JACC: CARDIOVASCULAR IMAGING VOL. 1, NO. 2, 2008

ISSN 1936-878X/08/$34.00
PUBLISHED BY ELSEVIER INC. DOI:10.1016/j.jcmg.2007.12.003

Invasive Versus Noninvasive Evaluation of Coronary Artery Disease

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OBJECTIVES We sought to compare the diagnostic information obtained from noninvasive characterization of coronary artery disease by using multidetector computed tomography (MDCT) and myocardial perfusion imaging (MPI) and to compare findings with the use of invasive coronary angiography and intravascular ultrasound (IVUS).

BACKGROUND Preliminary comparisons have suggested that abnormal myocardial perfusion studies correlate well with significant luminal stenosis on MDCT coronary angiography. However, atherosclerotic coronary lesions may be detectable with the use of MDCT even in the presence of normal myocardial perfusion

METHODS We performed MDCT, MPI, and conventional coronary angiography in 70 patients. In addition, IVUS was performed in 53 patients. Quantitative information was obtained from quantitative coronary angiography (QCA) and IVUS assessment of plaque burden and minimal luminal area.

RESULTS Of 26 patients with an abnormal MPI study, 23 (88%) showed significant stenosis on MDCT. As compared with QCA, MDCT showed a sensitivity of 96% and specificity of 67% for the detection of stenoses ≥50% diameter narrowing in these patients. Mean diameter stenosis on QCA was 76% and mean minimal lumen area in IVUS was 3.3 mm^2. On the other hand, 27 (84%) of 44 patients with normal MPI had evidence of coronary atherosclerosis on MDCT (luminal stenosis ≥50%: n = 15, luminal stenosis <50%: n = 12, sensitivity of 100% and specificity of 83% as compared with QCA). Using IVUS, we found substantial plaque burden (mean 58.9 ± 18.1% of cross-sectional area), but presence of a stenosis (minimal lumen area <4.0 mm^2) in only 14 patients (mean minimal lumen area, 5.8 ± 3.3 mm^2). Only 7 patients with normal myocardial perfusion scans demonstrated absence of coronary atherosclerosis by MDCT.

CONCLUSIONS Considerable plaque burden can be observed with MDCT even in the absence of myocardial perfusion abnormalities. This finding does not constitute a false-positive MDCT result, but rather reflects the fact that MDCT can detect atherosclerotic lesions that are not flow-limiting. (J Am Coll Cardiol Img 2008;1:190–9) © 2008 by the American College of Cardiology Foundation

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Manuscript received December 3, 2007; accepted December 16, 2007.

Traditionally, the evaluation and management of patients with suspected coronary artery disease (CAD) has been based on the noninvasive detection of ischemia followed by the use of invasive coronary angiography to confirm the presence of luminal stenosis. Generally, a very good correlation between the stress myocardial perfusion or echo studies and quantitative angiography is found. However, it is well established that acute coronary events usually result from voluminous atherosclerotic lesions but may not be associated with significant luminal obstruction. Intravascular ultrasound (IVUS) studies have demonstrated that even significant atherosclerosis burden may not always result in luminal obstruction and may be frequently associated with normal myocardial perfusion (1,2). The recent introduction of 64-slice multidetector computed tomography (MDCT) has allowed the opportunity to noninvasively characterize the atherosclerotic lesions and define luminal and vessel wall alterations alike. The technique has been demonstrated to have a high diagnostic accuracy as compared with invasive coronary angiography (3). It is conceivable that the majority of patients with abnormal myocardial perfusion imaging (MPI) also will show high-grade stenoses on MDCT. In addition, MDCT should allow recognition of plaque burden in patients with normal perfusion (4,5). These patients with normal perfusion may only show minimal changes on invasive coronary angiography despite definitive atherosclerotic disease. Accordingly, the purpose of the present study was to compare the diagnostic information obtained from noninvasive characterization of CAD by MDCT and MPI and to compare findings with invasive coronary angiography and IVUS.

METHODS

Patients and study protocol. The study group consisted of symptomatic patients who presented to the outpatient clinic (Leiden, the Netherlands, and Aalst, Belgium) for the evaluation of chest pain. Noninvasive imaging with the use of gated single-photon emission computed tomography (SPECT) and MDCT was performed and, on the basis of clinical presentation and/or imaging results, 70 of these patients were referred for invasive coronary angiography in combination with IVUS and enrolled in the present study. Exclusion criteria were contraindications to MDCT (6) and the presence of unstable angina, heart failure, myocardial infarction, or revascularization between the imaging procedures. Data of 15 patients have been previously reported in a study comparing MDCT and MPI (5). The study protocol was approved by the institutional ethics committee, and informed consent was obtained in all patients.

Clinical characteristics of the study population are presented in Table 1. Of the 70 patients (mean age 62 ± 11 years) included in the study, 46 (66%) were men. Diagnosis of CAD was established in 5 (7%) and suspected in the remaining 65 (93%) patients. Of the patients with known CAD, 4 had previous percutaneous coronary intervention (with stent placement in 2 patients), whereas 1 patient had previous coronary artery bypass grafting. In the latter patients, 2 bypassed (grafted) coronary vascular territories were excluded from analysis. In all patients, MPI, MDCT, and conventional coronary angiography (with quantitative coronary angiography [QCA]) were performed. In 53 patients, additional vascular imaging with IVUS was performed in a total of 109 coronary arteries. In the remaining 17 patients, IVUS imaging was not possible because of the presence of left main stenoses, severe coronary stenosis, or total occlusion (n = 10) and technical problems or time constraints during conventional coronary angiography (n = 7).

MDCT coronary angiography. We performed MDCT coronary angiography with either an Aquilion 64 (Toshiba Medical Systems, Tokyo, Japan) or a Sensation 64 (Siemens, Munich, Germany). First, a prospective coronary calcium scan was performed before MDCT angiography with a collimation 4 × 3.0 mm, gantry rotation time 500 ms, the tube voltage 120 kV, and tube current 200 mA. The temporal window was set at 75% after the R-wave for electrocardiographically triggered prospective reconstruction. For the contrast-enhanced scan, collimation was either 64 × 0.5 mm or 64 × 0.6 mm, respectively. The tube current was 300 mA, at 120 kV. Nonionic contrast material was administered in the antecubital vein with an amount of 80 to 110 ml for 64-slice MDCT, depending on the total scan time, and a flow rate of 5 ml/s (Iomeron 400, Bracco, Milan, Italy), followed by a saline flush. Subsequently, data sets were reconstructed and transferred to a remote workstation as previously described (6). Coronary calcium score was derived with the use of dedicated software. Coronary calcium was identified as a dense area in the coronary artery exceeding the

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
EEM = external elastic membrane
IVUS = intravascular ultrasound
MDCT = multidetector computed tomography
MLA = minimal lumen area
MPI = myocardial perfusion imaging
QCA = quantitative coronary angiography
RI = remodeling index
SPECT = single-photon emission computed tomography

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Table 1. Clinical Characteristics of the Study Population (n = 70)

Gender, M/F	46/24
Age, yrs	62 ± 11
Risk factors for CAD	
Diabetes mellitus	21 (30%)
Hypertension	46 (66%)
Hypercholesterolemia	35 (50%)
Positive family history	27 (39%)
Current smoking	25 (36%)
Obese (BMI ≥30 kg/m^2)	14 (20%)
Average BMI (30 kg/m^2)	27 ± 4
Previous CAD	
Previous myocardial infarction	5 (7%)
Anterior/inferior	4/1
Previous PCI	4 (6%)
Agatston calcium score	435 ± 789
Heart rate (beats/min) during MDCT	63 ± 9
LVEF on gated SPECT	58 ± 14%
No. of significantly stenosed vessels on conventional coronary angiography	
0	32 (46%)
1	17 (24%)
2	13 (19%)
3	8 (11%)

BMI = body mass index; CAD = coronary artery disease; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; MDCT = multidetector computed tomography; SPECT = single-photon emission computed tomography.

threshold of 130 HU. The global Agatston score as well as per coronary artery was recorded for each patient.

The MDCT angiographic examinations were evaluated in consensus by 2 experienced readers, including an interventional cardiologist who was blinded to the SPECT data for the presence of atherosclerosis. Coronary arteries were divided into 17 segments according to the modified American Heart Association classification (7). Each segment was evaluated for the presence of any atherosclerotic plaque with the use of axial images and curved multiplanar reconstructions. Coronary plaques were defined as structures >1 mm^2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue, as previously described (8). To describe the degree of stenosis, abnormal segments were further classified as showing: 1) nonobstructive disease (<50% luminal narrowing); 2) borderline stenosis (50% to 70% luminal narrowing); or 3) severe stenosis, showing ≥70% luminal narrowing. To describe the extent of disease on MDCT, for each patient and vessel, the number of segments showing disease as well as significant (≥50% luminal narrowing) was determined. Data were recorded on a patient and vessel basis and, in the vessel-based analysis, the left main coronary artery was considered part of the left anterior descending coronary artery.

Myocardial perfusion imaging. In all patients, stress MPI (with either technetium-99m tetrofosmin or technetium-99m sestamibi) was performed with symptom-limited bicycle exercise or pharmacological (dipyridamole, adenosine, or dobutamine) stress (9). Data were acquired with either a dual-head SPECT camera (Vertex Epic ADAC Pegasus, Philips Medical Systems, Eindhoven, the Netherlands) or a triple-head SPECT camera (GCA 9300/HG, Toshiba Corp., Tokyo, Japan) followed by reconstruction into long- and short-axis projections perpendicular to the heart axis; data were presented in polar map format (normalized to 100%), and a 17-segment model was used in which myocardial segments were allocated to the territories of the different coronary arteries as previously described (10,11). Perfusion defects were identified on the stress images (segmental tracer activity <75% of maximum) and divided into ischemia (reversible defects, with ≥10% increase in tracer uptake on the resting images) or scar tissue (irreversible defects) (5). Accordingly, examinations were classified as being either normal or abnormal, the latter being further divided in those demonstrating reversible defects and those demonstrating irreversible defects. We used the gated images to assess regional wall motion to improve differentiation between perfusion abnormalities and attenuation artifacts (12). The left ventricular ejection fraction was derived from the gated SPECT data using previously validated and automated software (quantitative gated SPECT [QGS], Cedars-Sinai Medical Center, Los Angeles, California); gating was only performed at rest.

Conventional coronary angiography. Conventional coronary angiography was performed according to standard clinical protocols. We performed QCA using QCA-CMS 6.0 (Medis, Leiden, the Netherlands). For each coronary artery, the most severe stenosis was identified. The tip of the catheter was used for calibration and, after automated vessel contour detection with manual correction if needed, percentage diameter stenosis was calculated.

IVUS. We performed IVUS imaging with 2.9-F 20-MHz catheters (Eagle Eye, Volcano, Brussels, Belgium). After intracoronary administration of nitrates, the IVUS catheter was advanced to the distal portion of coronary artery under fluoroscopic

guidance. Using automated pullback device, the transducer was withdrawn at a continuous speed of 0.5 mm/s up to the coronary ostium. Cine runs before and during contrast injection were performed to confirm the position of the IVUS transducer before IVUS evaluation was started. All data were stored digitally and were analyzed off-line with the use of QCU-CMS 4.0 (Medis). After motion correction had been applied, coronary arteries were divided into segments according to the modified American Heart Association classification (7) using coronary ostia and side branches as landmarks. In each coronary segment, the frame with the most severe cross-sectional area of narrowing was selected for analysis. In addition, proximal and distal reference sites that had the largest lumen area by IVUS in the proximal and distal portion of the vessel segment in the 10 mm adjacent (but before any side branch) to the lesion site were selected. Subsequently, lumen and external elastic membrane (EEM) contours were manually traced to determine lumen area and EEM area at the lesion site and proximal and distal reference site. EEM area was defined as the area that was circumscribed by the border between the hypoechoic media zone and the surrounding echocardiographically bright adventitia. Plaque plus media area was calculated as the difference between the EEM and the lumen area. Based on these parameters, minimal lumen area (MLA), lesion plaque area, lesion plaque burden, lumen area stenosis, lumen diameter stenosis, and corrected lumen area stenosis were calculated per coronary segment as previously described (1,2). In brief, lesion plaque burden was defined as plaque plus media area divided by the EEM area, resulting in the lesion percentage area stenosis due to plaque. Lumen area stenosis was calculated by subtracting the lumen area at the lesion site from the lumen area at the reference site and subsequently dividing by the lumen area at the reference site.

In addition, vascular remodeling was determined. The number of lesions with positive remodeling was determined by calculating the remodeling index (RI) by dividing the lesion EEM area by the average of the proximal and distal reference EEM area. Subsequently, positive remodeling was defined as a RI $\geq$1.0, whereas RI $<$1.0 was classified as negative remodeling (13).

Statistical analysis. Data were analyzed on a per-patient and per-vessel basis and, for the corresponding calculations, the coronary artery and coronary segment showing the most severe stenosis on either QCA or IVUS were used, respectively. Continuous variables were described by mean ± SD. Comparisons between patient groups were performed using the independent samples *t*-test for continuous variables. The chi-square test with Yates' correction as appropriate or Fisher exact test (2-sided) for sparse data were used for comparison of categorical variables. When not normally distributed (coronary calcium score), continuous variables were compared using the nonparametric 2-tailed Mann-Whitney *U* test. A p value $<$0.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 12.0.1., SPSS Inc., Chicago, Illinois).

Table 2. Angiographic Characteristics (MDCT and QCA) for Patients With Abnormal and Normal Perfusion, Respectively (Patient-Based Analysis)

	MPI Abnormal (n = 26 Patients)	MPI Normal (n = 44 Patients)	p Value
Calcium score	751 ± 1,143	255 ± 415	<0.01
MDCT			
Normal	0	7 (16%)	
Abnormal	26 (100%)	37 (84%)	0.041
Nonobstructive stenosis	3 (12%)	22 (59%)	
Borderline stenosis	9 (35%)	12 (32%)	
Severe stenosis	14 (54%)	3 (8%)	<0.01
Number of diseased segments	6.4 ± 3.1	5.0 ± 3.0	0.080
Number of segments with >50% stenosis	2.5 ± 2.5	0.61 ± 1.2	<0.01
QCA	75.9 ± 19.2%	26.7 ± 17.7%	<0.01

MDCT = multidetector computed tomography; MPI = myocardial perfusion imaging; QCA = quantitative coronary angiography.

RESULTS

Comparison of MDCT with MPI and invasive angiography. The results of the analysis on a patient basis (n = 70) are presented in Table 2 and Figure 1. Abnormal perfusion on SPECT was noted in 26 (37%) patients. The abnormal perfusion was associated with an average coronary calcium score of 751 ± 1,143. Calcium scores ≥400 were observed in 11 (42%) patients. Using MDCT coronary angiography, we found atherosclerosis in all 26 patients; severe stenosis was observed in 14 patients, 9 patients revealed borderline stenosis, and the remaining 3 patients presented with nonobstructive disease. The average number of diseased segments was 6.4 ± 3.1, whereas the average number of significantly stenosed segments was 2.5 ± 2.5 per patient. Considering the most severe stenosis per patient on conventional angiography, QCA showed an average percentage stenosis of 75.9 ± 19.2% with 23 patients showing significant stenosis (≥50% luminal narrowing). When validating

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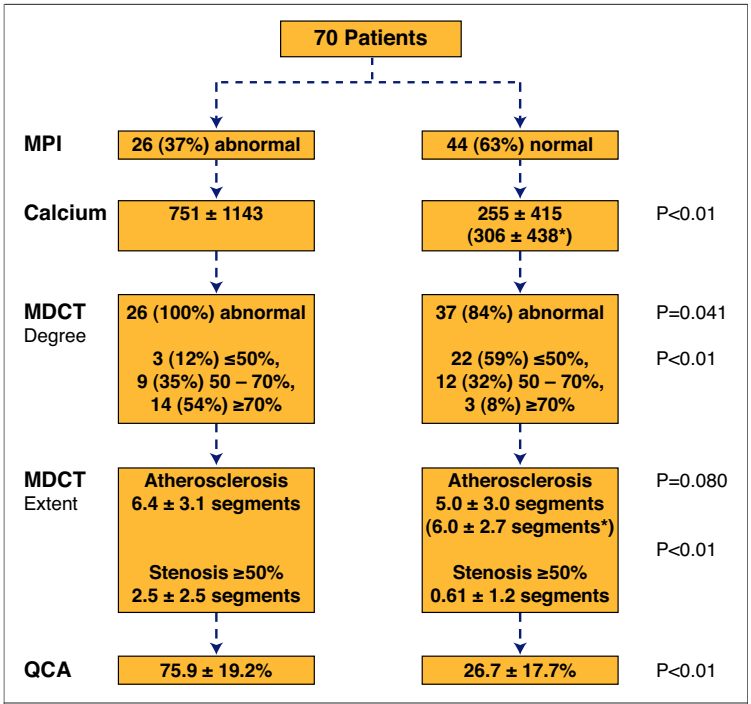

Figure 1. MDCT and QCA Findings in 70 Patients With Abnormal and Normal MPI Results, Respectively

Note the discrepancy between the imaging modalities in patients with normal myocardial perfusion imaging (MPI). In most of these patients, multidetector computed tomography (MDCT) was abnormal, with no significant difference in the number of segments with atherosclerosis either (as compared with patients with abnormal perfusion. However, number of significantly stenosed segments was significantly lower in patients with normal MPI, as also reflected by minimal luminal narrowing on quantitative coronary angiography (QCA). *Average in patients with atherosclerosis on MDCT.

MDCT results against QCA, the sensitivity of MDCT to detect coronary artery stenoses ≥50% luminal narrowing was 96% (22 of 23) and specificity was 67% (2 of 3).

Table 3. Angiographic Characteristics (MDCT and QCA) of Coronary Arteries With Abnormal And Normal Perfusion, Respectively, in the Corresponding Vascular Territory (Vessel-Based Analysis)

	MPI Abnormal (n = 36 Vessels)	MPI Normal (n = 172 Vessels)	p Value
Calcium score	281 ± 590	116 ± 232	<0.01
MDCT			
Normal	0	45 (26%)	
Abnormal	36 (100%)	127 (74%)	<0.01
Nonobstructive stenosis	10 (28%)	93 (54%)	
Borderline stenosis	10 (28%)	27 (16%)	
Severe stenosis	16 (44%)	7 (4%)	<0.01
Number of diseased segments	2.6 ± 1.3	1.7 ± 1.3	<0.01
Number of segments with >50% stenosis	1.1 ± 1.2	0.29 ± 0.67	<0.01
QCA	71.0 ± 22.1%	22.7 ± 19.1%	<0.01

Abbreviations as in Table 2.

The remaining 44 (63%) of 70 patients demonstrated a normal myocardial perfusion on SPECT imaging. In these patients, average coronary calcium score was 255 ± 415 ($p < 0.01$) as compared with patients with abnormal perfusion). In total, a calcium score ≥400 was observed in 8 (18%). The MDCT was abnormal in 37 (84%) patients, with 22 patients showing nonobstructive disease, 12 with borderline stenosis, and 3 patients showing severe stenosis. The average number of diseased segments (5.0 ± 3.0) was statistically insignificantly lower than the patients with abnormal perfusion scans (6.4 ± 3.1, $p = 0.08$). After excluding patients with completely normal coronary arteries, average number of diseased segments was 6.0 ± 2.7 ($p = 0.10$). However, the average number of segments with significant stenosis was significantly lower (0.61 ± 1.2, $p < 0.01$) as compared with patients with abnormal perfusion. Average percentage lumen stenosis of the most severe lesion on QCA was also considerably lower (26.7 ± 17.7%, $p < 0.01$) compared with patients with abnormal SPECT. All 9 patients with significant stenosis on QCA were detected by MDCT (sensitivity 100%), wheresa MDCT correctly demonstrated absence of stenosis in 29 of 35 patients (specificity 83%).

Upon analysis by vascular territories instead of patient basis, abnormal myocardial perfusion was noted in 36 (17%) of 208 vascular territories with ischemia in 33 and fixed perfusion defects in 3 vascular territories (Table 3). In the remaining 172 (83%) vascular territories, myocardial perfusion was normal.

Comparison of MDCT with MPI, invasive angiography, and IVUS. We found that the MPI was abnormal in 17 of 53 (32%) of patients in whom IVUS imaging was available. We could not perform IVUS imaging of the coronary artery corresponding to the territory with abnormal perfusion in 4 patients. Therefore, these patients were excluded from the patient-based analysis, but the available data were included in the vessel-based analysis. Accordingly, on a patient basis, MPI was abnormal in 13 of 49 (27%) patients. Average coronary calcium score in these patients was 355 ± 355, with 3 (18%) patients showing calcium scores ≥400. In all patients, MDCT was abnormal with severe stenosis in 4 (31%), borderline stenosis in 7 (54%), and nonobstructive lesions in 2 (31%) patients. The average number of MDCT-verified diseased segments was 5.5 ± 3.0, whereas the average number of significantly stenosed segments was 1.5 ± 1.2. Average percent luminal narrowing as determined by QCA

was relatively low in these patients (68.5 ± 18.5%), possibly as a result of the exclusion of patients with severe stenosis in whom IVUS imaging could not be performed. Nonetheless, mean MLA was 3.3 ± 1.2 mm^2 with an average lesion plaque area and plaque burden of respectively 10.7 ± 4.9 mm^2 and 74.3% ± 8.8%, confirming the presence of potentially flow-limiting stenoses. Moreover, 9 (69%) lesions were associated with constrictive remodeling.

Normal perfusion was observed in the remaining 36 (73%) patients. Average coronary calcium score was 247 ± 395 ($p = 0.056$ as compared with patients with abnormal perfusion). In these patients, calcium scores exceeded 400 in 7 (19%) patients. MDCT revealed atherosclerosis in 32 (89%), of which 18 patients showed nonobstructive disease, 11 patients had borderline stenosis, and 3 patients had severe stenosis. Mean number of diseased segments was similar to that of patients with abnormal perfusion, 5.4 ± 3.1 ($p = 0.92$) compared with patients with abnormal perfusion, but the mean number of significantly stenosed segments was significantly lower, 0.58 ± 0.91 ($p = 0.028$). Considering only the most severe percent luminal stenosis per patient, mean luminal narrowing of only 26.2 ± 15.6% was observed on QCA, indicating minimal angiographic stenosis. In line with these observations, preservation of the lumen was confirmed by IVUS with an average MLA of 5.8 ± 3.3 mm^2, which was significantly greater as compared with patients with abnormal MPI ($p < 0.01$). Nonetheless, considerable atherosclerosis was identified on IVUS with an average lesion plaque area of 8.7 ± 4.3 mm^2, which was not significantly different compared with patients with perfusion abnormalities ($p = 0.17$). Also substantial plaque burden was observed, with an average of 58.9 ± 18.1% ($p < 0.01$) of the lesion cross-sectional area as compared to abnormal MPI. A positive remodeling was identified in 16 (44%) of patients with normal MPI, as compared with 31% in patients with abnormal MPI ($p = 0.20$) (Table 4). The results are summarized in Figure 2, whereas in Figure 3, an example of a patient with MDCT- and IVUS-verified significant atherosclerotic burden is presented who had normal myocardial perfusion.

Upon analysis by vessel basis, 15 (14%) of 109 coronary arteries were associated with abnormal perfusion in the corresponding vascular territory during MPI. The average coronary calcium score was 120 ± 115 per vessel. In all coronary arteries with abnormal perfusion, atherosclerosis was identified on MDCT, with nonobstructive stenosis in 5 (33%), borderline stenosis in 6 (40%), and severe stenosis in 4 (27%). With regard to the extent of disease on MDCT, a mean of 2.5 ± 1.2 diseased segments per vessel was observed, while mean of significantly diseased segments was 1.0 ± 1.0. Mean extent of stenosis on QCA was 63.4 ± 23.5%.

Table 4. Intravascular Ultrasound Characteristics of the Most Severe Lesion in Patients With Abnormal and Normal Perfusion, Respectively, on MPI (Patient-Based Analysis)

	MPI Abnormal (n = 13 Patients)	MPI Normal (n = 36 Patients)	P Value
Reference section			
EEM area, mm^2	14.2 ± 5.8	14.6 ± 4.5	0.68
Lumen area, mm^2	8.5 ± 3.4	9.6 ± 3.7	0.28
Lesion section			
EEM area, mm^2	14.0 ± 5.6	14.5 ± 4.8	0.76
MLA, mm^2	3.3 ± 1.2	5.8 ± 3.3	<0.01
Lesion plaque area, mm^2	10.7 ± 4.9	8.7 ± 4.3	0.17
Lesion plaque burden, %	74.3 ± 8.8	58.9 ± 18.1	<0.01
Lumen area stenosis, %	66.9 ± 13.8	41.7 ± 23.1	<0.01
Lumen diameter stenosis, %	44.1 ± 14.1	25.3 ± 15.8	<0.01
Corrected lumen area stenosis, %	77.2 ± 9.1	61.5 ± 20.1	<0.01
Remodeling			
Positive remodeling, n (%)	4 (31)	16 (44)	0.20

EEM = external elastic membrane; MLA = minimal lumen area.

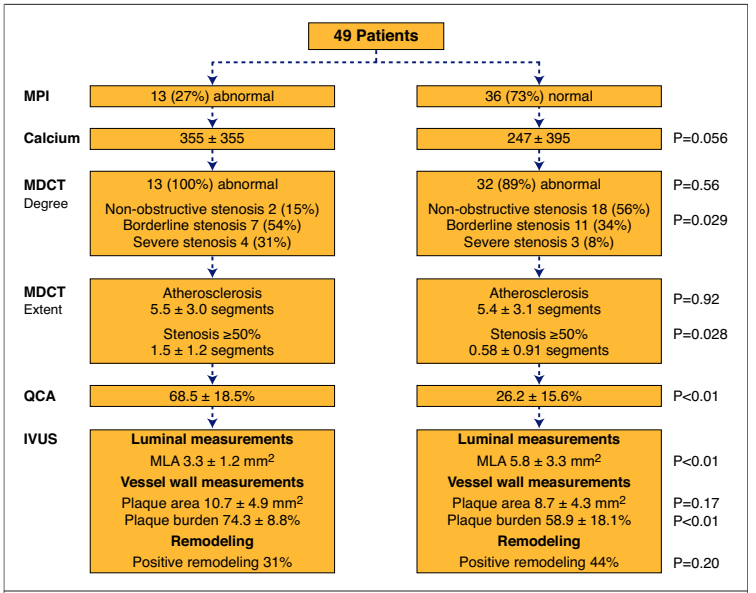

Figure 2. MPI, MDCT, and QCA Observations in 49 Patients in Whom Additional IVUS Imaging Was Performed

In almost all patients with normal MPI, the presence of atherosclerosis was observed on MDCT with negligible luminal narrowing identified on QCA. Intravascular ultrasound (IVUS) imaging confirmed the presence of substantial atherosclerosis (mean lesion plaque burden 58.9%), yet without luminal compromise (mean minimal lumen area [MLA] 5.8 mm^2). Abbreviations as in Figure 1.

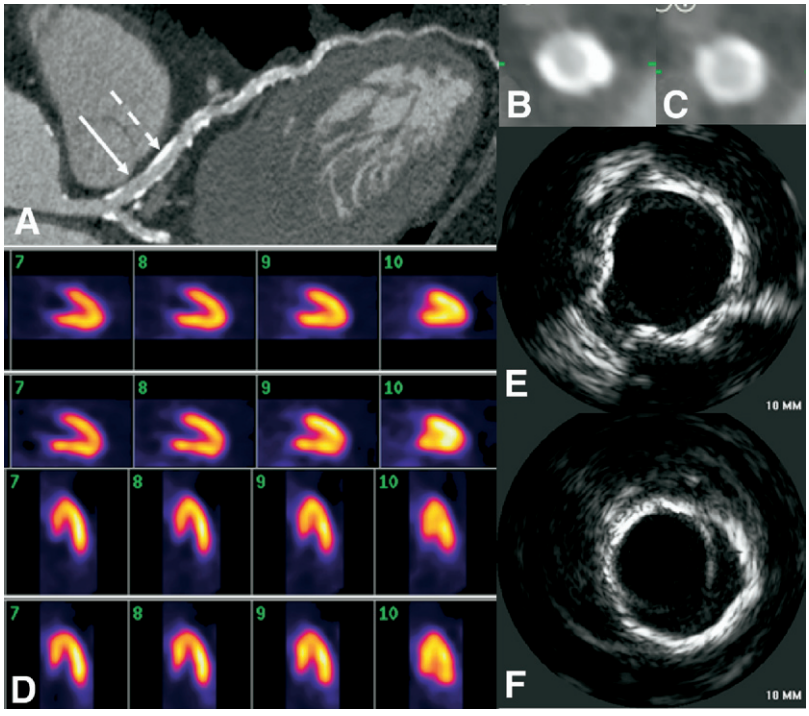

Figure 3. Coronary Artery Disease by MDCT Coronary Angiography With Normal Myocardial Perfusion

A 60-year old male presented to the outpatient clinic with dyspnea and an elevated risk profile for coronary artery disease, including hypertension, hypercholesterolemia, and smoking. Contrast-enhanced multidetector computed tomography (MDCT) coronary angiography revealed considerable atherosclerosis in the left anterior descending coronary artery **(A). B and C** are cross-sectional images of the areas indicated by the arrows in **(A)**. In contrast, myocardial perfusion imaging **(D)**, which was performed during exercise stress **(first and third row)** and rest **(second and fourth row)**, showed normal perfusion. On intravascular ultrasound imaging **(E and F)**, considerable plaque burden was demonstrated, yet with preserved coronary lumen.

In the remaining 94 (86%) coronary arteries without perfusion abnormalities, average coronary calcium score was 94 ± 178 (p = 0.04) as compared with coronary arteries with abnormal perfusion. On MDCT, aatherosclerosis was absent in 19 (20%), whereas the average degree of luminal stenosis on QCA was 21.4 ± 13.8%. Further details of the IVUS measurements on a vessel basis are provided in Table 5. Finally, as shown in Figure 4, significant differences in IVUS measurements were observed when comparing patients with and without atherosclerosis on MDCT.

Table 5. Intravascular Ultrasound Characteristics in Coronary Arteries With Abnormal and Normal Perfusion, Respectively, in the Corresponding Vascular Territory (Vessel-Based Analysis)

	MPI Abnormal (n = 15 Vessels)	MPI Normal (n = 94 Vessels)	p Value
Reference section			
EEM area, mm^2	15.6 ± 6.1	15.1 ± 5.4	0.57
Lumen area, mm^2	9.3 ± 4.1	9.8 ± 3.5	0.45
Lesion section			
EEM area, mm^2	14.4 ± 5.3	14.0 ± 5.2	0.85
MLA, mm^2	3.6 ± 1.5	6.5 ± 3.6	<0.01
Lesion plaque area, mm^2	10.8 ± 4.6	7.6 ± 4.0	<0.01
Lesion plaque burden, %	73.5 ± 9.0	52.4 ± 17.5	<0.01
Lumen area stenosis, %	63.9 ± 18.0	33.2 ± 20.8	<0.01
Lumen diameter stenosis, %	41.9 ± 15.8	19.4 ± 13.6	<0.01
Corrected lumen area stenosis, %	76.2 ± 10.0	55.1 ± 18.7	<0.01
Remodeling			
Positive remodeling, n (%)	5 (33)	49 (52)	0.27

Abbreviations as in Table 4.

DISCUSSION

The present study, upon comparison of MDCT to MPI showed that abnormal perfusion was always associated with an abnormal MDCT, with a majority of patients showing significant luminal stenosis. In these patients, significant CAD was also observed on invasive imaging verified by a mean percent diameter stenosis of 75.9 ± 19.2% on conventional invasive angiography as well as a mean MLA <4.0 mm^2 by IVUS. Thus, in case of advanced CAD, the different imaging modalities appear to be in agreement with abnormal results

obtained with all invasive and noninvasive techniques. However, in symptomatic patients who showed normal myocardial perfusion, MDCT revealed significant atherosclerotic burden; in these patients the invasive coronary angiography and QCA demonstrated only minor lesions with a mean diameter stenosis 26.7 ± 17.7%. IVUS clarified the discrepancy by revealing considerable lesion plaque burden (58.9 ± 18.1% of cross-sectional area), which often spared the lumen (mean MLA 5.8 ± 3.3 mm^2) due to positive remodeling. These findings are intuitively expected and pathologically well established and are reconfirmed in the present study by the use of multimodality invasive and noninvasive imaging strategies.

Hemodynamically relevant stenoses. The flow-limiting lesions as determined by MPI were also associated with significant focal luminal narrowing on MDCT as well as invasive imaging. In total, 14 patients showed severe stenosis on MDCT, confirmed by a stenosis ≥70% luminal narrowing on QCA in all patients. In all patients with abnormal MPI, a mean percent diameter stenosis of 75.9 ± 19.2% was observed whereas IVUS showed mean MLA of 3.3 ± 1.3 mm^2. This observation is in consonance with an earlier report that compared IVUS measurements in 70 coronary lesions to gated SPECT and observed a 3.3-mm^2 MLA of coronary lesions corresponding to a positive SPECT study (1). Similar findings have been obtained in other studies employing fractional flow reserve (13,14), indicating an agreement among various imaging modalities in the presence of hemodynamically relevant CAD.

Atherosclerosis in the presence of normal perfusion. In 63% of our patients, a normal MPI study was obtained. In these patients, only mild luminal narrowing (mean diameter stenosis 26.7 ± 17.7%) was observed during conventional invasive coronary angiography; 23% of patients had normal coronary angiograms (QCA <20% luminal narrowing). However, MDCT revealed normal coronary arteries only in 7 (16%) patients. In addition, the extent of disease, as reflected by a mean number of abnormal segments per patient, was not significantly different from patients with abnormal MPI. The presence of extensive atherosclerotic disease in such cases with normal MPI was confirmed by IVUS, which showed considerable plaque burden (average 58.9 ± 18.1 of cross-sectional area). These lesions were positively remodeled and did not inflict significant luminal stenosis (mean MLA of 5.8 ± 3.3 mm^2). The presence of extensive atherosclerotic disease in the setting of normal myocardial perfusion has been described previously. In a large cohort of 1,195 patients without historical CAD, extensive atherosclerosis, as reflected by a calcium score >400, was observed in 31% of patients with normal MPI studies (15). The presence of substantial disease has also been previously described in angiographically normal segments; Mintz et al. (16) showed in a large series of consecutive patients that atherosclerosis was commonly present in angiographic reference segments and <7% of segments were classified as entirely normal by IVUS imaging.

Accordingly, various imaging modalities provide distinct morphological and functional information about coronary atherosclerotic disease. Conven-

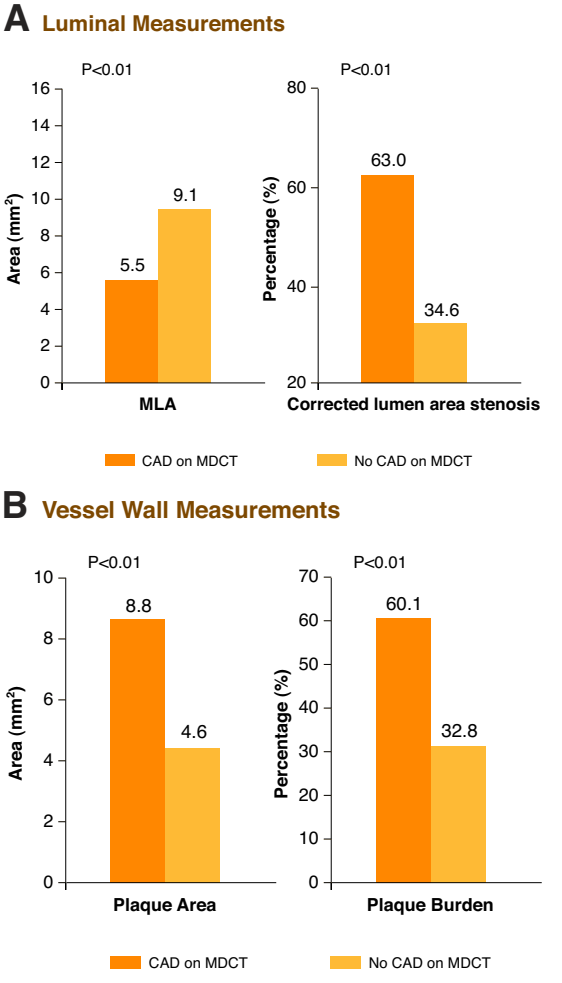

Figure 4. Differences in IVUS Measurements Between Coronary Arteries With CAD and Without CAD as Determined on MDCT

(A) MLA (mm^2) and corrected lumen area stenosis (%) and **(B)** plaque area (mm^2) and plaque burden (%). All measurements were significantly different between coronary arteries with and without coronary artery disease (CAD) identified on MDCT. Abbreviations as in Figures 1 and 2.

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tional coronary angiography and MPI detect anatomically significant and hemodynamically relevant stenoses, respectively. In contrast, the techniques remain limited in depicting the disease in its earlier stages, or even when the disease is mature but does not compromise luminal integrity because of expansive vascular remodeling.

Clinical implications. The current study reconfirms the expectation that the patients with perfusion defects on MPI indicating hemodynamically obstructive stenoses and representing advanced CAD, revealed significant stenoses on MDCT as well as on invasive angiography with QCA and IVUS. On the other hand, patients with (preclinical) atherosclerosis may present with normal perfusion on MPI, with (nearly) normal invasive angiography/QCA, but many of these patients may demonstrate extensive atherosclerosis in absence of obstructive stenoses on MDCT, which is verified subsequently by the IVUS observations. Thus, the presence of atherosclerotic plaque in MDCT in the setting of a normal MPI does not constitute a false-positive result. Rather, it reflects the fact that MDCT can detect atherosclerotic lesions that are not flow limiting, as confirmed by the use of IVUS in our study. Clinically, it is important to make a clear distinction between the presence of plaque and the presence of stenosis in MDCT. Since the large, positively remodeled lesions are harbingers of plaque rupture, it remains to be determined whether such advanced characterization of atherosclerotic lesions will result in superior prognostification of patients.

Study limitations. In the present study, MDCT examinations were visually assessed because no validated quantification algorithms are currently available. Moreover, it is important to realize that interpretation of MDCT results is seriously limited in presence of calcific lesions. Also, IVUS imaging was not performed in all vessels in every patient. Furthermore, the current observations should be confirmed in less selected populations that would decrease the influence of selection bias. Finally, as the patients underwent multiple examinations, the radiation burden in the current study was high. The radiation dose of MDCT in particular is high, although the recent development of dose reduction strategies such as tube modulation or snapshot pulse scanning mode will result in considerably lower radiation exposures.

CONCLUSIONS

The current findings demonstrate a good agreement between noninvasive imaging techniques (MPI, MDCT) and invasive techniques (angiography, QCA, and IVUS) in patients with flow-limiting CAD. These patients exhibited abnormal perfusion on MPI, predominantly obstructive atherosclerosis on MDCT, and obstructive stenoses on invasive quantitative angiography and IVUS. In another subset of symptomatic patient population with normal myocardial perfusion, the use of MDCT uncovered considerable atherosclerosis in a great number of patients. Although invasive angiography did not confirm severe coronary lesions, the presence of MDCT-based atherosclerosis was validated by the use of IVUS.

Accordingly, considerable plaque burden can be observed on MDCT without inducing perfusion abnormalities on MPI. Rather than MDCT being a false positive result, atherosclerosis without flow-limiting luminal narrowing is detected.

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