Cardiac Positron Emission Tomography/Computed Tomography Imaging Accurately Detects Anatomically and Functionally Significant Coronary Artery Disease

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Background—Computed tomography (CT) is increasingly used to detect coronary artery disease, but the evaluation of stenoses is often uncertain. Perfusion imaging has an established role in detecting ischemia and guiding therapy. Hybrid positron emission tomography (PET)/CT allows combination angiography and perfusion imaging in short, quantitative, low-radiation-dose protocols.

Methods and Results—We enrolled 107 patients with an intermediate (30% to 70%) pretest likelihood of coronary artery disease. All patients underwent PET/CT (quantitative PET with ^{15}O-water and CT angiography), and the results were compared with the gold standard, invasive angiography, including measurement of fractional flow reserve when appropriate. Although PET and CT angiography alone both demonstrated 97% negative predictive value, CT angiography alone was suboptimal in assessing the severity of stenosis (positive predictive value, 81%). Perfusion imaging alone could not always separate microvascular disease from epicardial stenoses, but hybrid PET/CT significantly improved this accuracy to 98%. The radiation dose of the combined PET and CT protocols was 9.3 mSv (86 patients) with prospective triggering and 21.8 mSv (21 patients) with spiral CT.

Conclusion—Cardiac hybrid PET/CT imaging allows accurate noninvasive detection of coronary artery disease in a symptomatic population. The method is feasible and can be performed routinely with <10 mSv in most patients.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00627172.

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Key Words: computed tomography ■ coronary disease ■ imaging ■ perfusion ■ positron emission tomography

Accurate noninvasive assessment of coronary artery disease (CAD) is challenging. Several imaging techniques such as single-photon emission tomography (SPECT), stress echocardiography, magnetic resonance imaging, and positron emission tomography (PET) have been used to detect myocardial ischemia.

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Computed tomography (CT) enables visualization of coronary stenoses. Meta-analyses show that CT can rule out the presence of CAD while positive predictive values (PPVs) are moderate.[1–3] Of the 2 multicenter trials published, 1 study was consistent with the results of meta-analyses,[4] and the other showed only mediocre negative predictive value (NPV) for CAD.[5]

Although CT is able to assess coronary artery lumen, there may be a discrepancy between anatomy and myocardial blood supply. The vasomotor tone and coronary collateral flow cannot be estimated because the degree of stenosis is only a weak descriptor of coronary resistance.[6] Therefore, only about half of the anatomically significant lesions detected with CT coronary angiography (CTA) are flow limiting. Meijboom et al[4] reported 49% accuracy of CTA in predicting reduced fractional flow reserve (FFR), whereas Gaemperli and colleagues[7] found that 50% of the lesions in CTA were associated with perfusion defects in SPECT. Functional assessment is needed, particularly in the evaluation of intermediate lesions,[8–10] and therapy for nonsignificant stenoses can be deferred.[11–14] The measurement of FFR during invasive coronary angiography (ICA) has been used as a gatekeeper for angioplasty.[11–14]

Although the use of FFR is likely to increase, its invasiveness and cost warrant noninvasive alternatives. Combined imaging of coronary anatomy and perfusion is possible with commonly available hybrid PET/CT scanners. With PET/CT, the location, severity, and composition of the plaques and

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Table 1. Patient Characteristics

Gender, M/F	64/43
Mean age (range), y	63.6±7.0 (49–80)
Weight (range), kg	77.9±17.8 (50–113)
BMI (range), kg/m^2	26.6±3.9 (18.4–39.1)
Risk factors for CAD, n positive (%)	
Family history	48 (45)
Diabetes mellitus	15 (14)
Impaired glucose tolerance	9 (8)
Hypertension	44 (41)
Hypercholesterolemia	54 (50)
Smoker or ex-smoker	28 (26)
Exercise test, n (%)	90 (84)
Medication, (%)	
Statins	54 (50)
β-blockers	64 (60)
Acetylsalicylic acid	78 (73)
Long-acting nitrates	10 (9)

n=107.

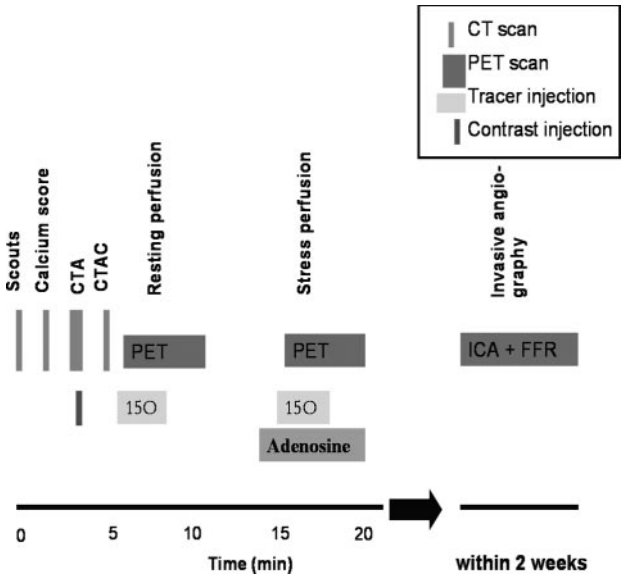

Figure 1. Imaging protocol. All imaging studies were performed within 2 weeks. CTAC indicates CT attenuation correction scan; 15O, oxygen-15–labeled water.

stenoses can be correlated with their significance.[6,8,9] Comprehensive noninvasive evaluation of CAD may be obtained in a single session, obviating the need for repeated visits. The unique characteristics of PET are the quantification of myocardial blood flow (MBF) in absolute terms and the low radiation dose[15] to the patients. In a meta-analysis, PET demonstrated 92% sensitivity and 85% specificity compared with invasive morphological imaging.[16] In another meta-analysis, the clinical value of PET perfusion imaging was higher than myocardial perfusion SPECT.[17] However, few data exist on PET/CT hybrid imaging for the assessment of CAD.

The aim of our study was to evaluate the accuracy of PET/CT imaging in the evaluation of CAD. This study was prospective and blinded, applied absolute quantification, enrolled only patients with moderate (30% to 70%) pretest likelihood of CAD, and used both ICA and FFR measurements. All patients entered ICA independently of noninvasive imaging results, and the treatment decisions were based on ICA and FFR. To the best of our knowledge, this is the first such study and provides unbiased data about the potential of hybrid imaging.

Methods

Patient Population

We prospectively enrolled 107 consecutive outpatients (64 men and 43 women) with a history of stable chest pain and 30% to 70% pretest likelihood of CAD after the analysis of risk factors and exercise tests.[18,19] Exclusion criteria were atrial fibrillation, iodine allergy, unstable angina, severe loss of renal function, second- or third-degree atrioventricular block, severe congestive heart failure (New York Heart Association class IV), symptomatic asthma, and pregnancy. Patients with angiographically proven CAD or previous myocardial infarction were not eligible. Patient characteristics are shown in Table 1.

The study was conducted according to the guidelines of Declaration of Helsinki, and the study protocol was approved by the ethics committee of the Hospital District of Southwest Finland. All patients gave their informed consent.

General Study Protocol

All patients underwent coronary CTA and myocardial PET perfusion imaging with the PET/CT hybrid scanner, followed by ICA within 2 weeks. No cardiac events took place during the interval. FFR measurements[20] were performed for stenoses >30% when feasible. However, some stenoses were not subjected to FFR because of logistics or the operator's clinical and visual assessments of complicated lesions. The decision for further therapy was based only on clinical information and ICA with FFR.

CT Imaging

The imaging protocol is demonstrated in Figure 1. All patients were scanned with a 64-row PET/CT scanner (GE Discovery VCT, General Electric Medical Systems, Waukesha, Wis). Intravenous metoprolol 0 to 30 mg was administered before the scan to reach a target heart rate of <60 bpm. Sublingual nitrate 800 μg was given before the scan.

Iodinated contrast infusion (60 to 80 mL of 400 mg iodine/mL iomeprol at 4 to 4.5 mL/s) was followed by a saline flush. The collimation was 64×0.625 mm, gantry rotation time was 350 ms,

Table 2. Results per Patient

		ICA+FFR	
CTA-PET hybrid (n=104)		+	−
	+	36	0
	−	2	66
CTA (n=107)		+	−
	+	38	9
	−	2	58
PET (n=104)		+	−
	+	36	6
	−	2	60

In CTA (107 patients) and hybrid imaging (104 patients), the left main artery, LAD, LCx, and RCA were assessed. In PET (104 patients), the LAD, LCx, and RCA were analyzed.

Table 3. Results per Vessel

		ICA+FFR	
CTA-PET Hybrid (n=416)		+	−
	+	71	3
	−	5	337
CTA (n=428)		+	−
	+	60	19
	−	20	329
PET (n=312)		+	−
	+	70	20
	−	4	218

tube current was 600 to 750 mA, and voltage was 100 to 120 kV, depending on patient size. To reduce radiation dose, prospectively triggered acquisition was applied whenever possible (86 of 107 patients). The technique has been described elsewhere in detail.[21] When the retrospectively gated mode was used (21 patients), ECG-based current modulation was used to decrease the radiation dose.

An experienced cardiologist (H.U.) and radiologist (S.K.) analyzed the vessels separately and then in consensus on an ADW 4.4 Workstation (General Electric, Piscataway, NJ) blinded to other results and clinical data using a standard 17-vessel segment system adapted from the original American Heart Association model.[22]

PET Imaging

Rest-stress perfusion cardiac PET was performed immediately after CT. ^{15}O-labeled water (900 to 1100 MBq) was injected (Radiowater Generator, Hidex Oy, Finland) at rest as an intravenous bolus over 15 seconds. A dynamic acquisition of the heart was performed (14×5 seconds, 3×10 seconds, 3×20 seconds, and 4×30 seconds), after which an adenosine-induced stress scan was performed. Adenosine was started 2 minutes before the start of the scan and was infused at 140 μg/kg body weight per minute. Images were quantitatively analyzed with Carimas software[23] by an experienced reader (M.M.) blinded to other results and clinical data. Both standard polar plots and parametric volume of the heart were produced, allowing image fusion with CTA with ADW 4.4 software (CardiIQFusion).

ICA and FFR

All coronary angiographies were performed on Siemens Axiom Artis coronary angiography system (Siemens, Erlangen, Germany). In the presence of intermediate stenoses, FFR measurement was performed with the ComboMap pressure/flow instrument and a 0.014-in BrightWire pressure guidewire (Volcano Corp, San Diego, Calif). The pressure was measured distally to the lesion during maximal hyperemia induced by 18-μg intracoronary boluses of adenosine with simultaneous measurement of aortic pressure through the catheter. FFR was calculated as the ratio between mean distal pressure and mean aortic pressure.[24,25]

Quantitative analysis of coronary angiograms (Quantcore, Siemens) was performed by an experienced reader (M.P.) blinded to other results. Seventeen standard segments were analyzed.

Interpretation of the Imaging Results

The analysis was performed on both a per-patient and a per-main-vessel basis. The 4 main vessels (left main artery, left anterior descending artery [LAD], left circumflex artery [LCx], and right coronary artery [RCA]) were assessed in CTA with stenoses ≥50% classified as significant. In PET, the 3 main vessel regions (LAD, LCx, and RCA) were analyzed. The quantitative values during stress were classified as follows: Absolute myocardial stress perfusion of <2.5 mL · g^{-1} · min^{-1} was considered abnormal.[23] In addition, a receiver-operating characteristic (ROC) curve was calculated to determine optimal cutoff points of MBF stress alone and the MBF from the regions with a stenosed vessel in the CTA. CT and PET images were fused to assign the stenoses to areas of myocardial perfusion. The results were interpreted as follows: (1) When both CTA and perfusion were normal, the vessel was normal; (2) when CTA detected a ≥50% stenosis causing abnormal perfusion, the vessel was significantly stenosed; (3) when CTA detected a ≥50% stenosis that was assigned to normal perfusion, the vessel was nonsignificantly stenosed; and (4) when CTA detected no significant stenosis but a vessel was assigned to abnormal perfusion, the vessel was nonsignificantly stenosed with the presence of microvascular disease. PET perfusion imaging was successfully performed in 104 of 107 patients; the remaining 3 had technical problems with tracer production. In ICA, luminal diameter narrowing ≥50% was considered significant. When FFR was available, stenoses with FFR >0.8 were classified as nonsignificant.[20]

Statistical Methods

Sensitivity, specificity, PPV, NPV, and accuracy were calculated for each imaging method (PET, CT, and PET/CT). An ROC analysis curve was used to reconfirm the best cutoff points of MBF stress in the current population. The McNemar test was performed to compare the accuracy of PET, CT, and PET/CT against the gold standard (ie, ICA with FFR). A value of $P<0.05$ was considered statistically significant. Statistical tests were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC).

Results

Forty-four patients of 107 (41%) had stenoses ≥50% in their coronary arteries in ICA. Significant lesions after invasive angiography and FFR were detected in 40 patients. In 18 of them, the lesions were either total occlusions or extremely tight (>90%) stenoses in which FFR was not possible. Four other patients had intermediate (30% to 70%) stenoses in which FFR could not be performed because of scheduling or technical reasons. In patients without FFR, quantitative coronary angiography ≥50% was considered positive, and the vessel was graded accordingly. Overall, 80 of 428 arteries were significantly stenosed by the combination of ICA and FFR. There were 67 patients with no significant CAD, 17 patients with single-vessel disease, and 23 patients with multivessel disease. The results are summarized in Tables 2 through 5 and Figures 2 and 3.

Table 4. Patients With Diffuse Perfusion Abnormalities but Nonstenotic Epicardial Coronary Arteries

Patient	Gender	Smoker	Body Mass Index, kg/m^2	Diabetes Mellitus	Family History of CAD	PET Stress MBF, mL · g^{-1} · min^{-1}	Agatston Score
P006	M	No	21.8	No	No	1.7–2.1	117
P010	M	Yes	33.1	No	Yes	1.2–2.3	6
P077	M	No	19.4	No	Yes	1.4–1.8	16
P079	F	No	19.1	No	Yes	1.6–2.0	0
P090	M	Yes	25.7	No	Yes	1.7–1.8	0

Table 5. Discrepant Findings Between Combined CTA and PET Against the Gold Standard in Vessel-Based Analyses

Patient	Vessel	CTA Stenosis, %	PET Stress MBF, mL · g^{-1} · min^{-1}	Invasive Stenosis (QCA), %	Suspected Explanation for Discrepancy
P020	LAD	50–69	3.1 (Normal)	55	Mid LAD intermediate stenosis, no successful FFR
P020	RCA	50–69	2.1 (Abnormal)	39	2 Stenoses distally in RCA, no FFR
P031	RCA	50–69	2.0 (Abnormal)	40	In CTA, severe calcifications and reduced flow; in ICA, intermediate stenosis in mid RCA, no FFR
P033	LAD	>70	3.0 (Normal)	50–60	Proximal and mid LAD intermediate stenoses, no successful FFR
P070	LAD	50–69	3.1 (Normal)	50	50% Stenosis was interpreted as significant, no FFR
P071	LM	<30	2–2.3 (Abnormal)	50	Severe triple-vessel disease with global reduction in perfusion, CTA did not note LM stenosis
P084	RCA	50–69	1.9 (Abnormal)	39	Distal RCA intermediate stenosis, no FFR
P094	LAD	30–49	3.2 (Normal)	61	No FFR of the LAD

QCA, quantitative coronary angiography; LM, left main artery.

CT Angiography

CTA alone had a PPV of 81%, an NPV of 97%, and an accuracy of 90% per patient; the corresponding numbers from the vessel analysis were 76%, 94%, and 91%. In most discrepant cases, CT overestimated stenosis. There were only 2 patients in whom CAD was missed, but in 10 additional patients, at least 1 significantly stenosed vessel was not detected. These lesions were evenly distributed into different coronary branches.

PET Perfusion Imaging

Perfusion at rest was normal in all patients. The stress perfusion in patient-based analysis had a PPV, an NPV, and an accuracy of 86%, 97%, and 92%, respectively. The corresponding values for vessel analysis were 78%, 98%, and 92%. Two patients had potentially false-negative PET perfusion results with ≥50% stenosis detected at ICA but FFR could not be performed. Six patients had false-positive PET perfusion, 5 of whom had diffusely reduced myocardial perfusion but no epicardial coronary disease (Table 4); in 1 patient a regional perfusion defect was incorrectly diagnosed. In vessel analysis, 4 other patients exhibited at least 1 perfusion abnormality in a region without significant epicardial disease.

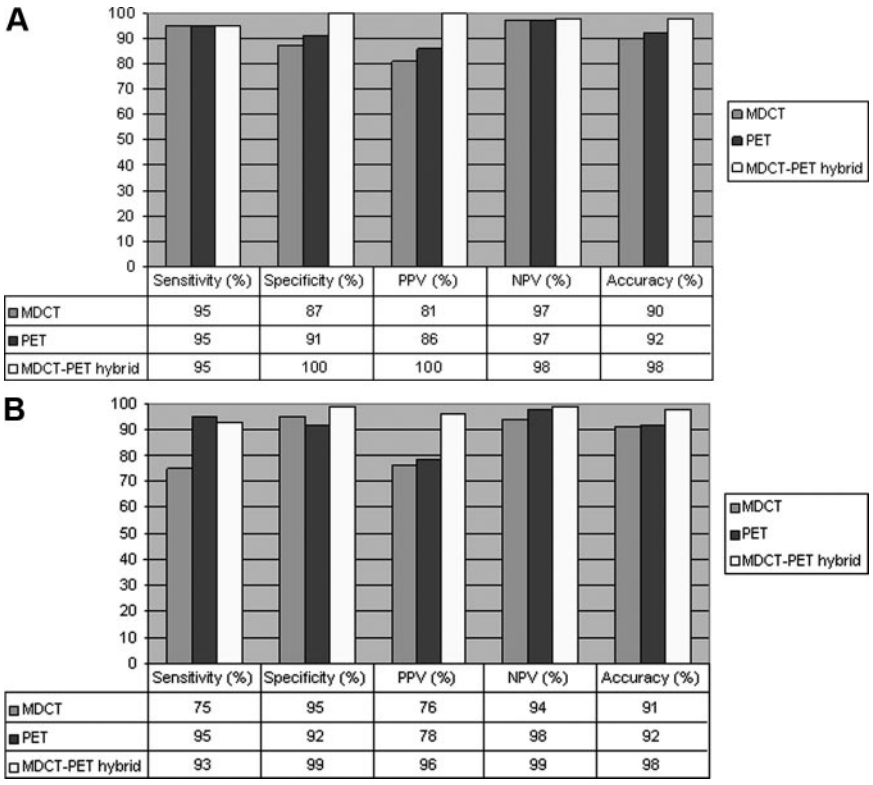

Figure 2. Sensitivity, specificity, PPV, NPV, and accuracy of stand-alone CT and PET and hybrid imaging against combined ICA and FFR. A, Analysis per patient. Hybrid imaging was more accurate than either CTA alone ($P=0.0039$) or PET alone ($P=0.014$). The difference between CTA and PET was not significant ($P=0.32$). B, Analysis per vessel. Hybrid imaging was more accurate than either CTA ($P<0.0001$) or PET ($P<0.0001$). The difference between CTA and PET was not significant ($P=0.08$).

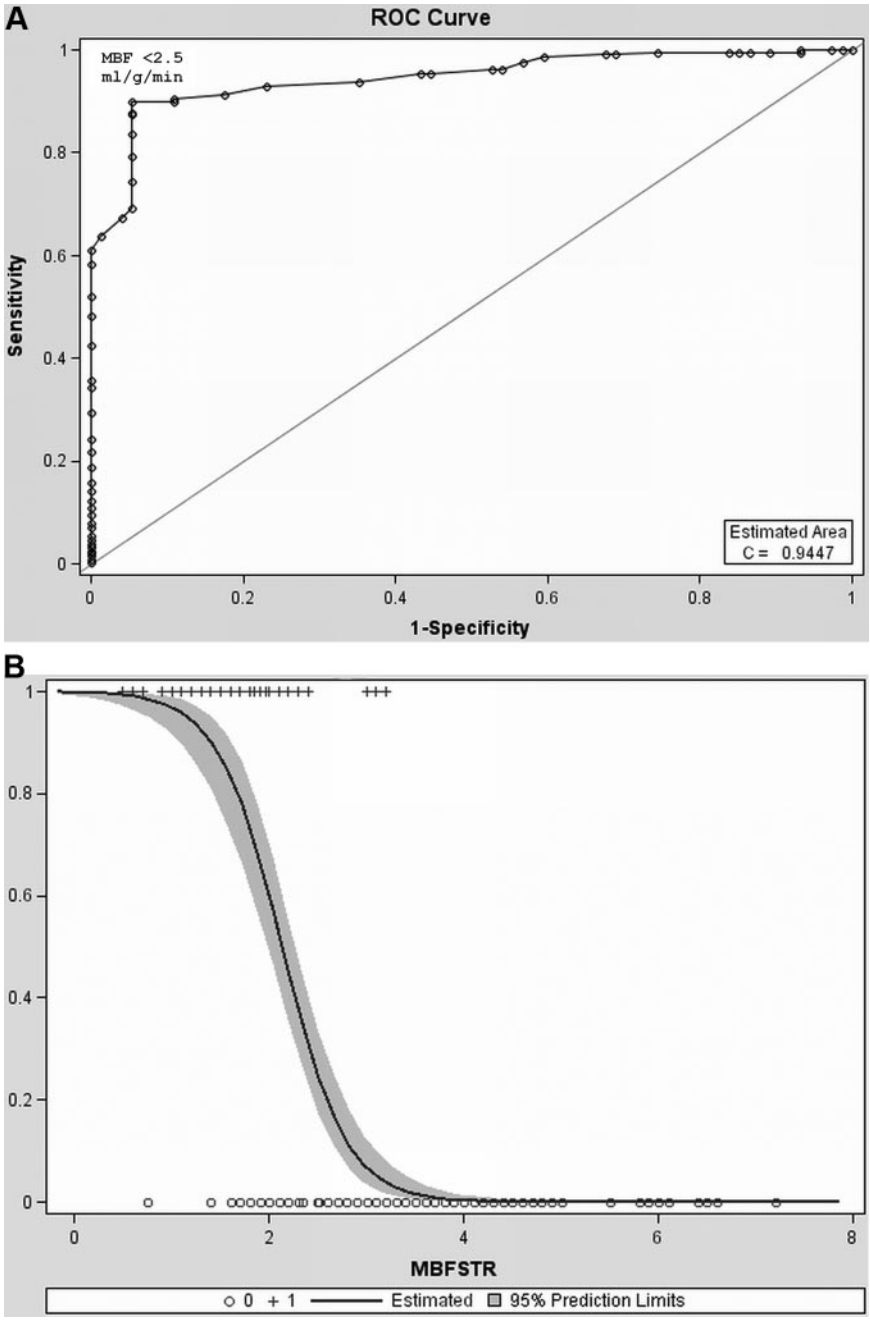

Figure 3. ROC analysis. A, ROC curve of vessel-based analysis of PET perfusion against the gold standard (ICA+FFR) with cutoff values. B, Estimated probability of significant CAD (*y* axis) based on gold standard (ICA+FFR) vs stress MBF in PET imaging (MBFSTR). B, Estimated probability of significant CAD.

Hybrid Imaging

Most patients with false-positive CT angiography had normal PET perfusion, thus correcting the diagnoses (see criteria above). On the other hand, 4 of 5 patients with false-positive PET findings had diffuse perfusion abnormalities but no epicardial disease in CT, the cases correctly identified in hybrid imaging. In 1 case, there was diffusely reduced perfusion with 1 stenosed vessel. Table 4 gives the characteristics of the 5 patients with suspected microvascular disease (ie, those with diffusely reduced perfusion without accompanying epicardial lesions). In addition, CTA vessel analysis helped to assign the perfusion zones of the LCx and the RCA because the dominant vessel is easily distinguished. In combined analysis, only 1 false-negative and no false-positives were diagnosed (Table 2). PPV, NPV, and accuracy were 100%, 97%, and 98%, respectively.

PPV, NPV, and accuracy of vessel analysis were 96%, 99%, and 98%, respectively. In 3 vessels with intermediate (30% to 70%) stenoses in CTA, hybrid imaging was abnormal but invasive tests supported nonsignificant lesions. In 5 other vessels, hybrid imaging suggested nonsignificant lesions but ICA showed ≥50% stenosis. All of these vessels, however, were classified according to ICA alone because of a lack of FFR. Table 5 summarizes the discrepant findings between hybrid imaging and the gold standard.

Hybrid imaging was more accurate per patient than CTA ($P=0.0039$) or PET alone ($P=0.014$) and was better in the vessel analysis ($P<0.0001$ and $P<0.0001$, correspondingly).

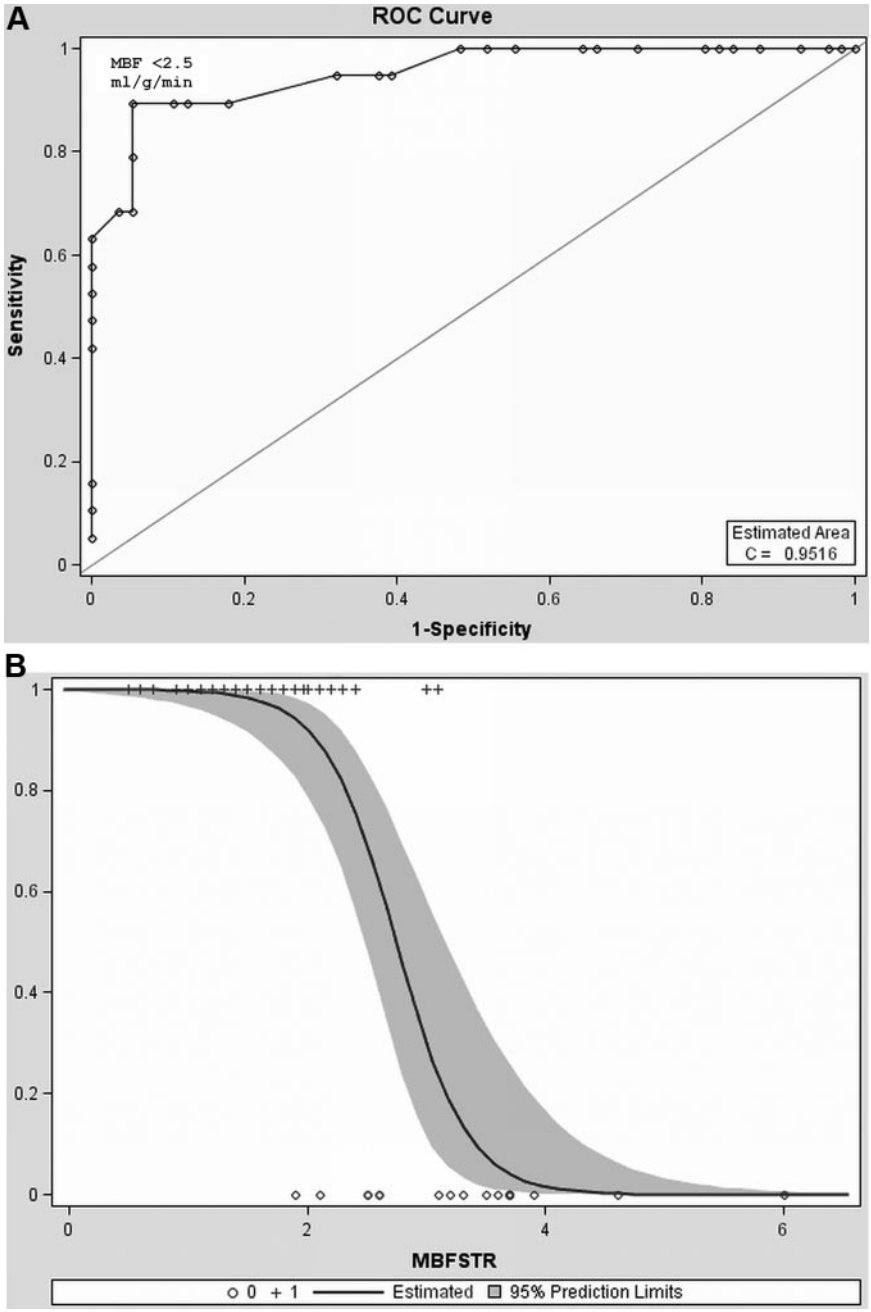

Figure 4. ROC analysis of myocardial regions with significant stenoses in corresponding vessels at CTA. A, ROC curve of PET perfusion against the gold standard (ICA+FFR) with cutoff values. B, Estimated probability of significant CAD (*y* axis) based on gold standard (ICA+FFR) vs stress MBF in PET imaging (MBFSTR). B, Estimated probability of significant CAD.

Figures 3 and 4 present ROC tables that are in agreement with our earlier cutoff values.[23] An MBF value of 2.5 $mL \cdot g \cdot^{-1} min^{-1}$ gives the best combination of sensitivity and specificity analyzed both with and without CTA information. The estimated probability of CAD based on ROC analysis (Figures 3B and 4B) demonstrated that practically all regions with MBF <2.0 $mL \cdot g \cdot^{-1} min^{-1}$ were abnormal.

An example of a case in which all anatomically significant lesions were proven functionally nonsignificant is demonstrated in Figure 5. Figure 6 presents a patient in whom functional imaging correctly detected the culprit lesion. Figure 7 displays a case with probable small-vessel disease.

Radiation Dose Analysis

The effective dose of the CT was calculated with a method proposed by the European Working Group for Guidelines on Quality Criteria in CT (EC99 1999). The average radiation dose of CTA was 7.6 mSv with prospective ECG triggering and 19.9 mSv with retrospective gating. ^{15}O-water dose from 2 injections of 1100 MBq results in 1.7 mSv.[15] The radiation dose of the hybrid PET/CT protocol was 9.3 mSv with prospective triggering and 21.8 mSv with spiral CT. The estimated radiation dose of ICA was ≈7 mSv.

Discussion

To the best of our knowledge, no large clinical study has previously provided a direct comparison between noninvasive and invasive imaging that combines anatomy and function. In this prospective study, we enrolled 107 symptomatic patients investigating a novel imaging technique, hybrid PET/CT, in the detection of CAD. This study has several

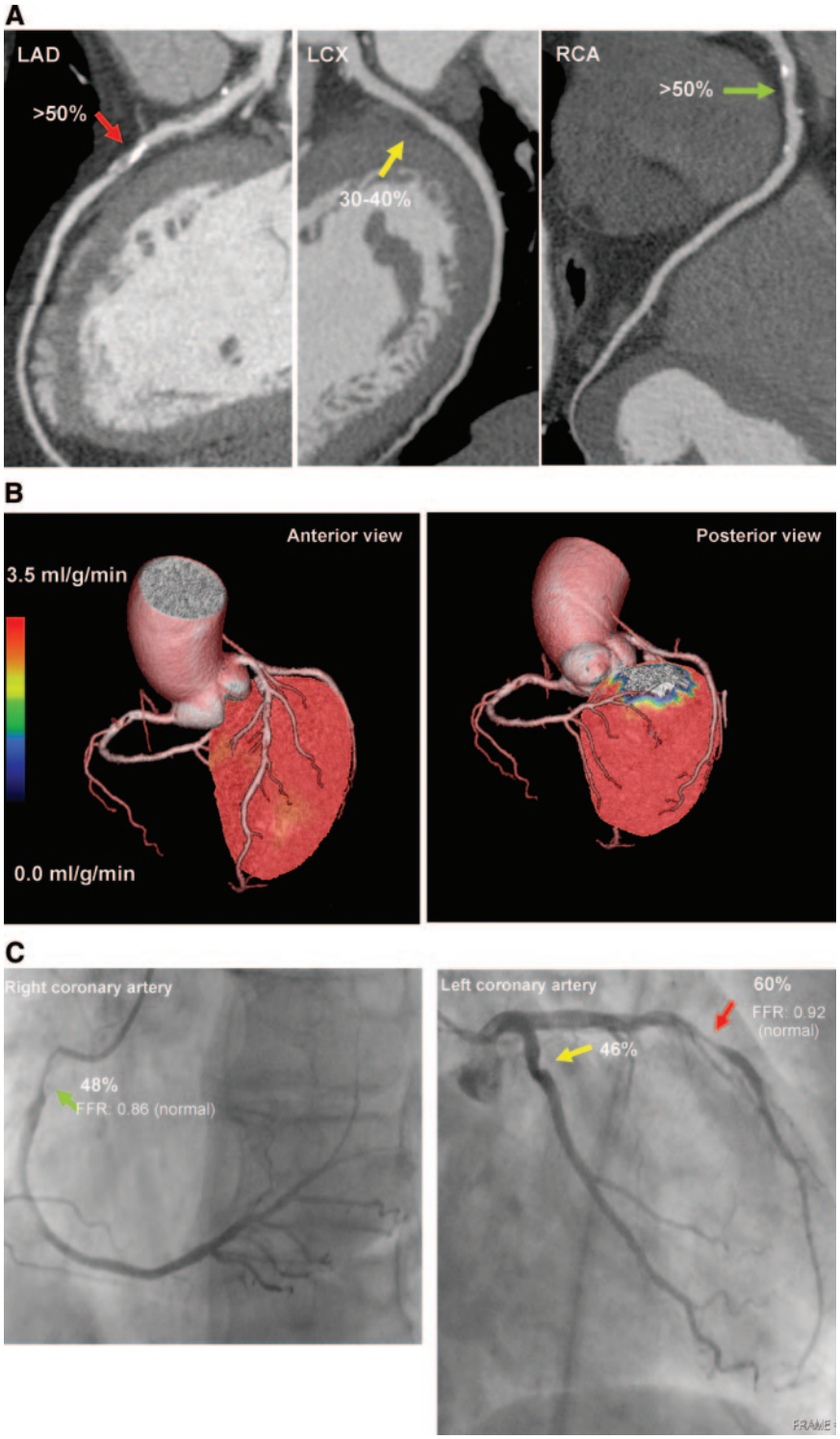

Figure 5. A 69-year-old man with attacks of atypical anginal pain. A, CT showed significant LAD and RCA stenoses with only mild stenosis in the LCx. B, Hybrid images with normal stress PET perfusion (absolute scale, 0 to 3.5 $mL \cdot g^{-1} \cdot min^{-1}$). Normal perfusion is >2.5 $mL \cdot g^{-1} \cdot min^{-1}$ (yellow or red). C, ICA with quantitative analysis and FFR. Despite anatomically significant narrowing of the LAD and borderline changes in the RCA, FFR was normal in both vessels, indicating functionally nonsignificant disease.

unique features. First, it is the first study to take full advantage of both CT angiography and PET perfusion imaging, was performed with a hybrid imaging device, and included quantitative analysis. Second, the patients had a moderate pretest likelihood of CAD (a clinically appropriate population). Third, to avoid referral bias, all patients entered invasive tests independently of the noninvasive imaging results. Finally, to avoid unfair comparison between anatomic and functional imaging, the combination of ICA and FFR was used as reference. Our results show that noninvasive hybrid PET/CT imaging is a superb diagnostic method for the comprehensive diagnosis of CAD and its severity and can be performed routinely with a short, low-radiation-dose protocol.

CTA can rule out significant CAD with an extremely high NPV (97% per patient and 94% per vessel). On the other hand, it is difficult to evaluate the degree of stenoses accurately. This problem has been demonstrated in many

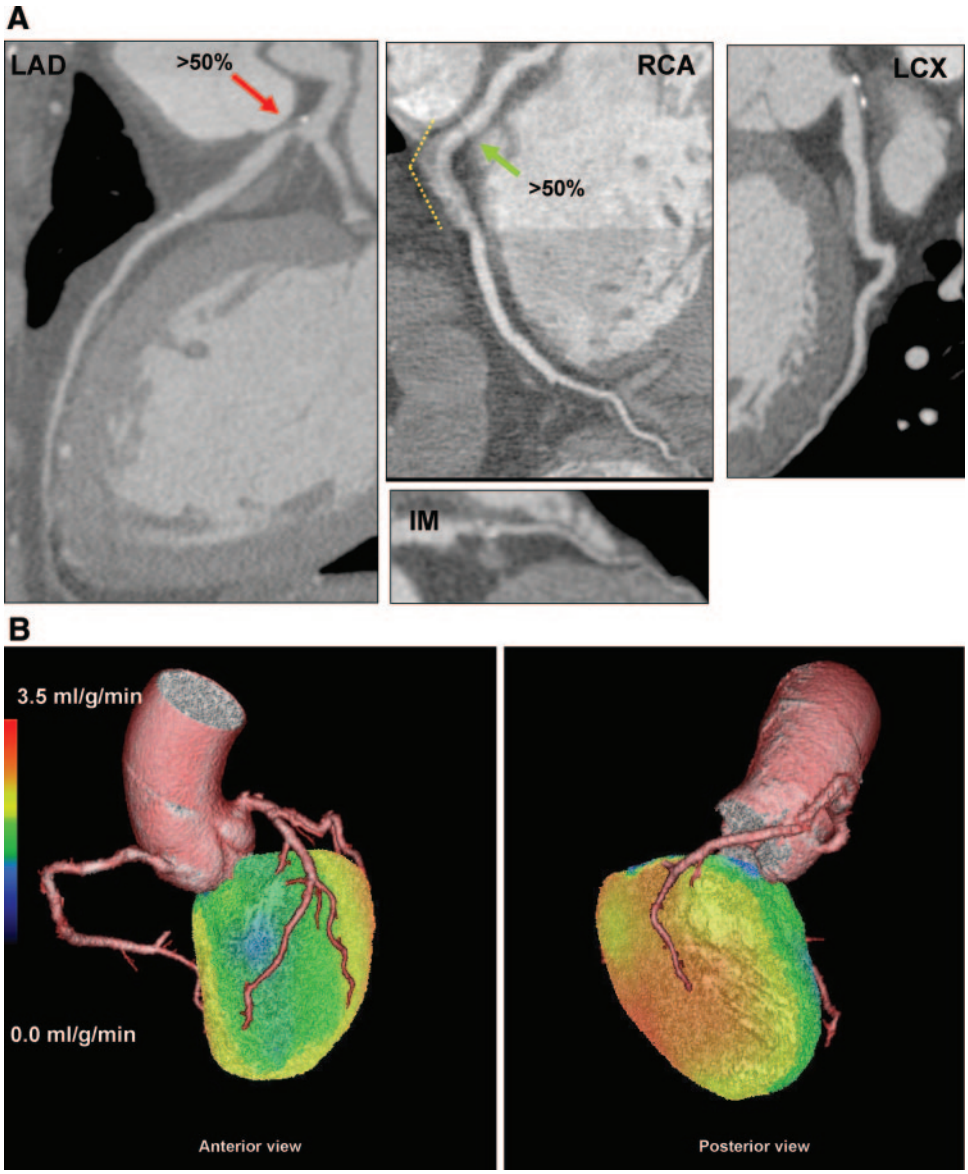

Figure 6. A 57-year-old man with atypical chest pain during exertion. A, CT reconstructions show significant stenoses in the LAD, RCA, and a small intermediate branch (IM). LCx was nonstenosed. Yellow dotted line denotes motion artifacts in the RCA. B, Hybrid volume-rendered image. Stress myocardial perfusion was reduced only in the area supplied by the LAD. C, ICA with quantitative analysis showed significant 73% luminal narrowing in the LAD. Other vessels were not stenosed.

studies and results in modest PPV compared with ICA. Second, even when the degree of anatomic changes is accurately detected, it is difficult to estimate the functional significance of borderline stenoses. This handicap is inherent in all anatomic imaging, including ICA.[13]

PET perfusion imaging also can rule out significant CAD with an extremely high NPV (97% per patient and 98% per vessel). Thus, normal perfusion means no hemodynamically compromising disease is present. Reduced perfusion, however, may mean not only significant epicardial disease but also the presence of microvascular abnormalities in coronary vasculature. These changes increase the risk for cardiac events and death[26] but are difficult to distinguish from epicardial disease by perfusion alone. Our results of PPV of 86% (78% per vessel) suggest that a considerable amount of small-vessel disease was present.

We used absolute quantification of perfusion, whereas the traditional clinical method is to identify relative inducible perfusion defects during stress. Although absolute quantification with PET has been well validated with various tracers,[23,27–29] it has rarely been used in clinical studies. Our ROC analysis shows that in stress, the optimal cutoff between normal and pathological MBF is <2.5 mL · g · $^{-1}$min^{-1}, confirming our previous findings.[23] Practically all regions with MBF <2.0 mL · g · $^{-1}$min^{-1} were abnormal, suggesting that MBF between 2.0 and 2.5 mL · g · $^{-1}$min^{-1} can be considered mildly abnormal and values <2.0 mL · g · $^{-1}$ min^{-1} clearly abnormal. These values are also consistent with earlier results obtained.[30] Quantification makes it possible to asses each myocardial region individually without relative changes in perfusion distribution and allows using only a single stress perfusion imaging in a population without

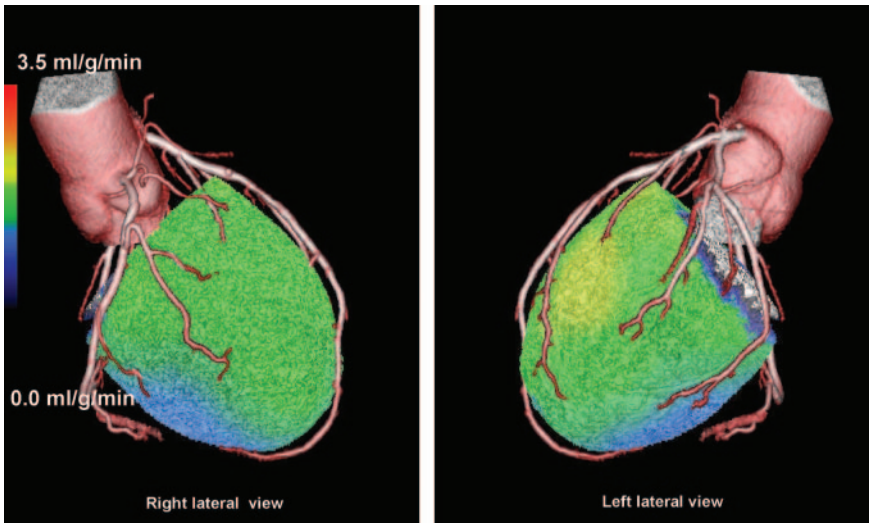

Figure 7. A 63-year-old man with positive family history. Good performance, atypical chest pain, and 2-mm ST depression in the ECG at the exercise test. In hybrid images, stress myocardial perfusion was reduced in most regions (green and blue). However, both CT and ICA showed normal coronary arteries, indicating possible microvascular disease.

previous cardiac events. This technique enables accurate detection of both unbalanced and balanced multivessel disease with reduced radiation dose and shorter protocol.

This study demonstrates the power of hybrid PET/CT imaging combining both anatomy and function. When myocardial perfusion is restricted, CT angiography can demonstrate the degree and location of stenosis and separate microvascular from epicardial disease. When CT angiography shows coronary plaques, possible perfusion deficits can be related to their epicardial locations. In our study, the accuracy of the hybrid technique was excellent (98% per patient and per vessel).

The primary limitation of this study is the lack of FFR measurements in some stenoses. This was due to the nature of some vessels and lesions but also to logistics in a busy invasive laboratory. These measurements could have potentially improved the results because most discrepant results were in the vessels with no successful FFR (Table 5). Although the agreement between hybrid imaging and combined ICA and FFR was very good, FFR has its limitations, too. In addition to the technical problems with complicated lesions, the catheter itself can cause some gradient increase at least in lesions with small luminal area. FFR was originally validated against SPECT perfusion imaging. Direct comparisons and validation of cutoff values in larger patient populations are scarce.

Another limitation is the relatively small population, and because of predefined characteristics of the patients, more than half of the patients did not have obstructive CAD. However, the latter can be also regarded as a strength because negative findings are as important as positive findings and must be detected. In particular, the avoidance of referral bias to invasive tests is critical for transferring the results to clinics. Further studies with larger populations are still warranted.

In the present study, we used ^{15}O-water as a perfusion tracer. This tracer is not widely available because it requires an onsite cyclotron. However, other validated tracers such as ^{13}N-ammonia[31] and ^{82}Rb[32–34] or novel ^{18}F-labeled tracers should provide comparable results if proper protocols and quantification are applied. In the recent study by El Fakhri et al,[34] MBF obtained with ^{82}Rb was comparable to that of ^{13}N-ammonia with a slight tendency to underestimate MBF during stress. ^{82}Rb can easily be distributed to clinical sites without a tracer production laboratory, which may facilitate wider distribution of the technique into clinical practice.

In the present protocol, we performed CTA before PET because in the future we aim to avoid perfusion imaging completely when CTA is normal. Another reason for the "CT first" approach is its ability to detect and characterize plaques even when they are not flow limiting. It is important to assess these changes to warrant suitable medication. Although we did not perform a cost-benefit analysis, it is likely that such a protocol is efficient because the cost of a CTA examination is lower than that of a PET study, and about half of the patients undergoing CTA will not require perfusion imaging in an appropriate population. β-Blockers were used in most patients before imaging. Theoretically, this could reduce the sensitivity of perfusion imaging, which seems, however, not to be a problem because the sensitivity of PET was excellent.

Combining 2 techniques that use radiation will obviously increase the radiation dose. However, novel CT techniques reduce the radiation strikingly,[21] and we applied one such technique to the majority of patients. The dose from PET is only a fraction of the dose in SPECT and can be further reduced by performing stress imaging only. Therefore, our hybrid protocol, whenever prospective ECG triggering was used, caused only modest radiation doses, clearly lower than, for example, in a recent study with CTA only.[6] ^{13}N-ammonia and ^{82}Rb can be used in a similar low-dose CT protocol.[35] If one chooses a "PET first" protocol and performs CT only in those patients with impaired MBF, total radiation dose may be further lowered.

Conclusions

We tested the performance of cardiac PET/CT hybrid imaging in symptomatic patients with 30% to 70% pretest probability of CAD. All patients entered invasive measurements independently of noninvasive imaging results. Although both stand-alone PET and CT provided excellent exclusion of

CAD, false-positive findings were not uncommon. Using hybrid imaging and thus by combining anatomic and functional information, we greatly improved the accuracy. The hybrid method was clinically feasible and can be performed with <10-mSv radiation dose in most patients.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Accurate noninvasive assessment of coronary artery disease is a challenging task. In a cohort of 107 patients at intermediate clinical risk, we measured the power of hybrid positron emission tomography and computed tomography coronary angiography against invasive coronary angiography with fractional flow reserve for the detection of obstructive coronary artery disease. Although both computed tomography angiography and positron emission tomography individually were able to rule out significant coronary artery disease (negative predictive value, 97%), both approaches showed only modest positive predictive value. Positron emission tomography perfusion imaging alone could not always separate microvascular dysfunction from epicardial stenoses, whereas computed tomography angiography was limited in defining the physiological significance of anatomic stenosis. Hybrid positron emission tomography/computed tomography significantly improved this accuracy to 98%. This was achieved with a rapid 30-minute imaging protocol with a reasonable radiation dose (<10 mSv) to the patient. These data suggest that hybrid positron emission tomography/computed tomography imaging of the heart is a feasible, accurate method to assess coronary artery disease noninvasively in a symptomatic, moderate-risk patient population.

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