains poorly defined.

Contrast-enhanced MSCT has the potential to go beyond imaging of coronary anatomy to the assessment of myocardial perfusion and viability. MSCT may be a practicable alternative to cardiac magnetic resonance (MR) imaging for the assessment of myocardial viability in patients already undergoing MSCT angiography. In the setting of acute, subacute, and chronic myocardial infarction, myocardial perfusion defects can be observed during the early phase of the contrast bolus (“early defect”).<sup>37</sup> Subsequently, five to 15 minutes following contrast infusion, late hyperenhance-

ment of infarcts becomes apparent (Figure 5).

Excellent agreement in infarct sizing in the setting of acute myocardial infarction (MI) and chronic myocardial scar has been demonstrated in preclinical animal models of MI compared with gross pathology.<sup>38</sup> Preclinical evidence also shows that contrast-enhanced MSCT can provide assessment of myocardial perfusion. MSCT angiography protocols, when performed during adenosine infusion, can provide semiquantitative measures of myocardial perfusion.<sup>39</sup> Limitations of this technique include adenosine-mediated tachycardia and attenuation and motion artifacts. Clinical data on the use of CT for assessment of perfusion and viability, however, are still very limited, and the techniques require validation in larger trials.

**INTEGRATION OF PET AND CT FOR CAD WORKUP**

Imaging parameters determined by cardiac CT and PET are listed in the table. As described above, CT has a focus on morphologic imaging, while PET determines function, physiology, and biology. This different spectrum of information suggests that the techniques are complementary. Although the development of hybrid PET/CT systems was historically driven by oncology, cardiac applications for PET/CT seem to be equally attrac-

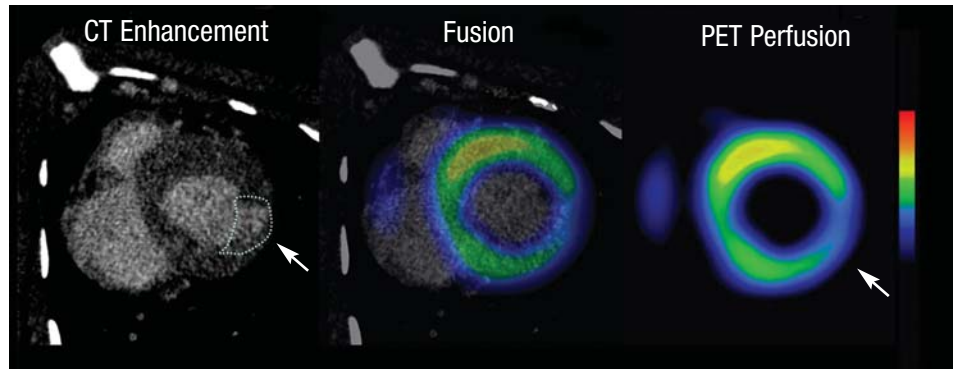


Figure 5. Delayed enhancement of contrast agent in repeat CT acquisition five minutes after injection. There is contrast retention in inferolateral wall of short-axis CT image (left), consistent with perfusion defect, as shown on Rb-82 perfusion PET (right, fusion image shown in the middle).

tive in the era of multislice CT. The most basic utilization of CT in hybrid systems is for attenuation correction of PET data. This is achieved by a low-dose CT scan acquired shortly before or after the PET acquisition.

Misalignment of CT and PET in cardiac imaging needs to be considered as an important potential source of artifacts in PET images,<sup>40</sup> because the PET image is acquired during breathing and a subsequent CT scan reflects a “frozen” segment of the respiratory cycle. Software is available for realignment,<sup>41</sup> and other algorithms such as cine CT and respiratory gating are under development to improve the a priori coregistration of both data sets. To optimize information from PET and CT, further software tools have been introduced that allow for cre-

ation of fusion images of PET function and CT morphology (Figure 6). This approach is expected to be beneficial for colocalization of myocardial perfusion defects with vascular lesions, and it facilitates study interpretation.<sup>42</sup>

Several studies have clearly shown that results of cardiac CT and myocardial perfusion imaging do not necessarily match.<sup>34,43,44</sup> Especially in the case of an abnormal CT indicating obstructive atherosclerosis, tissue perfusion may or may not be abnormal (Figure 7). Combination of PET and CT may thus be attractive for a complete functional and morphologic workup of CAD, although the ideal group of patients for such a combined test needs to be defined in prospective clinical studies. It has been proposed that in individuals with a lower

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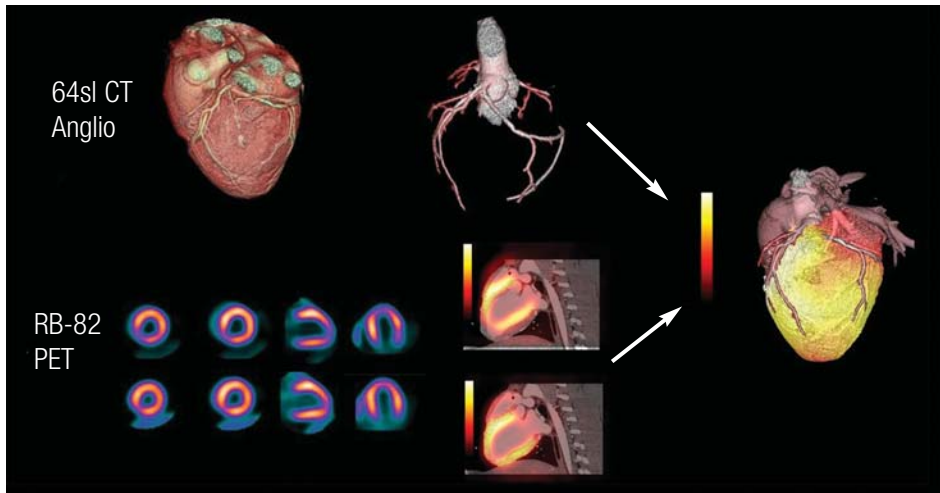


Figure 6. Fusion software for integrated analysis of PET and CTA. Coronary tree is separated from volumetric CT data (upper row, middle); PET data are fused and realigned to myocardium on CT images (lower row, middle); images are then merged again to 3D data set, which shows coronary tree morphology along with PET tissue perfusion superimposed to CT myocardial surface (right).

pretest likelihood of CAD, CT angiography should be performed first.<sup>45</sup>

The high negative predictive value of CT means that perfusion imaging would follow as a second step only if computed tomography angiography (CTA) reveals evidence of significant coronary atherosclerosis. Detailed diagnostic criteria for deciding whether to proceed with perfusion imaging, however, have not yet been defined, and the cost-effectiveness and prognostic validity of such an algorithm remain to be determined. With increasing pretest likelihood of disease, the expected prevalence of coronary artery lesions will also increase, and, concomitantly, the need for additional perfusion imaging will increase to define hemodynamic relevance of the disease and need for revascularization. Higher demand for a combination of CT and perfusion imaging is thus expected with higher disease prevalence in the referred population.

Combination of PET perfusion imaging with computed tomography angiography (CTA) may thus be attractive in a large group of individuals referred for the workup of coronary disease. Combining both studies within one scanner system and one single imaging session is expected to be more effective than sequential imaging using two stand-alone systems

because it minimizes the waiting time between the two studies, which is usually needed for scheduling the second test after reading the first.

Because CTA is rapidly performed and increases scanning time in a PET/CT protocol by no more than 15 minutes, the major arguments against routine combination of PET perfusion imaging and CTA are radiation exposure and complications of x-ray contrast such as nephrotoxi-

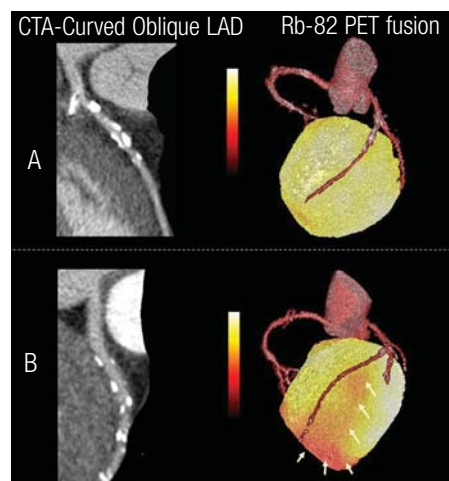


FIGURE 7. Two cardiac Rb-82 PET/CTA cases. CTA shows extensive calcifications in left anterior descending artery in both cases (left), associated with atherosclerotic plaques which were considered borderline occlusive in both cases. Fusion with perfusion PET (right) shows normal stress perfusion in case A, while there is extensive hypoperfusion in LAD territory in case B.

city. While the latter remains an issue, radiation exposure from both CT and PET is expected to decrease dramatically with the introduction of prospectively gated step-and-shoot CT algorithms and more sensitive 3D PET systems.

The integration of PET and CT into hybrid systems will also be a key component in the clinical introduction of novel molecular imaging techniques, in which the accumulation of highly specific radiotracers is often limited to small areas, such as a region of stem cell injection or a coronary plaque, that are difficult to visualize on PET scans and require coregistration with CT-defined morphology.

If concerns of radiation exposure are overcome by novel technical developments, combined assessment of coronary morphology by CT angiography and of the functional consequences of morphologic disease by perfusion PET may become the test of choice in a large fraction of individuals referred for the workup of CAD. The test is rapidly performed and provides a complete biomorphologic picture of the disease. It is expected that hybrid cardiac PET/CT will play a central role as a molecular imaging tool in the future development toward imaging-driven personalized medicine, which bases therapeutic decisions in each patient on individual disease biology.

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