**New Drugs and Technologies**

### New Technology for Noninvasive Evaluation of Coronary Artery Disease

**Marcelo F. Di Carli, MD; Rory Hachamovitch, MD, MSc**

Cardiac computed tomography (CT) and positron emission tomography (PET) are emerging as powerful noninvasive imaging tools for the evaluation of atherosclerosis in patients with known or suspected coronary artery disease (CAD). Unlike invasive coronary angiography, CT coronary angiography (CTA) not only assesses disease within the coronary lumen but can also provide direct qualitative and quantitative information about nonobstructive atherosclerotic plaque burden within the vessel wall. Thus, it is possible that CTA-based patient evaluation may provide more clinically relevant information on which to base risk assessments compared with conventional “lumenography.” On the other hand, PET is rapidly growing as a powerful and efficient alternative to conventional single-photon emission CT (SPECT) imaging to evaluate regional myocardial perfusion and metabolism in patients with CAD. In addition, PET scanners are now being converted to hybrid PET/CT devices, which, in the setting of CAD, offer the potential for a comprehensive noninvasive cardiac evaluation of anatomy and function. This review will discuss current and potential future applications of cardiovascular CT, PET, and hybrid PET/CT, with a particular focus on ischemic heart disease.

#### Conceptual Framework of Noninvasive Imaging Strategies for CAD

The information provided by noninvasive imaging generally falls into 1 of 3 categories: myocardial perfusion, left ventricular (LV) function, or coronary anatomy. The clinical utility, value, and role of a noninvasive modality are based on 2 test characteristics: What type of information is provided (eg, stress perfusion, stress and/or rest LV function, coronary anatomy), and what is the accuracy of the information provided. For example, SPECT and PET both provide stress and rest perfusion information, but the latter will be a superior clinical tool if the imaging data better represent the actual defect size and are subject to less artifact. The advantage of PET over SPECT will be further enhanced, as will be discussed later, if it provides additional clinically relevant information not provided by SPECT, such as coronary flow reserve data. On the other hand, CTA represents the first means to assess anatomic CAD noninvasively and thus is a potential replacement for invasive angiography. Additionally, CTA is also a means to assess atherosclerosis, both with respect to its presence and potentially to define plaque morphology.

In considering the potential clinical application of these modalities, the evidence supporting the role of assessment of ischemia versus anatomy must be considered. Data from the Coronary Artery Surgery Study (CASS) registry show that even in the setting of anatomic multivessel CAD, a survival benefit from revascularization compared with medical therapy only occurred in the setting of ECG evidence of ischemia, poor exercise tolerance, or both.\(^1,2\) A similar finding has been reported more recently with stress SPECT imaging.\(^3\) On the other hand, evidence exists that survival after catheterization is a function of the anatomic extent of CAD (1, 2, or 3 vessels), stenosis severity, location of stenoses, and presence of left anterior descending coronary artery disease, and thus is a surrogate of the extent of jeopardized myocardium.\(^4\) Although CTA shares the limitations of anatomic assessments (and has additional intrinsic limitations of its own), it also provides objective estimates of atherosclerosis burden and potentially of plaque morphology, and thus, it may have an important clinical role. Hence, although a pathophysiologically-based approach may continue to play an important role in decisions on revascularization, the anatomy-based approach may provide important clinical information to define the goals of medical therapy.

#### Evaluation of Obstructive CAD

**CT Coronary Angiography**

Using state-of-the-art technology in carefully selected patients, it is possible to obtain high-quality images of the coronary arteries (Figure 1). Table 1 summarizes the current evidence\(^5-23\) supporting a role for CTA with 16- and 64-slice CT scanners in the diagnosis of CAD. The series published to date are limited to selected cohorts that consisted of stable patients with known or suspected CAD who were undergoing elective catheterization and who were recruited to also undergo CTA. Hence, reported accuracies of CTA to date should be interpreted in light of the relatively narrow range of CAD likelihood in patients examined (ie, high or...
intermediate-high), as evidenced by the high prevalence of obstructive CAD in these series (62%; range 25% to 91%). In these series, results are generally limited to relatively large vessel sizes (>1.5 mm), which excludes the results of smaller or uninterpretable vessels (generally distal vessels and side branches), the inclusion of which lowers sensitivity.

On a per-patient basis, the average weighted sensitivity for detecting at least 1 coronary artery with \( \geq 50\% \) stenosis is 94% (range 75% to 100%), whereas the average specificity is 77% (range 49% to 100%). The corresponding average positive predictive value (PPV) and negative predictive value (NPV) are 84% (range 50% to 100%) and 87% (range 35% to 100%), respectively, and the overall diagnostic accuracy is 89% (range 68% to 100%; Table 1). On a per-segment basis, the average weighted sensitivity for detecting at least 1 coronary artery with \( \geq 50\% \) stenosis is 83% (range 30% to 99%), whereas the average specificity is 92% (range 64% to 98%). The corresponding average PPV and NPV are 67% (range 14% to 91%) and 97% (range 83% to 99%), respectively, and the overall diagnostic accuracy is 92% (range 66% to 98%).

The Coronary Assessment by Computed Tomography Scanning and Catheter Angiography (CATSCAN) study examined the diagnostic accuracy of multidetector CT in coronary artery segments larger than 2.0 mm in diameter. The 11 participating sites recruited 238 patients between the ages of 30 and 70 years, who were referred for clinically indicated nonemergency coronary angiography for evaluation of chest pain and for intermediate or high probability of disease. Of these patients, only those with Agatston calcium score \( \geq 600 \) on a noncontrast calcium score scan went on to have CTA (n=187). Importantly, separate analyses were performed, first including then excluding segments with a reference diameter of 2 mm or larger that were found to be uninterpretable. Because disease could not be excluded in the absence of evaluation, it was assumed that “this finding would also lead to conventional angiography in clinical practice.” On the basis of this approach, the authors reported PPVs that were markedly reduced compared with those previously reported (50% stenosis criteria: 13% [per segment], 50% [per patient]; 70% stenosis criteria: 6% [per segment], 28% [per patient]). The primary results of that study suggest that 16-slice CTA is limited by the large number of false-positive studies related to uninterpretable segments (38%).

The available evidence suggests that the ability of CTA to accurately assess the degree of luminal narrowing (a surrogate of physiological significance) is only modest. Recent studies with 64-slice CT indicate that quantitative estimates of stenosis severity by CTA correlate only modestly with quantitative coronary angiography (Figure 2), the former explaining only a small proportion of the variability in the latter.\(^{11,18,23}\) The limited accuracy for defining stenosis severity (a surrogate of physiological significance) by CTA can be explained by its limited spatial and temporal resolution compared with conventional coronary angiography, which leads to image degradation by motion and calcium. The bright (blooming) signal from high-density objects such as calcified coronary plaques extends beyond their true size in neighboring volume voxels, thereby leading to overestimation of stenosis severity.\(^{10,17}\) In addition, photon flux through such

Figure 1. Curved multiplanar reconstructions and multiple-intensity projection CTA. The left main (LM) coronary artery shows a calcified plaque with \( <50\% \) stenosis. The left anterior descending artery (LAD) shows calcified plaque in its proximal and mid segments with apparent moderate-to-severe stenosis. The distal segment of the left circumflex artery (LCX) is free of disease. The dominant right coronary artery (RCA) shows a noncalcified plaque in its mid segment with moderate stenosis and a small calcified plaque in its distal segment with \( <50\% \) stenosis.
high-density areas occasionally leads to a signal void adjacent to calcified plaques that can be interpreted as “noncalcified” plaque, which could further overestimate plaque burden in individual patients. Although improvements in spatial resolution would decrease the impact of high-density objects, with current detector technology, this would significantly increase radiation exposure to maintain noise at a constant level.

In addition, growing and consistent evidence suggests that anatomy-based predictions of physiological significance by CTA differ substantially from direct measures of inducible myocardial ischemia, as assessed by myocardial perfusion imaging26–29 (Figure 3). Given the evidence above, it is clear that CTA has superior performance for excluding obstructive CAD (ie, consistently high NPV) versus for predicting who has obstructive disease and needs to be referred for coronary angiography for possible revascularization.

### Evaluation of Coronary Artery Stents

Owing to the artifacts caused by metal, visualization of the coronary lumen within stents by CTA is more challenging than evaluation of the native coronary arteries (Figure 4). To date, a limited number of studies assessing the value of CTA to detect in-stent restenosis have been published30–35; however, they all show a consistently low sensitivity to identify in-stent restenosis. The limited spatial resolution of CT,36,37 the type of stent,36,37 and, especially, stent diameter (<3 mm being associated with the highest number of partial lumen visualization and nondiagnostic scans) contribute to limited clinical results.

### Evaluation of Bypass Grafts

Assessing patency and progression of CAD in bypass grafts is less challenging than in the native coronary arteries because

### Table 1. Summary of Published Literature Regarding Diagnostic Accuracy of CTA (Per-Patient– and Per-Segment–Based Analyses)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Women</th>
<th>Prior CAD</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>Sens</th>
<th>Spec</th>
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Sens indicates sensitivity; Spec, specificity; and NR, not reported.
*Studies used 64-slice multidetector CT.
†Studies included all coronary vessels in the analysis.

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**Figure 2.** Correlation between quantitative coronary angiography (QCA) and 64-slice CTA measurements of diameter stenosis in diseased coronary artery segments. Pearson’s correlation coefficient $r = 0.54$. Reproduced with permission from Leber et al18 with permission from the publisher. Copyright © 2005, the American College of Cardiology Foundation.
they are generally larger and less subject to motion (Figure 4). Occasionally, evaluation of internal mammary grafts can be difficult owing to blooming artifact from metal clips. On a per-graft basis, the average sensitivity for detecting at least 1 graft with $>$50% stenosis or total occlusion is 99% (range 96% to 100%), whereas the average specificity is 93% (range 68% to 100%). The corresponding average PPV and NPV are 96% (range 37% to 100%), and 83% (range 37% to 98%), respectively, and the overall diagnostic accuracy is 97% (range 95% to 99%).

Importantly, no appreciable difference exists in the reported diagnostic accuracies for the detection of stenosis or total occlusions between arterial and vein grafts. In general, false-positive findings are related to difficulties in evaluating distal anastomosis. Despite the high degree of accuracy to detect occlusions and stenosis within grafts, CTA has limited value in the evaluation of the patient with recurrent chest pain after coronary artery bypass grafting, because this also requires an assessment of the native coronary arteries, which tend to be more challenging because they are usually very small and heavily calcified.

Assessing Coronary Plaque Burden

Cardiac CT can provide objective estimates of calcified and noncalcified atherosclerosis burden. The measurement of coronary artery calcification (CAC) has been widely used and reported as a means of atherosclerosis testing in at-risk patients. The presence and amount of calcium, as measured in Hounsfield units (HU), has been shown to be strongly associated with the amount of atherosclerotic plaque present in autopsy studies. The clinical value and application of CAC with both electron-beam CT and multidetector CT, however, have been very controversial. Although determination of CAC may be used to estimate the likelihood of significant stenoses, this approach is limited by a poor specificity (52%) despite its high sensitivity (91%). Many believe, however, that the NPV and low likelihood of CAD associated with the absence of coronary calcium (CAC=zero) may be clinically relevant. Furthermore, CAC scoring has been shown to provide incremental value over conventional risk factors and biochemical markers for the prediction of both significant and nonsignificant luminal narrowing on angiography. More importantly, the risk of adverse cardiovascular events increases as a function of CAC in both asymptomatic individuals and symptomatic patients. The future role of CAC is likely to be in the stratification of asymptomatic patients found to be at intermediate risk after the application of clinical risk scores.

It is important to appreciate that a number of limitations to CAC exist. For example, the association between the site of calcification on calcium scoring and the actual location of the stenosis is relatively poor. Hence, the results of testing will not localize disease and will at best form an estimate of CAD likelihood. Furthermore, the prevalence of patients with atherosclerosis, and possibly significant coronary artery obstructions, on the basis of noncalcified plaque has not been studied thoroughly.

The presence of significant coronary calcium, as measured by CAC, may also play an important role in identifying optimal candidates for CTA. Because the prevalence of CAC increases with age, particularly in males, the amount of calcium routinely encountered in older individuals can potentially compromise the ability to perform technically adequate CTA. For example, CAC in normal men aged 65 to 69, 70 to 74, and $\geq$75 years has been reported as 464±731, 665±921, and 836±1053 HU, respectively. Indeed, certain centers have adopted the policy of routine CAC before CTA to minimize uninterpretable CTA studies. Interestingly, at this time, 1 state Medicare authority has refused to reimburse CTA studies in patients with significant CAC levels. Alternatively, many centers go directly to CTA and do not perform CAC as a means of atherosclerosis testing because of the perceived superiority of CTA in this role.

Positron Emission Tomography

PET is a nuclear medicine technique that uses positron-emitting radionuclides to obtain images of myocardial perfusion and metabolism. Fortunately, atoms of high biological significance (eg, carbon, oxygen, and nitrogen) also have radionuclide species that decay by positron emission. Thus, the use of positron-emitting radionuclides allows unique quantitative information of important biological processes to be obtained in vivo (eg, myocardial perfusion, glucose metabolism, and fatty acid metabolism). The fundamental principle of positron tomography is that positron-emitting radionuclides (eg, carbon-11, nitrogen-13, oxygen-15, and fluorine-18) decay by emitting “positively” charged electrons (positrons). Once released from the nucleus, these positrons travel short distances in tissue and annihilate with the encounter of nearby electrons. This annihilation releases energy in the form of 2 gamma rays.
or photons that are emitted in opposite directions (180° from each other). These opposite high-energy photons (511 keV) are captured externally by an array of detector elements (scintillators) in the PET gantry. The electronics of the PET system are arranged to facilitate detection of 511-keV photons arriving at opposite detectors within a narrow temporal window and rejection of scattered photons arriving outside the preset temporal window, thereby enhancing the spatial and contrast resolution. Several technical advantages account for the improved image quality (Figure 5) and diagnostic ability of PET compared with SPECT, such as the following: (1) routine measured (depth-independent) attenuation correction, which decreases the number of false-positives and, thus, increases specificity; (2) high spatial and contrast resolution (heart-to-background ratio) that allows for improved detection of small perfusion defects, thereby decreasing the number of false-negatives and increasing sensitivity; (3) high temporal resolution that allows fast dynamic imaging of tracer kinetics, which makes absolute quantification of myocardial perfusion (in milliliters per minute per gram of tissue) possible. In addition, the use of short-lived radiopharmaceuticals allows fast, sequential assessment of regional myocardial perfusion (eg, rest and stress), thereby improving laboratory efficiency and patient throughput. Although these technical advantages have been recognized for a long time, the use of PET for routine detection of CAD has only gained clinical momentum in recent years. Recent Food and Drug Administration approval of PET agents for imaging myocardial perfusion (ie, 15O-water [generator product] and 13N-ammonia [cyclotron product]) and the subsequent changes in reimbursement are responsible for much of the recent growth in clinical cardiac PET. Despite these advantages, SPECT scanners and imaging radiotracers (eg, 99mTc agents and 201Tl) are still more widely available and less expensive than PET scanners and positron-emitting radiotracers (eg, 82Rb, 13N-ammonia).

Table 2 summarizes the published studies documenting the diagnostic accuracy of myocardial perfusion PET imaging for detecting obstructive CAD. The average weighted sensitivity for detecting at least 1 coronary artery with >50% stenosis is 90% (range 83% to 100%), whereas
the average specificity is 89% (range 73% to 100%). The corresponding average PPV and NPV are 94% (range 80% to 100%) and 73% (range 36% to 100%), respectively, and the overall diagnostic accuracy is 90% (range 84% to 98%).

Comparative Studies of PET Versus SPECT
Three studies have performed a direct comparison of the diagnostic accuracy of $^{82}$Rb myocardial perfusion PET and $^{201}$Tl or $^{99m}$Tc SPECT imaging in the same or matched patient populations. Go and colleagues compared PET and SPECT in 202 patients. Their results showed a higher sensitivity with PET than with SPECT (93% versus 76%, respectively), without significant changes in specificity (78% versus 80%, respectively). In another study, Stewart et al compared PET and SPECT in 81 patients. They observed a higher specificity for PET than with SPECT (83% versus 53%, respectively), without significant differences in sensitivity (86% versus 84%, respectively).

Figure 5. Dipyridamole stress and rest $^{82}$Rb PET/CT images (CT used for attenuation correction only) in corresponding short-axis (top), vertical long-axis (middle), and horizontal long-axis (bottom) slices in a 56-year-old man with atypical chest pain (body mass index 33.2 kg/m$^2$). The images are abnormal and consistent with a medium-sized area of prior myocardial infarction (fixed defect) in the lateral wall with a large area of residual stress-induced peri-infarct ischemia throughout the inferior and inferoseptal walls (reversible defect).

### TABLE 2. Summary of Published Literature on Diagnostic Accuracy of PET

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<tr>
<th>Study</th>
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<th>Women</th>
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<tr>
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<td>193</td>
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Sens indicates sensitivity; Spec, specificity.
*Study used PET/CT (CT was used for attenuation correction only).
Diagnostic accuracy was higher with PET than with SPECT (89% versus 78%, respectively).

More recently, Bateman et al. compared 82Rb PET and 99mTe sestamibi SPECT in 2 matched patient cohorts undergoing clinically indicated pharmacological-stress perfusion imaging using contemporary technology for both SPECT and PET. Overall diagnostic accuracy with either a 50% (87% versus 71%) or a 70% (89% versus 79%, respectively) angiographic threshold was higher for PET than for SPECT. Differences in diagnostic accuracy reflected primarily the increased specificity (with a marginal advantage in sensitivity) of PET versus SPECT and applied to both men and women and to obese and nonobese individuals.

**Diagnosing Multivessel CAD With Myocardial Perfusion PET**

As depicted in Table 2, the relative assessment of myocardial perfusion with PET remains a sensitive means for diagnosing or ruling out the presence of obstructive CAD. As with SPECT, however, PET often uncovers only that territory supplied by the most severe stenosis. This is based on the fact that in patients with CAD, coronary vasodilator reserve is often abnormal even in territories supplied by noncritical angiographic stenoses, thereby reducing the heterogeneity of flow between “normal” and “abnormal” zones and limiting the ability to delineate the presence of multivessel CAD.

Alternatively, PET measurements of myocardial blood flow (in milliliters per minute per gram of myocardium) and coronary vasodilator reserve also help improve detection of multivessel CAD. The reports evaluating the diagnostic performance of myocardial perfusion PET to detect angiographic stenoses (Table 2) examined imaging results in terms of sensitivity and specificity rather than considering CAD as a continuous spectrum of severity. In patients with CAD, noninvasive measurements of coronary blood flow and vasodilator reserve by PET are inversely and nonlinearly related to stenosis severity, as defined by quantitative angiography. Importantly, coronary lesions of intermediate severity have a differential coronary flow reserve that can be detected by PET, which decreases as stenosis severity increases, thereby allowing better definition of the functional importance of known coronary epicardial stenosis.

Two reports demonstrate the potential added clinical value of measures of coronary vasodilator reserve as assessed by PET to delineate the extent of underlying CAD. Yoshinaga et al. compared the clinical value of measures of coronary vasodilator reserve as assessed by PET to relative assessments of myocardial perfusion by SPECT in 27 patients with CAD. They showed good agreement between SPECT defects and PET measures of vasodilator reserve in only 16 (28%) of 58 myocardial regions supplied by coronary stenosis >50% as assessed by quantitative angiography. The remaining 42 (72%) of 58 regions with angiographic stenoses showed no regional perfusion defects by SPECT but a definitely abnormal vasodilator reserve by PET. Similarly, Parkash et al. recently reported on the value of quantification of coronary flow reserve versus the traditional relative assessment of myocardial perfusion to delineate the extent of CAD in a relatively small group of 23 patients. In patients with 3-vessel CAD, they found that defect sizes were significantly larger with quantification methods than with the traditional method (44±18% versus 69±24%). In patients with single-vessel CAD, defect sizes were smaller by quantification methods than with the traditional method (10±12% versus 18±17%). Thus, this is clearly an area of great clinical interest, and future studies are warranted to evaluate the added value of quantitative flow measurements for the noninvasive diagnosis of CAD.

Another potential advantage of PET is its distinct ability to assess LV function at rest and during peak stress (as opposed to poststress with gated SPECT). Recent data from our laboratory suggest that in normal subjects, LV ejection fraction (LVEF) increases during peak vasodilator stress. In patients with CAD, however, changes in LVEF (from baseline to peak stress) are inversely related to the magnitude of perfusion abnormalities during stress (reflecting ischemic myocardium). Indeed, patients with multivessel disease or left main disease show a frank drop in LVEF during peak stress even in the absence of apparent perfusion defects (Figure 6). In contrast, patients without significant CAD or with 1-vessel disease show a normal increase in LVEF. Consequently, the NPV of a delta increase in LVEF (from rest to peak stress) of ≥5% to exclude 3-vessel and/or left main CAD is 97%.

**PET and Stratification of Risk**

To date, very limited data exist on the prognostic implications of stress PET results and the added value of stress PET over pre–myocardial perfusion imaging data for the identification of patients at risk for adverse cardiovascular events. The prognostic value of dipyridamole stress 82Rb PET was recently investigated in 367 patients followed up for 3.1±0.9 years. As has been described previously with SPECT, an increase in the extent and severity of perfusion defects with stress PET was associated with an increasing frequency of adverse events. Importantly, the hard event rate in patients with normal stress PET was 0.4% per year; however, this study, the largest PET prognosis study to date, was limited by the occurrence of only 17 hard events. Given the increased availability and use of stress PET, more and larger studies validating the prognostic value of stress PET will be available in the near future.

**PET Measurements of Myocardial Perfusion to Monitor Progression and Regression of CAD**

Lipid-lowering trials in patients with coronary atherosclerosis have demonstrated no progression or only modest regression of anatomic coronary artery stenoses compared with control patients. Despite the lack or modest regression in coronary artery stenoses, these studies have reported a proportionately greater decrease in coronary events in treated than in control patients. This has led to the hypothesis that stabilization of atherosclerotic plaques, reduction of inducible myocardial ischemia (caused by an improvement in coronary vasodilator function), or both effects combined may be more closely related to improved clinical outcomes than the simple anatomic change in plaque burden. This is based on the fact that myocardial blood flow is a function of the arterial radius raised to the fourth power. Consequently, small changes in...
diameter not measurable by anatomic imaging are magnified into much larger changes in blood flow that are readily seen and quantifiable by perfusion imaging. For diffuse coronary atherosclerosis, a mild anatomic reduction in diameter that may be difficult to detect by invasive coronary angiography or CTA (due to limitations in spatial resolution) will cause cumulatively increasing resistance along the length of the coronary artery. This cumulative resistance from base to apex causes a longitudinal perfusion gradient that can be identified by stress PET perfusion imaging. As with SPECT, several studies have also demonstrated the value of PET perfusion imaging to follow up changes in CAD, which can show rapid improvement in perfusion abnormalities after intense medical treatment is initiated. These changes are proportionately greater than those demonstrated by quantitative coronary angiography.

**Integrated Evaluation of Coronary Anatomy and Myocardial Perfusion With Hybrid PET/CT**

The availability of hybrid PET/CT scanners that allow a true integration (fusion) of structure and function has interesting potential in cardiology (Figure 7). This technology enables detection and quantification of the burden of the 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 (through fusion of anatomy and biology with molecularly targeted PET imaging) in the coronary and other arterial beds in the same setting. Together, by revealing the degree and location of anatomic stenoses and their physiological significance and the plaque burden and its composition, integrated PET/CT can provide unique information that may improve noninvasive diagnosis of CAD and the prediction of cardiovascular risk.
Assessing Atherosclerosis Burden

Integrated PET/CT offers an opportunity to assess the presence and magnitude of subclinical atherosclerotic disease burden and to measure myocardial blood flow (in milliliters per minute per gram of myocardium) as a marker of endothelial health and atherosclerotic disease activity. Recent evidence comparing the results of cardiac CT and myocardial perfusion imaging suggest that a significant proportion of patients with normal myocardial perfusion studies have evidence of subclinical atherosclerosis (sometimes extensive) by CTA. This finding is not unexpected, because the myocardial perfusion imaging method is designed for and targets the identification of flow-limiting stenoses. Although it is premature to predict the clinical significance of this observation, it provides intriguing evidence for future investigations of the potential complementary role of CTA and perfusion imaging for individualizing risk stratification and patient management. Although myocardial perfusion imaging will likely continue to define the need for revascularization, the objective assessment of atherosclerotic burden (both calcified and noncalcified plaques) by CTA might be able to play a role in individualizing the intensity and goals of medical therapy.

Potential for Plaque Characterization

PET/CT also offers an opportunity for direct molecularly targeted imaging of atherosclerotic disease activity. The detailed anatomic information about vascular disease provided by contrast-enhanced CT can be complemented by the molecular insights of positron tomography. In a pilot study of symptomatic patients with carotid atherosclerosis, Rudd and colleagues demonstrated a relationship between anatomic plaque by CTA, glucose uptake by PET (reflecting inflammation), and patients’ symptoms. The net 18F-fluorodeoxyglucose (FDG) accumulation rate in symptomatic lesions was 27% higher than in contralateral asymptomatic lesions (Figure 8). No measurable glucose uptake existed in normal carotid arteries. Autoradiography of excised plaques confirmed accumulation of FDG in macrophage-rich areas of the plaque. Similar findings have also been reported in experimental studies of atherosclerosis. This suggests that the phenotyping potential of hybrid PET/CT could provide mechanistic insights into atherothrombotic processes, better risk stratification, optimal selection of therapeutic targets, more individualized treatment, and the means for monitoring therapeutic responses.

Guiding Management of CAD

Because not all coronary stenoses detected by CTA are flow-limiting, the stress myocardial perfusion PET data complement the CT anatomic information by providing instant readings about the clinical significance (ie, ischemic burden) of such stenoses (Figures 9 and 10). As described above, recent data from multiple laboratories using either sequential imaging (CTA followed by SPECT27,29 or hybrid imaging (SPECT/CT or PET/CT)26,28 suggest that the PPV of CTA for identifying coronary stenoses that produce objective evidence of stress-induced ischemia is suboptimal (Figure 3). This is consistent with the well-described limitations of anatomic measures of CAD for delineating the physiological implications of stenoses. First, percent diameter stenosis is only a modest descriptor of coronary resistance because it does not incorporate other lesion characteristics (eg, length, shape, and eccentricity) or stenoses in series that may greatly affect the impedance to blood flow. Second, vasomotor tone and coronary collateral flow, both of which are known to affect myocardial perfusion, are not assessed by simple measures of stenosis severity. Finally, as described above, CTA is limited in its ability to accurately define the severity of stenosis (a surrogate of physiological significance; Figure 2). In contrast, myocardial perfusion imaging provides a simple and accurate integrated measure of the effect of all these parameters on coronary resistance and tissue perfusion, thereby optimizing the selection of patients who may ultimately benefit from revascularization. This finding, if confirmed in larger studies, would suggest that additional noninvasive testing would be required after CTA before consideration for invasive catheterization. Furthermore, the use of CTA alone in patients with atherosclerosis without myocardial perfusion imaging would potentially result in an enormous increase in costs of care and resource utilization.
due to unnecessary downstream catheterization and revascularization procedures. In addition, image fusion of the stress perfusion PET data with the coronary CT information can help identify the culprit stenosis in a patient presenting with chest pain and help guide targeted coronary interventions.

As is the case for CTA, insufficient data currently exist to guide the optimal, efficient use of hybrid imaging in the patient with known or suspected CAD. The complementary nature of stress PET and CTA make a hybrid approach appealing as a potential “one-stop shop” for CAD patients in that the reported data will include rest and peak stress LV perfusion, rest and peak stress LV size and function, coronary anatomy, and atherosclerosis assessment. In the near future, this is likely to also include plaque morphology, coronary

**Figure 9.** Integrated PET/CTA study. The CTA images demonstrate a noncalcified plaque (arrowhead) in the proximal left anterior descending coronary artery (LAD) with 50% to 70% stenosis; however, the rest and peak dobutamine stress myocardial perfusion PET study (lower left panel) demonstrates only minimal inferoapical ischemia. In addition, LVEF was normal at rest and demonstrated a normal rise during peak dobutamine stress. Full-motion cines can be viewed in the online-only Data Supplement (Movies VI and VII). Ant indicates anterior; Endo+Epi, endocardial plus epicardial; Inf, inferior; LCX, left circumflex; LM, left main; and RCA, right coronary artery.

**Figure 10.** Integrated PET/CTA study. An extensive calcified plaque burden can be seen throughout the coronary arteries. The left anterior descending (LAD) and circumflex (LCX) coronary arteries show severe calcified plaque in their proximal and mid segments. The dominant right coronary artery (RCA) shows multiple calcified plaques, with a severe predominantly noncalcified plaque in its mid segment; however, the rest and peak adenosine stress myocardial perfusion PET study (lower left panel) demonstrates only moderate ischemia in the inferior wall (arrowheads). In addition, LVEF was normal at rest and demonstrated a normal rise during peak stress, effectively excluding the presence of flow-limiting 3-vessel CAD. Full-motion cines can be viewed in the online-only Data Supplement (Movies VIII and IX). Ant indicates anterior; Endo+Epi, endocardial plus epicardial; Inf, inferior; and RPL, right posterolateral artery.
reserve, and image fusion to assess culprit lesions. A pivotal question for future research is whether the hybrid approach is a cost-effective one or whether the CTA and PET data are better acquired in a staged approach, with 1 of the 2 tests serving as a screen for the other. Software will permit the same image fusion to be achieved whether the data were acquired on a hybrid system or 2 individual PET and CTA systems. It is feasible that depending on a patient’s pretest likelihood of CAD and underlying risk, a patient with a lower likelihood of CAD may be optimally imaged with a CTA-first approach, with patients with a higher likelihood of CAD being imaged with PET as the first approach or, in certain subsets, with a hybrid approach. We await ongoing studies to define these cohorts.

Areas of Uncertainty for CTA, PET, and Hybrid PET/CT

With respect to diagnostic accuracy, the CTA and PET series to date have relatively limited representation of important patient subgroups, namely, women, obese individuals, and people with diabetes mellitus (Tables 1 and 2). These subgroups are relevant because they comprise a large segment of patients referred for testing for known or suspected CAD. With respect to CTA, extrapolation of the results presented in Table 1 to these patient subgroups is problematic because they pose potential challenges for this technology that are related to smaller coronary vessels (eg, women and diabetic patients) and large body mass, potentially resulting in limited image quality. For example, some studies have reported higher sensitivity for CAD detection for men than for women without changes in specificity.16,19 Although these apparent differences may be related to a higher prevalence of disease in men in these series with limited statistical power, the value of CTA for CAD diagnosis in women requires further study. With PET, diagnostic accuracy appears comparable in men and women.61,62 Likewise, the diagnostic accuracy of CTA in frankly obese individuals (body mass index >30 kg/m²) appears to be lower than among nonobese subjects,23 although this too requires further investigation. To date, no studies have been published evaluating the diagnostic accuracy of these approaches in patients with diabetes mellitus.

Finally, considerable further information will be needed to identify where CTA and PET or hybrid PET/CT will fit in a clinical strategy. In light of the poor PPV of CTA for predicting ischemia, its use as a gatekeeper to catheterization may result in considerable downstream overutilization of catheterization and, possibly, revascularization procedures. However, CTA may eventually develop 1 or more possible roles, which could include its use as an initial test of atherosclerosis in at-risk individuals and as a means of resolving equivocal or uncertain stress perfusion studies. It is currently premature to predict with certainty which of these may be validated owing to insufficient available data.

Many of these questions may be addressed by the Study of Perfusion versus Anatomy’s Role in CAD (SPARC) a prospective multicenter registry comparing stress SPECT, stress PET, PET/CTA, and CTA alone with respect to outcomes and resource utilization.95 This study, designed to enroll 3700 patients in 35 to 40 sites, will shed light on the relative value of these newer modalities (PET, CTA, and hybrid PET/CT) compared with standard approaches (SPECT). In particular, insights may be gained into questions such as which test or combination of tests should be used, sequentially or in combination, in which patients.

Evaluation of Myocardial Viability and Infarction

Cardiac CT

Much like contrast magnetic resonance (CMR), CT can also be used for assessing the extent of scar and tissue viability. Although the notion of using contrast-enhanced CT to assess viability is not new,96–101 recent advances in its temporal and spatial resolution with multidetector CT technology have renewed the clinical interest for this application.102–104

Recent studies in experimental models of ischemia/reperfusion have shown that iodinated contrast agents share many of the kinetic features seen with Gd-DTPA used in CMR studies. First-pass (referred to as early) images of iodinated contrast through the infarcted myocardium (especially acutely reperfused) frequently demonstrate the presence of so-called “cold spots” (ie, lack of contrast enhancement in an area surrounded by normal myocardial contrast opacification), which reflect impaired tissue perfusion that results from microvascular obstruction from distal embolization and surrounding tissue edema (Figure 11). However, a few minutes after contrast administration, accumulation of the contrast agent increases as a result of an increased volume of distribution in areas of myocyte necrosis, which results in so-called “bright spots” (or delayed hyperenhancement), reflecting areas of myocardial scarring. Experimental studies suggest that peak enhancement occurs approximately 5 to 10 minutes after contrast injection.102,103

Signal-to-noise ratio, which reflects image quality, between reperfused and normal myocardium is comparable to that of CMR in the early (first-pass) images but significantly lower than that obtained with CMR in the delayed images.102,106 However, quantitative estimates of infarct size with delayed CT imaging appear to be comparable to those achieved with CMR, both in experimental102,103,106 and clinical102,104 models of myocardial infarction. The results thus far show that similar to CMR, early CT images consistently underestimate the extent of myocardial scar, especially in areas of chronic myocardial injury.102,104 thereby necessitating a second scan (delayed images) to accurately measure infarction and viability. The need for a second (albeit low-dose) scan (after a CTA) obviously increases the radiation dose to the patient and thus makes it somewhat less attractive clinically than CMR for this application. However, the relative clinical utility of these approaches may depend on future research demonstrating head-to-head differences or similarities of these methods to predict functional recovery and survival in heart failure patients after revascularization.

Positron Emission Tomography

The use of metabolic imaging with PET for evaluating myocardial viability has been extensively validated. Although several approaches have been documented,107–109 the use of
FDG to assess regional myocardial glucose utilization (an index of tissue viability) is the most common approach in clinical practice.\textsuperscript{110} With this approach, specific abnormalities in myocardial metabolism that reflect viable and scarred myocardium have been described (Figure 12). Contractile dysfunction is predicted to be reversible after revascularization in regions with increased FDG uptake or a perfusion-FDG mismatch and irreversible in those with reduced FDG uptake or a perfusion-FDG match pattern. With these criteria, the average PPV for predicting improved segmental function after revascularization is 76\% (range 52\% to 100\%), whereas the average NPV is 82\% (range 67\% to 100\%).\textsuperscript{110}

Several studies using different PET approaches have shown that the gain in global LV systolic function after revascularization is related to the magnitude of viable myocardium assessed preoperatively.\textsuperscript{111} These data demonstrate that clinically meaningful changes in global LV function can be expected after revascularization only in patients with relatively large areas of hibernating and/or stunned myocardium (\textasciitilde 20\% of the LV mass). Similar results have been reported using estimates of myocardial scar with PET.\textsuperscript{112} The inverse relationship between the extent of scar assessed by FDG PET and the changes in LVEF after revascularization are consistent with those obtained with SPECT,\textsuperscript{113} dobutamine echocardiography,\textsuperscript{114} and contrast-enhanced magnetic resonance imaging.\textsuperscript{115} In keeping with the observed changes in LV function after revascularization, the magnitude of improvement in heart failure symptoms also correlates with the preoperative extent of viable myocardium.\textsuperscript{116} Furthermore, the observed improvement in symptom status in patients with viability by PET also appears to correlate with the reduced frequency of hospital readmission for decompensated heart failure after revascularization.\textsuperscript{117} The notion that noninvasive imaging of viability can predict the degree of symptomatic improvement in heart failure patients has been confirmed in studies involving PET\textsuperscript{118} and SPECT imaging of \textsuperscript{201}TI or \textsuperscript{99m}Tc sestamibi,\textsuperscript{119} as well as identification of contractile reserve by dobutamine echocardiography.\textsuperscript{120} Taken

Figure 11. Short-axis view magnetic resonance imaging (A, D, G) and short-axis multislice spiral computed tomography images (B, C, E, F, H, I) in 3 different patients with acute myocardial infarction (arrows) attributable to left anterior descending coronary artery (A to C), right coronary artery (D to F), and left circumflex artery (G to I) occlusion after successful revascularization. An excellent agreement was shown between delayed-enhancement magnetic resonance imaging (A, D, G) and late-enhancement multislice spiral computed tomography (B, E, H). Agreement with arterial-phase multislice spiral computed tomography (C, F, I) was slightly worse. Reproduced from Mahnken et al\textsuperscript{104} with permission from the publisher. Copyright © 2005, the American College of Cardiology Foundation.

Figure 12. PET patterns of myocardial viability. Left, Concordant reductions in myocardial perfusion (\textsuperscript{82}Rb) and glucose metabolism (FDG), reflecting myocardial infarction. Right, Preserved glucose metabolism (FDG) in a territory with decreased myocardial perfusion (\textsuperscript{82}Rb), reflecting complete tissue viability.
together, these data suggest that the extent of dysfunctional ischemic viable myocardium in heart failure patients can be used as a potential marker of the symptomatic benefit that will accrue as a result of revascularization.

An issue of even greater clinical relevance is whether viability imaging may help identify patients with low ejection fraction for whom revascularization may offer a survival advantage. Early PET reports showed that patients with viable myocardium treated medically had a consistently higher event rate than those without viability. These data also suggested that the poor event-free survival of patients with viable myocardium undergoing medical therapy was improved significantly and consistently by early referral to revascularization. These initial findings with FDG PET have been confirmed by virtually all subsequent studies using noninvasive imaging with either nuclear testing or echocardiography. Together, these findings imply that despite an increasing clinical risk of revascularization with worsening LV dysfunction, noninvasive imaging evidence of preserved viability may provide information on clinical benefit to balance against that risk, which could help inform clinical decision making.

Technology Trends

Innovations in imaging technology, especially for CT and hybrid PET/CT and SPECT/CT, are occurring rapidly, and significant improvements are expected within the next 2 to 5 years. In CT, technology is rapidly evolving with regard to several important specifications. With respect to temporal resolution, the gradual improvement seen with newer-generation scanners is expected to improve further by the introduction of dual x-ray source CT technology. Temporal resolution is particularly important in imaging the beating heart, especially for good-quality imaging of the coronary arteries after intravenous contrast administration. With respect to axial coverage, it appears inevitable that multislice CT will continue to evolve in this way (128 and 256 multidetector CT scanners are announced or already in early testing) until coverage becomes sufficient to eliminate the need for couch translation during cardiac imaging. This is expected to improve image quality by minimizing artifacts caused by cardiac and/or breathing motion. It may also facilitate dynamic imaging for the evaluation of myocardial perfusion and may possibly help to reduce radiation exposure. One other important specification is spatial resolution, which is not expected to improve significantly by the advancements in volume CT. This limits accurate assessments of stenosis severity and possibly the reproducibility of quantitative evaluation of plaque burden. Area detectors, such as flat-panel technology, have the potential to produce significant improvements in spatial resolution; however, this technology does not yet provide the low-noise characteristics of the scintillator arrays used in multislice CT. Technology advances are also focused at limiting the radiation dose to patients. The routine implementation of ECG-dependent dose modulation (whereby the intensity of the x-ray dose is significantly reduced during end systole); potential implementation of "step-and-shoot" protocols in which the entire heart volume is collected over a series of sequential, contiguous stops (as opposed to a helical acquisition), thereby enabling the x-ray beam to be turned on only during data acquisition; and the expected reductions in scanning time with increased axial coverage and possible prospective gating should all help reduce radiation exposure.

PET has already evolved (likely irreversibly) into hybrid PET/CT imaging. Advances in both PET and CT technology are also being rapidly incorporated into hybrid scanners, to improve both sensitivity and spatial resolution. These specifications are crucial as the field rapidly evolves to in vivo imaging of small quantities of molecularly targeted agents. Changes in radiotracer technology are also expected to expand the clinical use of cardiac PET/CT. For example, introduction of 18F-based PET imaging agents will potentially reduce cost because it would enable unit-dose distribution of radiopharmaceuticals, similar to oncology PET/CT applications.

Summary

Innovations in noninvasive cardiovascular imaging are rapidly advancing our ability to image in great detail the structure and function of the heart and vasculature. Cardiac CT and hybrid PET/CT are clear examples of this innovation. Multidetector cardiac CT now allows rapid, detailed imaging of the coronary arteries and other vascular beds, with quantitative assessments of plaque burden and morphology. By providing concurrent quantitative information about myocardial blood flow and metabolism with coronary and cardiac anatomy, PET/CT offers the opportunity for a comprehensive noninvasive evaluation of the consequences of atherosclerosis in the coronary arteries and myocardium. This integrated platform for assessing anatomy and biology offers great potential for translating advances in molecularly targeted imaging into humans. The goals of future investigation will be to refine these technologies, establish standard protocols for image acquisition and interpretation, address the issue of cost-effectiveness, and validate a range of clinical applications in large-scale clinical trials.

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