Cardiac Imaging

Diagnostic Accuracy of Rubidium-82 Myocardial Perfusion Imaging With Hybrid Positron Emission Tomography/Computed Tomography in the Detection of Coronary Artery Disease

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Objectives	Our objective was to determine the accuracy of rubidium-82 myocardial perfusion positron emission tomography-computed tomography (PET-CT) imaging for detecting obstructive coronary artery disease (CAD).
Background	Hybrid PET-CT is a new noninvasive imaging modality for evaluating patients with known or suspected CAD.
Methods	We evaluated 64 consecutive patients with suspected CAD undergoing rest-stress rubidium-82 cardiac PET-CT (CT was only used for attenuation correction) and coronary angiography within 7 days (range 1 to 180 days). Patients with known CAD, previous myocardial infarction, or revascularization were excluded. Thirty-eight patients with a low likelihood for CAD were also studied. Obstructive CAD was defined as ≥70% diameter stenosis on angiography.
Results	The mean age of the patients was 62 ± 15 years, with a body mass index of 31 ± 8 kg/m^2. Chest pain and/or dyspnea were the predominant reasons for evaluation. Stress perfusion defects were detected in 41 of 44 patients with obstructive CAD (sensitivity 93%, 95% confidence interval [CI] 87 to 99). The specificity of PET-CT was 83% (48 of 58, 95% CI 71 to 91), and its overall diagnostic accuracy was 87% (95% CI 79 to 93). All patients with a low likelihood for CAD showed normal scans, for a normalcy rate of 100% (38 of 38, 95% CI 91 to 100). The sensitivity for detecting CAD in patients with single and multivessel (≥2 vessels) disease was 92% (22 of 24, 95% CI 74 to 99) and 95% (19 of 20, 95% CI 74 to 99), respectively.
Conclusions	Myocardial perfusion PET-CT affords high sensitivity and overall accuracy for detecting CAD, including patients with single-vessel disease, women, and obese patients. (J Am Coll Cardiol 2007;49:1052–8) © 2007 by the American College of Cardiology Foundation

Early detection and treatment of coronary artery disease (CAD) remains paramount given its morbidity, mortality, and economic consequences. Over the last 2.5 decades, cardiac single-photon emission computed tomography (SPECT) has played a dominant role in the detection of obstructive CAD, risk stratification, and prediction of therapeutic benefit (1–4). Cardiac positron emission tomography (PET) imaging using rubidium-82 or N-13 ammonia is emerging as a potential alternative to SPECT in selected patients (e.g., obese patients), owing to its higher spatial resolution, accurate attenuation correction, quantitative capabilities, and improved availability (5–12).

Over the past few years, we have witnessed a rapid evolution of PET instrumentation, which now offers higher sensitivity and hybrid scanners integrating PET and computed tomography (CT). Hybrid PET-CT scanners account for approximately 80% of the new PET units installed (13). Although CT-based attenuation correction for PET has been widely adopted in oncology, it presents challenges in cardiac imaging. Differences in spatial resolution and breathing patterns between CT and PET may occasionally lead to misregistration of imaging data, resulting in incorrect attenuation correction and ensuing artifacts that may impact diagnostic accuracy. Accordingly, we sought to determine the diagnostic accuracy of rubidium-82 myocardial perfusion imaging for detecting obstructive CAD in subjects referred for diagnosis of chest pain or nonclassic symptoms with multiple risk factors using an integrated PET-CT system, whereas the CT scan was only used for purposes of attenuation correction.

Methods

Patient population. Our study sample was derived from a consecutive diagnostic cohort of patients with suspected CAD because of chest pain or nonclassic symptoms with multiple risk factors referred for cardiac PET-CT imaging from November 2003 to January 2005. We included patients who underwent coronary angiography within 6 months of their incident PET-CT study. Patients with a history of CAD (CAD on coronary angiography), myocardial infarction (MI) and/or evidence of pathologic Q waves on resting electrocardiogram, or prior revascularization were excluded. In addition, we included a group of patients with a low likelihood for CAD (<5% pretest likelihood) defined by the absence of symptoms; coronary risk factors including diabetes, hypertension, dyslipidemia, or smoking; and a normal resting electrocardiogram (14).

PET. All patients were studied using a whole-body PET-CT scanner (Discovery ST Lightspeed 16, GE Healthcare, Milwaukee, Wisconsin). Patients were studied after an overnight fast and 24-h cessation of all caffeine-containing or methylxanthine-containing substances. After a scout CT acquisition (120 kVp, 10 mA) used for proper patient positioning, a CT transmission scan (140 kVp, 20 to 30 mA, pitch 1.35) was acquired. The patients were then injected with 40 to 60 mCi of rubidium-82 at rest, and after a 90- to 120-s delay (to allow for adequate blood pool clearance), gated emission images were obtained for 5 min. Immediately after rest imaging, patients underwent pharmacologic stress testing using standard infusions of dipyridamole (0.14 mg/kg/min for 4 min, n = 40), adenosine (0.14 mg/kg/min for 6 min, n = 20), or dobutamine (10 μg/kg/min increments to a maximum of 40 μg/kg/min or until achieving 85% of maximum predictive heart rate, n = 4). At peak stress, a second dose of 40 to 60 mCi of rubidium-82 was administered and emission images were acquired as previously described. On completion of the stress images, a post-emission CT transmission scan (140 kVp, 20 to 30 mA, pitch 1.35) was repeated and used for attenuation correction of the stress images. The second CT transmission scan is important because during pharmacologic stress (especially vasodilator stress), the heart changes its size and position within the chest (because of the different breathing pattern during pharmacologic stress). The gated PET images were reconstructed using an ordered subset expectation maximization algorithm (2 iterations, 30 subsets), and then were summed for review. The effective radiation dosimetry from this study was 13.8 mSv (12 mSv from the rest-stress rubidium-82 injections, 1.4 mSv from the 2 CT transmission scans, and 0.4 from the 2 scout scans).

Data analyses. Two experienced nuclear cardiologists (S.D., M.D.C.) reviewed each rest-stress myocardial perfusion PET study blinded to the results of the coronary angiograms. A 17-segment, 5-point (0 = normal uptake, 4 = absent uptake) scoring system was used to compute a summed stress score, a summed rest score, and a summed difference score. Regional perfusion abnormalities were assigned to a coronary arterial territory based on a generally accepted standard (15).

Coronary angiography. All patients underwent coronary angiography using a standard technique within 6 months of the index PET-CT study. Cineangiograms of the coronary arteries were obtained in multiple projections using a Phillips Integris BH3000 angiographic system (9-inch [22/17/13 cm] triple-mode high-contrast image intensifier) (Philips Medical Systems, Rotterdam, the Netherlands). The angiographic criterion used to define the presence of significant CAD was a visually determined diameter stenosis of ≥70% for the left anterior descending, left circumflex, and right coronary arteries or their major branches, and ≥50% for the left main coronary segment.

Statistical analysis. Continuous data are presented as mean ± SD, whereas categorical and ordinal data are presented as counts and simple proportions. We used a binary classification for the presence or absence of CAD using angiographic results as the reference standard. By means of a 2 × 2 table, sensitivity, specificity, and diagnostic accuracy rates were derived according to the standard definitions and were represented with 95% confidence intervals (CIs). The CIs were computed according to the Wilson method (16). Because of the small number of patients with angiographically normal coronary arteries, the calculated specificity in this analysis included the low-likelihood patients and those with angiographically normal coronary arteries. The possibility of verification bias (17,18) necessitated the derivation of a normalcy rate—a surrogate for true specificity from a group of 38 patients with a low likelihood for CAD but without coronary angiography. Interobserver variability was assessed in 20 additional patients (10 normal and 10 abnormal) using the kappa statistic.

Results

The study consisted of 102 consecutive patients (mean age 62 years, 61% male), of whom 64 patients compose our diagnostic group and 38 patients our low likelihood group (Table 1). The mean body mass index (BMI) was 30.8 kg/m^2, and the majority of patients (78%) were overweight or obese (BMI ≥25 kg/m^2). Coronary risk factors were prevalent, especially hypertension, dyslipidemia, and diabetes. The median time interval between the stress rubidium-82 PET-CT and coronary angiography was 7 days (range 1 to 180 days).

Abbreviations and Acronyms

BMI = body mass index

CAD = coronary artery disease

CI = confidence interval

CT = computed tomography

MI = myocardial infarction

PET = positron emission tomography

SPECT = single-photon emission computed tomography

Table 1	Characteristics of Patients With Suspected CAD
n	64
Age (yrs)	62 ± 14.9 (range 19–87)
Body mass index (kg/m^2)	31 ± 8 (range 17–54)
Male gender	39 (61%)
Hypertension	55 (86%)
Dyslipidemia	34 (53%)
Diabetes	23 (36%)
Family history of CAD	20 (31%)
Cigarette smoking	16 (25%)
Endstage renal disease	3 (5%)
Peripheral vascular disease	5 (8%)
Chest pain	29 (45%)
Dyspnea	28 (44%)

Values expressed as n (%) or mean ± SD.
CAD = coronary artery disease.

Agreement between rubidium-82 PET-CT and coronary angiography. OVERALL DETECTION OF CAD. Stress PET correctly identified 41 of the 44 patients with evidence of ≥70% stenosis on coronary angiography (sensitivity 93%, 95% CI 87% to 99%) (Table 2). In patients with single-vessel disease and multivessel (≥2-vessel) disease, rubidium-82 PET-CT had a sensitivity of 92% (22 of 24 patients, 95% CI 74% to 99%), and 95% (19 of 20 patients, 95% CI 74% to 99%), respectively (Table 3). The overall sensitivity in this diagnostic population was equally high in men (90%, 27 of 30, 95% CI 73% to 98%) and women (100%, 14 of 14, 95% CI 77% to 100%). Likewise, stress rubidium-82 PET was also equally sensitive to detect obstructive CAD in obese (BMI ≥30 kg/m^2), (100%, 32 of 32 patients, 95% CI 84% to 100%), and nonobese individuals (87%, 32 of 32 patients, 95% CI 66% to 97%). Figures 1 and 2 are representative examples of normal and abnormal rubidium-82 myocardial perfusion PET-CT scans in obese women and men.

Stress PET correctly identified the absence of disease in 10 of 20 patients without significant angiographic CAD, and in all 38 low-likelihood patients (normalcy rate 100%, 95% CI 91% to 100%) (specificity 83%, 48 of 58 patients, 95% CI 71% to 91%).

ASSESSMENT OF ANATOMICAL CAD EXTENT. The exact agreement between stress rubidium-82 PET-CT and coronary angiography in assessing the anatomical extent of CAD (i.e., correctly identifying single-vessel or multivessel

Table 2	Detection of CAD by Cardiac PET-CT in 64 Patients Who Underwent Coronary Angiography		
	CAD by Angiography		
	No	**Yes**	**Total**
CAD by PET-CT			
No	10	3	13
Yes	10	41	51
Total	20	44	64

CAD = coronary artery disease; PET-CT = position emission tomography-computed tomography.

Table 3	Extent of CAD by Cardiac PET-CT in the 44 Patients With Significant Angiographic CAD		
	Number of Diseased Vessels by Angiography		
	1	**≥2**	**Total**
Number of diseased vascular territories by PET-CT			
0	2	1	3
1	17	8	25
≥2	5	11	16
Total	24	20	44

Abbreviations as in Table 2.

CAD [i.e., ≥2-vessel CAD]) was 64% (28 of 44) (Table 3). Of the 20 patients with multivessel disease by angiography, only 58% (11 of 20, 95% CI 32% to 77%) had concordant extent of disease on stress PET. Of the 9 discordant cases, 1 had no perfusion abnormalities on stress PET and the remainder had perfusion defects in only 1 vascular territory. Of the 24 patients with single-vessel disease by angiography, 68% (17 of 24, 95% CI 49% to 87%) had concordant extent of disease on stress PET; 5 of 7 discordant cases had stress perfusion defects extending into 2 vascular territories and 2 had normal myocardial perfusion.

OBSERVER AGREEMENT. Interobserver variability was determined in a separate subgroup of 20 patients. Both readers concordantly grouped 19 of 20 scans as normal or abnormal. Interobserver agreement for scan interpretation was found to be excellent (κ = 0.95) with regard to the overall diagnosis of CAD.

Discussion

We have evaluated the diagnostic performance of integrated rubidium-82 myocardial perfusion PET-CT imaging, in which the CT scan was used only for attenuation correction of the perfusion images, in the detection of obstructive atherosclerosis among patients with suspected CAD. The overall sensitivity for diagnosing obstructive CAD was 93% in overweight and obese individuals (mean BMI >30 kg/m^2), and it was equally high in men and women. Unlike previous reports on the diagnostic accuracy of PET (19,20), our study cohort was composed of only patients with suspected CAD. We excluded patients with prior MI, prior revascularization, or known CAD, whereas previous reports included patients with previous MI (range 13% to 75% of patients in those reports). Thus, our findings suggest an improvement in diagnostic accuracy with current PET-CT technology.

The diagnostic sensitivity of rubidium-82 myocardial perfusion PET-CT in patients with single-vessel disease (92%) was higher than that reported with conventional techniques (21). Further, the diagnostic sensitivity was equally high in obese and nonobese individuals (mean BMI >30 kg/m^2). The effective radiation dose from rubidium-82 myocardial perfusion PET-CT is comparable to that of
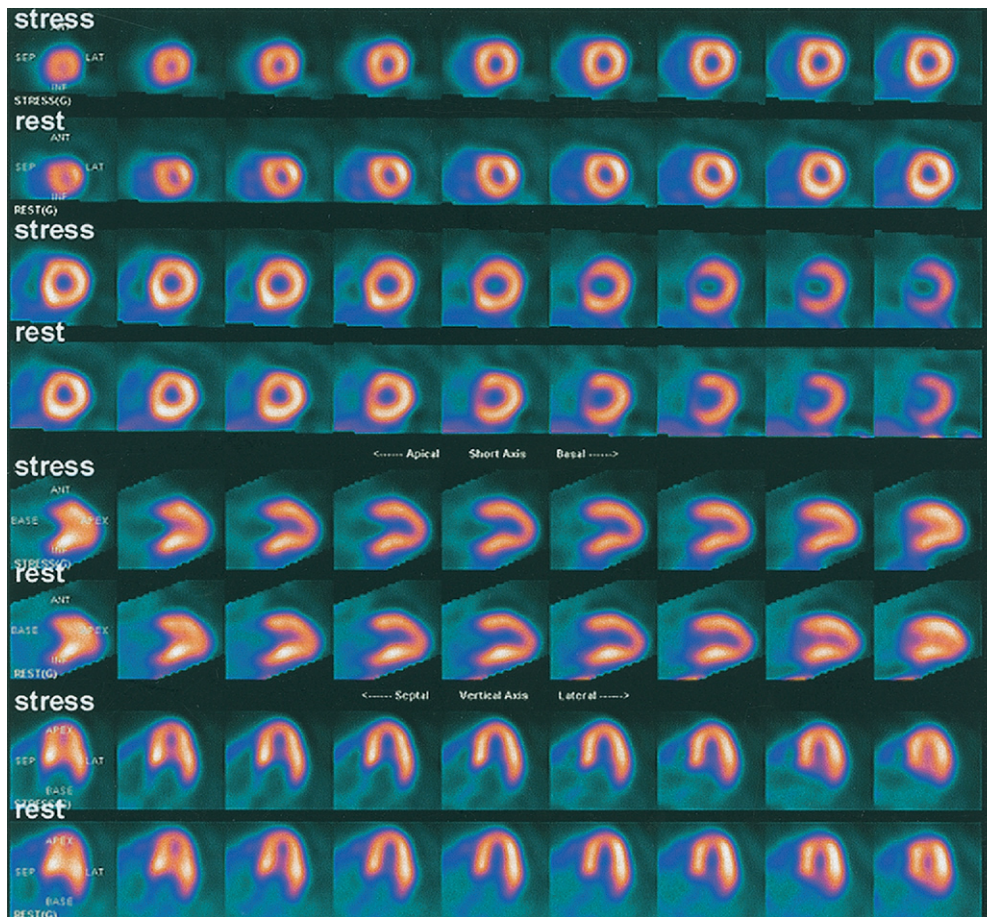
Figure 1   **Normal Rubidium-82 Myocardial Perfusion PET-CT Study**

Dipyridamole-stress and rest rubidium-82 positron emission tomography-computed tomography (PET-CT) images in corresponding short-axis **(top)**, vertical long-axis **(middle)**, and horizontal long-axis **(bottom)** slices in a 55-year-old woman with atypical chest pain (height 5′5″, weight 205 lbs, body mass index = 34). The short-axis slices represent progression from the apical **(left)** to the basal **(right)** part of the heart, and are oriented with the anterior wall on the top, the lateral wall to the right, the inferior wall at the bottom, and the interventricular septum to the left. The vertical long-axis slices represent progression from the septum **(left)** to the lateral **(right)** walls, and are oriented with the anterior wall on top, inferior wall at the bottom, and the left ventricular (LV) apex to the right. The horizontal long-axis slices represent progression from the inferior **(left)** to the anterior **(right)** walls, and are oriented with the septal wall on the left, lateral wall to the right, and the LV apex on the top. The images show normal myocardial perfusion throughout the LV and represent a normal scan.

[99m]technetium (Tc) SPECT and CT coronary angiography ([22]), and significantly lower than dual-isotope ([201]thallium/^{99m}Tc) SPECT ([22]). The overall sensitivity, specificity, and diagnostic accuracy of rubidium-82 myocardial perfusion PET-CT in the current study are comparable with that of CT coronary angiography, and higher than that reported with either stress SPECT or stress echocardiography ([21]). These results have important implications in light of the epidemic of obesity in the U.S., which now poses increased challenges to noninvasive diagnostic imaging ([23,24]).

Although stress PET had excellent diagnostic sensitivity for detecting patients with single or multivessel disease, its ability to delineate the anatomical extent of disease was somewhat limited. Only 11 of 20 patients (55%) with angiographic multivessel disease had concordant extent of disease on stress PET, whereas the remainder of patients had stress defects in

only 1 vascular territory. This suggests that as with SPECT, nonquantitative PET often uncovers only the 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 ([25,26]), thereby reducing the heterogeneity of flow between normal and abnormal zones and limiting the ability to delineate the presence of multivessel CAD. There is growing evidence showing that absolute quantification of coronary vasodilator reserve by PET can potentially overcome this limitation ([26,27]). However, quantitative measures of myocardial blood flow are not widely used clinically and were not performed in this study.

Of the 24 patients with angiographic single-vessel disease, 5 patients had perfusion defects in more than 1 vascular territory—a finding consistent with the notion of
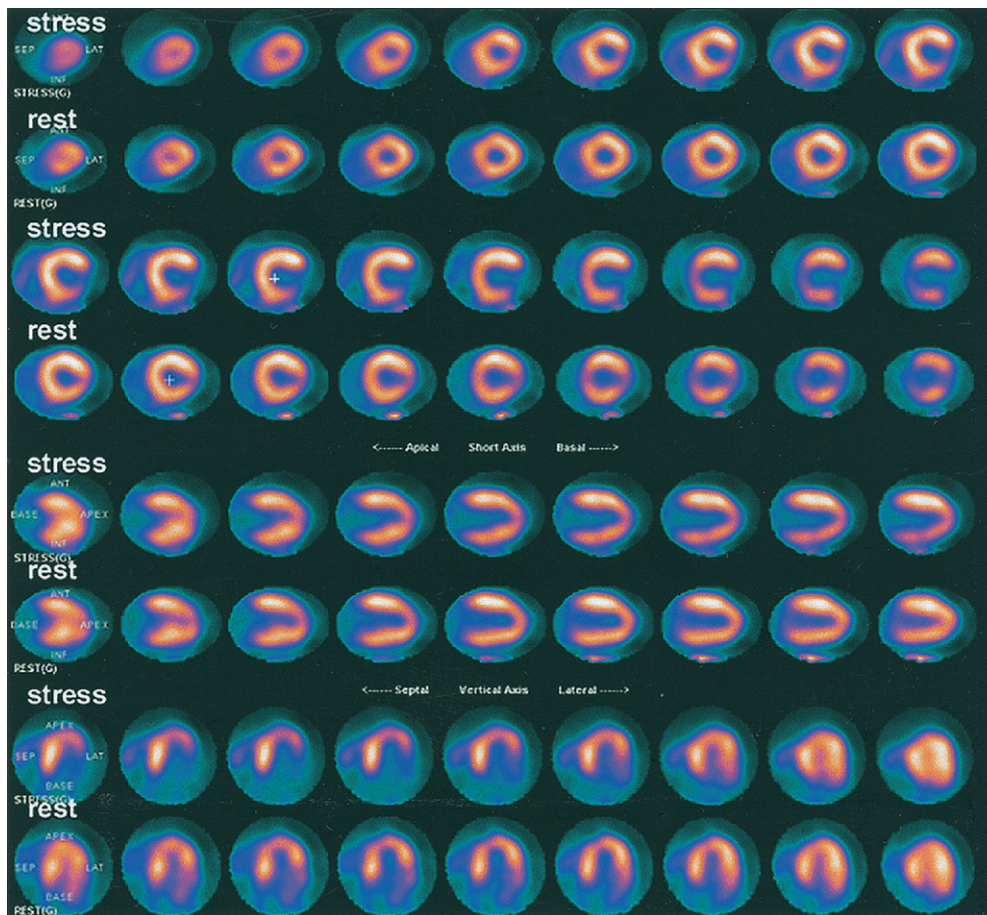
Figure 2   Abnormal Rubidium-82 Myocardial Perfusion PET-CT Study

Dipyridamole-stress and rest rubidium-82 PET-CT images in corresponding short-axis **(top)**, vertical long-axis **(middle)**, and horizontal long-axis **(bottom)** slices in a 62-year-old man with atypical chest pain (height 6'0", weight 235 lbs, body mass index = 31.9). The orientation is as in Figure 1. The images are abnormal and consistent with a moderately large area of severe ischemia in the lateral and inferolateral walls (left circumflex territory), and a small area of mild ischemia involving the apical LV segments and the apex (distal left anterior descending territory). Abbreviations as in Figure 1.

diffuse endothelial dysfunction (microvascular or macrovascular) in remote myocardium subtended by nondiseased vessels or noncritical coronary stenoses (i.e., <70%). This likely reflects the fact that patients with coronary risk factors, such as those in this study, show abnormal coronary vasodilator function that may manifest as a perfusion abnormality even in the absence of severe luminal narrowing in the epicardial coronary arteries (28).

In our calculation of specificity, we combined the PET results in the patients with no significant disease on angiography (i.e., <70%) and those in the group with a low likelihood of CAD because of the small number of patients without critical disease on angiography (17,18). The specificity of PET-CT in this study (83%) was comparable with that reported in previous studies using dedicated PET technology (86%) (19,20). The calculated specificity may be affected by several factors. First, most of our patients (>95%) with normal stress PET-CT results are not referred for coronary angiography, thereby introducing a potential

bias in the assessment of the true negative fraction (29). As in other studies, we also derived a normalcy rate as a proxy for true specificity based on a group of low-likelihood patients. The normalcy rate, reflecting the proportion of patients with a low likelihood for CAD with normal stress PET-CT study results, was 100%. This normalcy rate is consistent with preliminary results from our laboratory correlating myocardial perfusion PET with the results of CT coronary angiography using either 16- or 64-slice multidetector computed tomography scanners. Among 43 patients with angiographically normal coronary arteries based on CT coronary angiography, 39 had normal stress PET (91%) (30). Second, the calculation of specificity defines an artificial classification of anatomical CAD into a binary outcome (i.e., present or absent) rather than as a continuum spectrum of severity. It is possible that some patients with multiple risk factors may have shown true perfusion abnormalities reflecting vascular dysfunction that can be underestimated by conventional measures of stenosis

severity, and thus may have been misclassified as false-positive PET-CT studies. Indeed, studies of CAD regression show that improvements in endothelial function after statin therapy can lead to significant improvements in regional perfusion even in the absence of a change in the lumen diameter of a coronary stenosis (31). Despite our best efforts to exclude artifacts, however, it is also conceivable that potential misalignment between the CT transmission and emission data may have resulted in errors in attenuation correction, leading to artifacts and falsely positive studies.

Study limitations. This study has a relatively small sample size, and further confirmation of our results is necessary in larger patient groups. Future studies should also include quantitative measures of myocardial perfusion to test whether this approach can help improve the assessment of the anatomical extent of CAD. The severity of angiographic stenoses was assessed by expert visual analysis rather than by quantitative techniques. However, this analysis reflects current clinical practice and the way in which decisions regarding coronary revascularization are performed. As with other noninvasive modalities (21), the reported sensitivity and specificity estimates in this study may be distorted by referral bias. This is a common limitation of an angiography-based approach for defining the diagnostic accuracy of noninvasive testing (shared by all clinical modalities), in which the referral to cardiac catheterization is influenced by the amount of ischemia present on the study.

Conclusions

Myocardial perfusion PET-CT provides high sensitivity for the detection of CAD. The high diagnostic accuracy is applicable to both men and women, nonobese and obese patients, and to those with single-vessel as well as multivessel coronary disease. Rest and stress imaging is completed in approximately 25 min. Despite its high overall sensitivity, cardiac PET-CT may underestimate the anatomical extent of CAD in some patients with multivessel disease.

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