Cardiovascular computed tomography for diagnosis and risk stratification of coronary artery disease

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Chapter 8

Predictive value of multislice computed tomography variables of atherosclerosis for ischemia on stress-rest single-photon emission computed tomography

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Abstract

Previous studies have shown that the presence of stenosis alone on multislice computed tomography (MSCT) has a limited positive predictive value for the presence of ischemia on myocardial perfusion imaging (MPI). The purpose of this study was to assess which variables of atherosclerosis on MSCT angiography are related to ischemia on MPI. Both MSCT and MPI were performed in 514 patients. On MSCT, the calcium score, degree of stenosis (≥50% and ≥70% stenosis), plaque extent and location were determined. Plaque composition was classified as non-calcified, mixed or calcified. Ischemia was defined as a summed difference score ≥2 on a per patient basis. Ischemia was observed in 137 patients (27%). On a patient basis, multivariate analysis showed that the degree of stenosis (presence of ≥70% stenosis, OR 3.5), plaque extent and composition (mixed plaques ≥3, OR 1.7 and calcified plaques ≥3, OR 2.0) and location (atherosclerotic disease in left main coronary artery and/or proximal left anterior descending coronary artery, OR 1.6) were independent predictors for ischemia on MPI. In addition, MSCT variables of atherosclerosis such as plaque extent, composition and location had significant incremental value for the prediction of ischemia over the presence of ≥70% stenosis. In conclusion, in addition to the degree of stenosis, MSCT variables of atherosclerosis describing plaque extent, composition and location are predictive of the presence of ischemia on MPI.

Introduction

Over the past decade, multislice computed tomography (MSCT) angiography has emerged as a non-invasive modality for visualization of the coronary arteries. Recently, several studies have addressed the diagnostic accuracy of MSCT as compared to invasive coronary angiography reporting high accuracies for the detection of 50% stenosis.[1] Importantly, the high negative predictive value of 99% indicates that the technique may be particularly useful for ruling out the presence of coronary artery disease (CAD) in patients with lower likelihood of CAD. On the other hand, while MSCT angiography provides insight into the severity and extent of anatomical disease, it is currently unable to evaluate the hemodynamical relevance of CAD. In fact, previous studies have revealed a large discrepancy between the presence of atherosclerosis on MSCT angiography and the presence of ischemia during functional testing.[2-5] These investigations demonstrated that approximately only half of obstructive stenoses (≥50% luminal narrowing) on MSCT were associated with abnormal perfusion, whereas a large proportion of obstructive lesions on MSCT did not result in perfusion abnormalities. Therefore, identification of anatomical MSCT variables of atherosclerosis that are associated with ischemia on MPI, in addition to the presence of obstructive CAD, may improve selection of further diagnostic and/or therapeutic management. Thus, the purpose of this study was to identify variables of atherosclerosis on MSCT angiography that are related to ischemia on MPI, in addition to the presence of obstructive CAD.

Methods

Patients and study protocol

The study population consisted of 524 patients who were clinically referred for functional and anatomical imaging because of chest pain or an elevated risk profile as part of an ongoing registry addressing the relative merits of MSCT in relation to other imaging techniques. Patients underwent both myocardial perfusion imaging (MPI) with stress-rest gated single photon emission computed tomography (SPECT) and MSCT within 3 months in two different institutions. Patients were included at the University Hospital in Zurich, Switzerland (n=263) and at the Leiden University Medical Center, Leiden, the Netherlands (n=261). Exclusion criteria were: known CAD (previous myocardial infarction, percutaneous coronary intervention and coronary artery bypass surgery), atrial fibrillation, renal insufficiency (glomerular filtration rate <30 ml/min), known allergy to iodine contrast and pregnancy. The clinical symptoms of included patients were recorded and patients were further classified as having a low, intermediate or high pre-test likelihood of obstructive CAD using the method described by Diamond and Forrester.[6]

Stress-rest gated MPI

Patients were instructed to withhold beta-blocking medication and calcium antagonists 48 hours before examination and caffeine 12 hours before examination. For each center a different gated MPI protocol was used. In Leiden (n=261) a two-day gated stress-rest SPECT protocol was performed using either technetium-99 tetrofosmin (500 MBq) or technetium-99m sestamibi (500 MBq). In patients that were able to exercise, symptom-limited bicycle test was performed and in patients unable to exercise pharmacological stress was performed using adenosine or dobutamine. In Zurich (n=263) a one day gated stress-rest SPECT was performed using adenosine stress and technetium-99m tetrofosmin (300 MBq at peak stress and 900 MBq at rest). The images were acquired on a triple-head SPECT camera (GCA 9300/HG, Toshiba Corp., Tokyo, Japan) or a dual-head detector camera (Millennium VG & Hawk-eye, General Electric Medical Systems, Milwaukee, WI, USA; or Vertex Epic ADAC Pegasus, Philips Medical Systems, Eindhoven, the Netherlands). All cameras were equipped with low energy high resolution collimators. A 20% window was used with a 140-keV energy peak of technetium-99m, and data were stored in a 64x64 matrix. Subsequently, stress-rest gated MPI datasets were quantitatively evaluated using previously validated automated software.[7] The data were reconstructed into long- and short-axis perpendicular to the heart axis. A 20-segment model was used in which the myocardial segments were assigned to the different perfusion territories. Each segment was scored by an experienced observer according to the standard scoring scale of 0-4 (normal, mild, moderate, severe reduction or absence of uptake). The total segmental perfusion scores during stress and rest were added to calculate the summed stress score (SSS) and the summed rest score (SRS), respectively. The summed difference score (SDS) was calculated as the sum of difference between the SRS and SSS. Ischemia was defined as a SDS $\geq$2 and severe ischemia was defined as a SDS $\geq$8.[8] On a per vessel basis, the presence of ischemia was assessed visually in the corresponding vascular territory. Consequently, ischemia in the anterior and septal wall was allocated to the left anterior descending coronary artery, ischemia in the lateral wall was allocated to the left circumflex coronary artery and ischemia in the inferior wall was allocated to the right coronary artery.[9]

MSCT coronary angiography

Heart rate and blood pressure were evaluated before each scan. If a patient's heart rate was above 65 beats per minute and no contra-indications existed, beta-blocking medication was administered one hour before the examination (50-100 mg metoprolol orally or 5-10 mg metoprolol intravenously).

In the first 41 patients data acquisition was performed using a 16-slice MSCT scanner (Aquilion 16, Toshiba Medical Systems, Tokyo, Japan) with a collimation of 16 x 0.5 mm, a gantry rotation time of 400 ms, tube voltage of 120 kV and tube current of 250 to 350 mA.

A 64-slice MSCT scanner (Aquilion 64, Toshiba Medical Systems, Tokyo, Japan or General Electrics Lightspeed VCT, Milwaukee, WI, USA) was used for the remaining 483 patients with a collimation of 64 x 0.5 mm, a gantry rotation time of 400 ms, tube voltage of 100 to 135 kV and tube current of 250 to 350 mA, depending on body shape. First, a non-contrast enhanced low dose scan prospectively triggered at 75% of the R-R interval was performed before helical scanning. This examination was used for calcium scoring and followed by a triggered helical scan. For the 16-slice MSCT non-ionic contrast (Iomeron 400, Bracco, Milan, Italy) was administered in the ante-cubital vein, with a dose of 130 to 140 ml and a flow-rate of 4 ml/s, followed by a saline flush. For 64-slice MSCT, 80 to 110 ml contrast was administered with a flow rate of 5 ml/s followed by a saline flush. Automatic detection of peak enhancement in the descending aorta was used for timing. Subsequently data sets were reconstructed at the best phase of the R-R interval and transferred to dedicated work stations (Vitrea2, Vital Images, USA, or Advantage, GE Healthcare, USA).

The non-contrast enhanced CT images were used to calculate the calcium score using the Agatston method.[10] MSCT angiographic examinations were evaluated in consensus by 2 experienced readers including an interventional cardiologist blinded to stress-rest SPECT findings. A 17-segment model modified according to the American Heart Association was used and for each segment was determined if atherosclerosis was present using axial and/or orthogonal images and curved multiplanar reconstructions. If atherosclerosis was present, the degree of stenosis was graded as non-obstructive (<50% stenosis), obstructive (≥50% stenosis) and severely obstructive (≥70% stenosis). Additionally, the extent of atherosclerosis was determined by assessing the number of diseased segments. Consequently, plaques were scored according to plaque composition (non-calcified, mixed or calcified). Non-calcified plaques were regarded as plaques having a lower CT attenuation compared to the contrast lumen and no visible calcifications, calcified plaques were plaques with predominantly high CT attenuation and without non-calcified plaque elements, and mixed plaques were plaques consisting of both non-calcified and calcified elements. Lastly, the location of disease was classified as being present in left main coronary artery (LM) and/or proximal left anterior descending coronary artery (LAD) or not (example provided in Figure 1).

Statistical analysis

Continuous data were expressed as mean and standard deviation, and categorical data were expressed in numbers and percentages. Binary logistic regression analysis was performed to determine the predictive value of MSCT variables of atherosclerosis for presence of ischemia on MPI on both a patient and vessel basis. First univariate analysis of baseline clinical risk variables (age and gender), calcium score and MSCT variables was performed. To analyze the predictive value of variables of atherosclerosis on MSCT (degree of stenosis, plaque

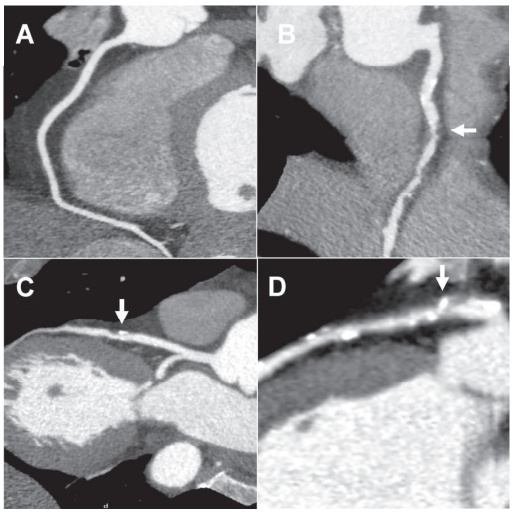

Figure 1. Examples of the classification of different variables of atherosclerosis on MSCT. Panel A: Assessment of the presence of atherosclerosis: curved multiplanar reconstruction (MPR) of right coronary artery (RCA) revealing the absence of atherosclerosis. Panel B: Assessment of the degree of stenosis: MPR showing a lesion resulting in ≥50% stenosis in the mid RCA (arrow). Panel C: Assessment of the extent and composition of atherosclerotic disease: MPR of the left anterior descending coronary artery (LAD) revealing a single mixed plaque (arrow). Panel D: Assessment of location of atherosclerosis: MPR of the LAD demonstrating the presence of an atherosclerotic lesion in the left main coronary artery and proximal LAD (arrow).

extent, composition and location), optimal binary cutoffs were created for analysis. For each variable, an odds ratio with 95% confidence interval (OR (CI 95%) was calculated.

The current study used 2 generations of MSCT scanners (16-slice and 64-slice), thus to correct for scanner type, scanner type was included in the univariate analysis. In addition, interaction was assessed between scanner type and MSCT variables of atherosclerosis (describing degree of stenosis, plaque extent, composition and location). In this analysis, no interaction was demonstrated between MSCT scanner type and MSCT variables of atherosclerosis (data not shown).

The intention was to build a multivariate model that combines clinical variables and MSCT variables of atherosclerosis for the prediction of ischemia on MPI, in a stepwise fashion. The first model consisted of clinical risk variables only. Consequently, the presence of (severely) obstructive CAD was added, followed by plaque extent and composition (≥3 mixed plaques and ≥3 calcified plaques). Finally, plaque location (atherosclerotic disease in the LM and/or proximal LAD) was added to the model. For each next iterative step, variables may not remain statistically significant. Thus, all variables with a p-value <0.15 were kept in the model in order not to miss clinically relevant predictors of ischemia.

The performance of the final multivariate model for prediction of ischemia on both a patient and vessel basis was studied with respect to discrimination and calibration. Discrimination was quantified by a measure of concordance, the c-index. For binary outcomes the c-index is identical to the area under the receiver operating characteristic (ROC) curve. The c-index lies between 0.5 and 1, and is better if closer to one.[11] Calibration refers to whether the predicted risks agree with the observed risk frequencies. Calibration was measured with the Hosmer-Lemeshow goodness-of-fit test ($p>0.10$ considered to indicate lack of deviation between the model and observed event rates). Statistical analysis was performed using SPSS software (version 16.0, SPSS inc., Chicago, IL, USA) and SAS software (The SAS system 6.12, Cary, NC, USA: SAS Institute Inc). A p-value <0.05 was considered statistically significant.

Results

Patient characteristics

In total, 524 patients were enrolled in the present study. In 10 patients (2%) the MSCT data set was not interpretable because of an irregular or elevated heart rate and these patients were excluded from the analysis. Therefore, 514 patients were included in the analysis. Baseline patient characteristics are described in Table 1.

Table 1. Baseline patient characteristics

Male	302 (59%)
Age (years)	60 ±11
Obesity (BMI ≥30 kg/m^2)	111 (22%)
Diabetes	155 (30%)
Hypercholesterolemia	209 (41%)
Hypertension	287 (56%)
Positive family history for CAD	191 (37%)
Smoking currently	153 (30%)
Pre-test likelihood	
Low pre-test likelihood	113 (22%)
Intermediate pre-test likelihood	334 (65%)
High pre-test likelihood	67 (13%)
Symptoms patient population	
Typical chest pain	78 (15%)
Atypical chest pain	146 (28%)
Non-anginal chest pain	41 (8%)
Asymptomatic	181 (35%)
Other (dyspnea, tiredness, dizziness ect.)	68 (13%)

Stress-rest gated MPI results

In 87 patients symptom-limited bicycle test was performed and in the remaining 427 patients pharmacological stress was applied using either adenosine (n=395) or dobutamine (n=32). MPI imaging results are presented in Table 2. The mean SSS was 2.8 ±4.5, the mean SRS was 1.5 ±3.0 and the mean SDS was 1.3 ±3.6. Ischemia (SDS ≥2) was observed in 137 patients (27%). Within this group, 16 patients (3%) were shown to have severe ischemia (SDS ≥8).

Baseline MSCT results

Average heart rate during MSCT acquisition was 63 ±10 beats per minute. The baseline calcium score and MSCT imaging results are shown in Table 2. The mean calcium score was 324±751.

MSCT predictors for ischemia on MPI: patient based analysis

Results of the univariate analysis regarding the predictive value of MSCT variables for ischemia on MPI (patient basis) are listed in Table 3. As demonstrated, scanner type (16-slice or 64-slice) was not related to the presence of ischemia on MPI. To determine the independent predictive value of MSCT variables of atherosclerosis for ischemia on MPI, multivariate models were created including MSCT variables of atherosclerosis corrected for baseline clinical variables and the presence of severely obstructive CAD (Table 4). Interestingly, several MSCT variables of atherosclerosis remained predictive of ischemia on MPI in

Table 2. Imaging results of MPI, calcium score and MSCT angiography

MPI	
Normal perfusion (SDS <2)	374 (73%)
Ischemia (SDS ≥2)	137 (27%)
Severe ischemia (SDS ≥8)	16 (3%)
Calcium score	
0	174 (34%)
1-100	140 (27%)
101-400	88 (17%)
>400	112 (22%)
MSCT angiography	
Degree	
Presence of non-obstructive CAD	354 (69%)
Presence of obstructive CAD (≥50%)	157 (31%)
Presence of severely obstructive CAD (≥70%)	83 (16%)
Extent and Composition	
Non-calcified plaques ≥3	39 (8%)
Mixed plaques ≥3	93 (18%)
Calcified plaques ≥3	126 (25%)
Location	
LM and/or proximal LAD diseased	74 (15%)

Table 3. Univariate analysis for prediction of ischemia on MPI on patient basis

	OR (CI 95%)	P-value
Clinical	2.0 (1.4-3.8)	<0.001
Calcium score		
1-100	0.6 (0.4-0.9)	0.02
101-400	1.2 (0.7-2.0)	0.48
>400	4.8 (3.1-7.5)	<0.001
MSCT angiography		
MSCT scanner type (64-slice)	1.3 (0.7-2.6)	0.46
Degree		
Number of obstructive segments	1.4 (1.3-1.6)	<0.001
Presence obstructive CAD	5.4 (3.5-8.3)	<0.001
Presence severely obstructive CAD	6.8 (4.1-11.2)	<0.001
Extent and Composition		
Number of non-calcified plaques	1.1 (1.0-1.2)	0.15
Number of mixed plaques	1.3 (1.2-1.4)	<0.001
Number of calcified plaques	1.3 (1.2-1.4)	<0.001
Non-calcified plaques ≥3	0.9 (0.4-2.0)	0.86
Mixed plaques ≥3	3.9 (2.5-6.3)	<0.001
Calcified plaques ≥3	3.3 (2.2-5.1)	<0.001
Location		
LM and/or proximal LAD diseased	3.4 (2.2-5.3)	<0.001

the multivariate model. Regarding contrast enhanced MSCT coronary angiography, degree of stenosis (presence of ≥50% and ≥70% stenosis), extent and composition (presence of ≥3 mixed plaques and/or ≥3 calcified plaques) and location (atherosclerotic disease in LM and/or proximal LAD) remained independent predictors of ischemia. An example of a patient with all predictors on MSCT is provided in Figure 2.

MSCT predictors for ischemia on MPI: vessel based analysis

Results of the univariate analysis regarding the predictive value of MSCT variables for ischemia on MPI (vessel basis) are listed in Table 5. To determine the independent predictive value of MSCT variables of atherosclerosis for ischemia on MPI on a vessel basis, multivariate models were created including MSCT variables of atherosclerosis which were corrected for baseline clinical risk variables (Table 6). Interestingly, several MSCT variables of atherosclerosis remained predictive of ischemia on MPI in the multivariate model on a vessel basis. Indeed, degree of stenosis (presence of ≥50% and ≥70% stenosis) and extent and composition (presence of ≥2 mixed plaques and/or ≥2 calcified plaques) remained significant independent predictors of ischemia.

Table 4. Multivariate models for prediction of ischemia on MPI on patient basis

	OR (CI 95%)	P-value
Model I		
Clinical	2.0 (1.4-3.8)	<0.001
Model II		
Clinical	1.6 (1.1-2.3)	0.01
Presence obstructive CAD	5.0 (3.3-7.7)	<0.0001
Model III		
Clinical	1.7 (1.2-2.5)	0.006
Presence severely obstructive CAD	6.2 (3.7-10.4)	<0.0001
Model IV		
Clinical	1.6 (1.1-2.3)	0.02
Presence severely obstructive CAD	3.8 (2.2-6.7)	<0.0001
Mixed plaques ≥3	2.0 (1.2-3.5)	0.012
Calcified plaques ≥3	2.3 (1.5-3.7)	<0.0001
Model V		
Clinical	0.7 (1.1-2.4)	0.008
Presence severely obstructive CAD	4.2 (2.5-7.3)	<0.0001
Calcified plaques ≥3	1.9 (1.2-3.1)	0.01
LM and/or proximal LAD diseased	1.8 (1.1-3.0)	0.03
Model VI		
Clinical	1.6 (1.1-2.4)	0.01
Presence severely obstructive CAD	3.5 (2.0-6.3)	<0.0001
Mixed plaques ≥3	1.7 (0.9-3.1)	0.053
Calcified plaques ≥3	2.0 (2.2-3.3)	0.007
LM and/or proximal LAD diseased	1.6 (0.9-2.7)	0.107

Incremental value of angiographic MSCT variables of atherosclerosis to predict ischemia on MPI

In total, 157 patients (31%) had obstructive CAD and 83 patients (16%) had severely obstructive CAD on MSCT. Regarding these patients, 80 patients (51%) and 52 patients (63%) revealed ischemia on MPI, respectively. Moreover, of the 259 patients with at least one of the significant predictors on MSCT, only 119 patients (33%) showed ischemia on MPI. Example of a patient demonstrating only one significant predictor and a normal MPI is provided in Figure 3. In addition, of the 22 patients with all of the significant predictors on MSCT (describing degree of stenosis, plaque extent, composition, and location), 18 patients (82%) showed ischemia on MPI.

Finally, the performance of the multivariate models for prediction of ischemia on both a patient (model V in Table 4) and vessel basis (model IV in Table 6) were studied with respect to discrimination and calibration. Discrimination was quantified by a measure of concordance, the c-index. In this model, plaque extent, composition and location had significant incremental value over clinical risk stratification and the presence of severely obstructive

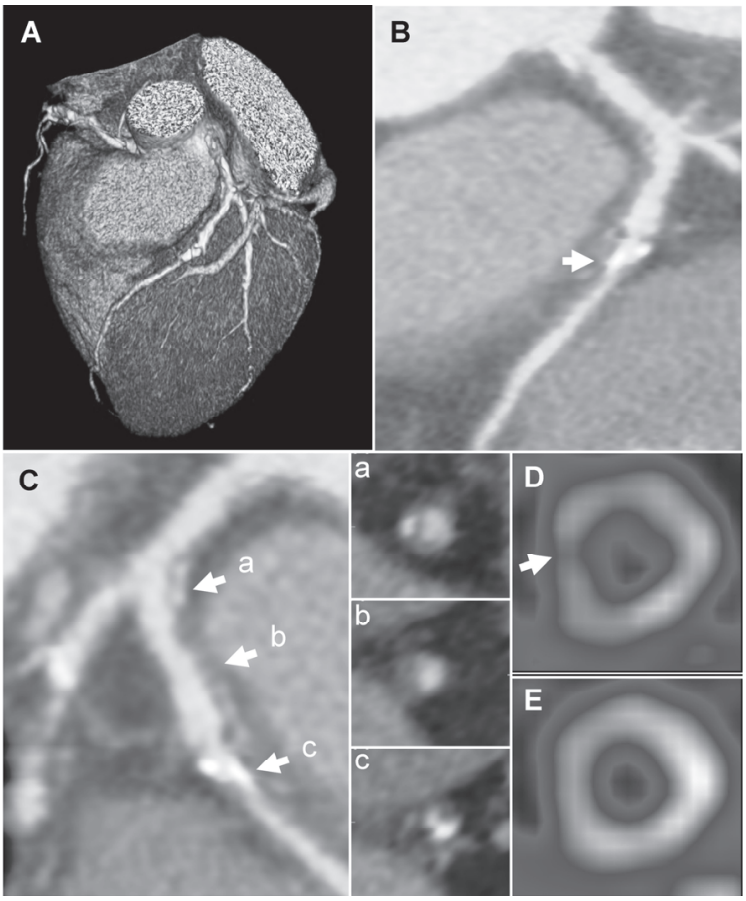

Figure 2. Example of a 72 year-old male patient exhibiting all the significant predictors on multislice computed tomography (MSCT) for prediction of ischemia on myocardial perfusion imaging (MPI). In panel A, a 3D volume rendered reconstruction is provided, showing the left anterior descending coronary artery (LAD). Panel B: A curved multiplanar reconstruction (MPR) of the LAD is shown demonstrating the presence of obstructive CAD (≥50%) in the proximal segment (arrow). Panel C: Another curved MPR of the LAD is shown in a different view, revealing the presence of multiple diseased segments (cross sectional images a, b and c), the presence of obstructive lesion in the LAD (arrow c) and the presence of mixed plaque (cross sectional images a, b and c). Panel D: Stress single photon emission computed tomography (SPECT) short axis image showing the presence of a perfusion defect, particularly evident in the antero-septal region (arrow). Panel E: Rest SPECT short axis image demonstrating normal perfusion.

CAD ($p<0.05$) for the prediction of ischemia on both a patient and vessel basis (Figure 4 and Figure 5, respectively). The performance of the model (calibration) was assessed by the Hosmer-Lemeshow goodness-of-fit test ($p>0.10$ considered to indicate lack of deviation between the model and observed event rates). As demonstrated in Figure 6, on both a patient and vessel basis, the estimated risk of the models showed good agreement with the observed risk frequencies.

Table 5. Univariate analysis for prediction of ischemia on MPI on vessel basis

	OR (CI 95%)	P-value
Clinical	1.9 (2.5-1.4)	<0.001
MSCT angiography		
Degree		
Number of obstructive segments	2.0 (1.7-2.4)	<0.001
Presence obstructive CAD	4.0 (3.0-5.3)	<0.001
Presence severely obstructive CAD	5.3 (3.6-7.8)	<0.001
Extent and Composition		
Number of non-calcified plaques	1.2 (1.0-1.4)	0.08
Number of mixed plaques	1.6 (1.4-1.8)	<0.001
Number of calcified plaques	1.4 (1.2-1.6)	<0.001
Non-calcified plaques ≥2	1.0 (0.6-1.9)	0.91
Mixed plaques ≥2	3.0 (2.1-4.2)	<0.001
Calcified plaques ≥2	2.1 (1.5-2.9)	<0.001

Table 6. Multivariate models for prediction of ischemia on MPI on vessel basis

	OR (CI 95%)	P-value
Model I		
Clinical	1.9 (2.5-1.4)	<0.001
Model II		
Clinical	1.8 (1.4-2.2)	<0.001
Presence obstructive CAD	3.8 (2.8-5.0)	<0.001
Model III		
Clinical	1.8 (1.5-2.2)	<0.001
Presence severely obstructive CAD	5.0 (3.3-7.3)	<0.001
Model IV		
Clinical	1.8 (1.4-2.2)	<0.001
Presence severely obstructive CAD	3.5 (2.3-5.3)	<0.001
Mixed plaques ≥2	1.9 (1.3-2.8)	<0.001
Calcified plaques ≥2	1.8 (1.3-2.5)	<0.001

Discussion

The main findings of the present study can be summarized as follows. In a population with predominantly low-to-intermediate pre-test likelihood for CAD, MSCT variables of atherosclerosis such as plaque extent, composition and location were significant predictors of ischemia on MPI, over the presence of obstructive CAD. Moreover, the incremental value of angiographic MSCT variables of atherosclerosis over clinical risk stratification and the presence of severely obstructive CAD was investigated. In this model, plaque extent, composition (presence of ≥3 mixed plaques and/or ≥3 calcified plaques) and location (ath-

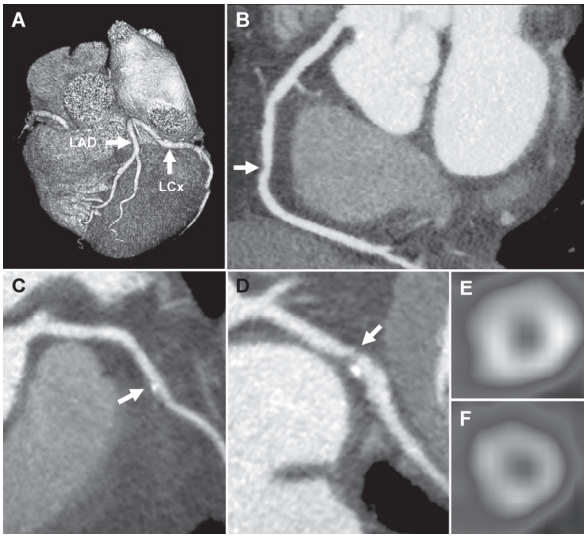

Figure 3. Example of a 69 year-old female patient exhibiting an obstructive lesion on multislice computed tomography (MSCT) while myocardial perfusion imaging (MPI) showed normal perfusion. A 3D volume rendered reconstruction is provided in panel A, showing the left anterior descending coronary artery (LAD) and left circumflex coronary artery (LCx). Panel B: A curved multiplanar reconstruction (MPR) of the right coronary artery (RCA) is shown demonstrating the presence of non-obstructive non-calcified plaque (arrow). Panel C: A curved MPR of the LAD is shown revealing the presence of a single non-obstructive mixed plaque (arrow). Panel D: A curved MPR of LCx is shown demonstrating the presence of obstructive lesion (however <70%) in the mid LAD (arrow). Panel E: Single photon emission computed tomography (SPECT) short axis image showing normal perfusion in stress and rest (panel F).

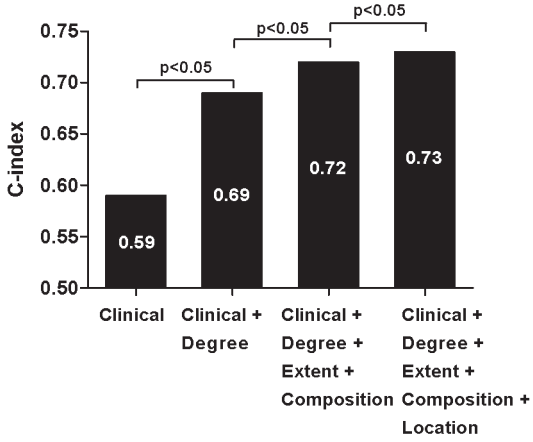

Figure 4. Bars representing the c-index (area under the curve) on the y-axis illustrating the incremental predictive value of angiographic multislice computed tomography (MSCT) variables of atherosclerosis for the prediction of ischemia on myocardial perfusion imaging (MPI) on a patient basis. The addition of the degree of stenosis (presence of ≥70% stenosis) provided incremental predictive information to baseline clinical variables for the prediction of ischemia on MPI on a patient basis. Furthermore the addition of extent and composition of atherosclerosis (≥3 calcified plaques) and location (atherosclerotic disease in the left main coronary artery and/or proximal left anterior descending coronary artery) on MSCT resulted in further incremental predictive value over baseline clinical variables, and degree of stenosis on MSCT.

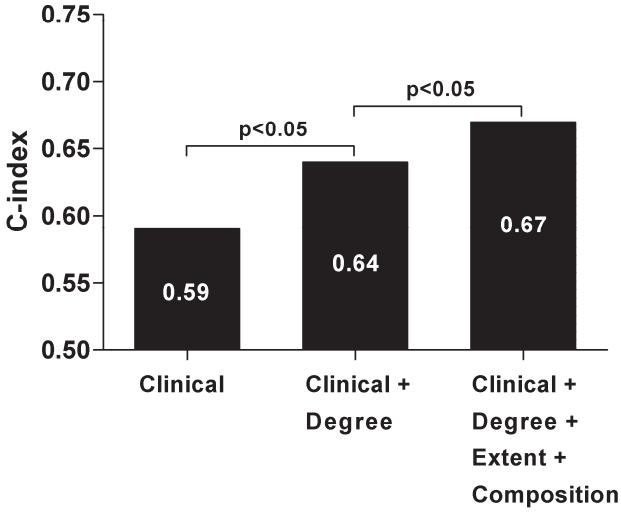

Figure 5. Bars representing the c-index (area under the curve) on the y-axis illustrating the incremental predictive value of angiographic multislice computed tomography (MSCT) variables of atherosclerosis for the prediction of ischemia on myocardial perfusion imaging (MPI) on a vessel basis. The addition of the degree of stenosis (presence of ≥70% stenosis) provided incremental predictive information to baseline clinical variables for prediction of ischemia on MPI on a vessel basis. Furthermore the addition of extent and composition of atherosclerosis (≥2 mixed plaques and ≥2 calcified plaques) on MSCT resulted in further incremental predictive value over baseline clinical variables, and degree of stenosis on MSCT.

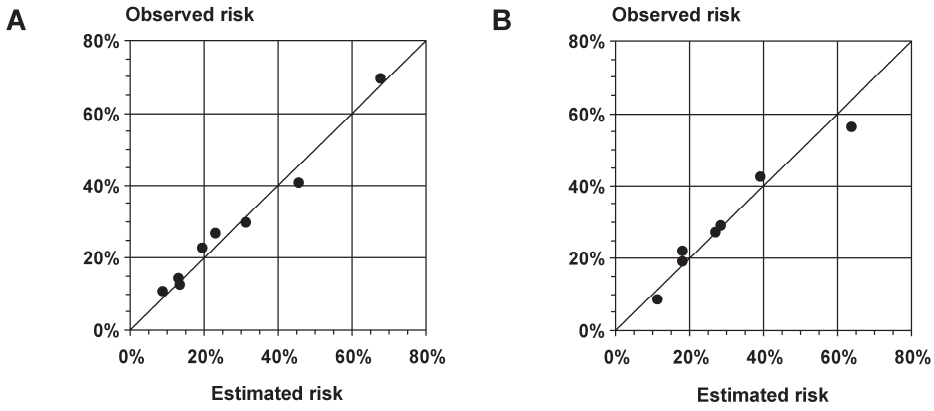

Figure 6. Hosmer-Lemeshow plot of estimated risk for ischemia on multislice computed tomography (MSCT) (x-axis) versus observed risk for ischemia on myocardial perfusion imaging (MPI) (y-axis) by decile of risk, on a patient (A) and vessel (B) basis. A calibration plot is shown for the prediction of ischemia on MPI (myocardial perfusion imaging) by the multivariate model of atherosclerosis variables on MSCT. Patient basis analysis is shown in panel A, describing model VI in Table 4. Vessel basis analysis is demonstrated in panel B, describing model IV in Table 5. The diagonal line in both plots demonstrates a good fit on both a patient and vessel basis. The Hosmer-Lemeshow goodness-of-fit test statistic was p=0.93 on a patient basis and p=0.11 on a vessel basis.

erosclerotic disease in LM and/or proximal LAD) further significantly enhanced prediction of ischemia over clinical risk stratification and the presence of severely obstructive CAD.

Previous investigations assessing the relation between MSCT and MPI demonstrated that normal coronary arteries on MSCT were highly associated with normal perfusion on MPI.[12] Accordingly, patients with normal coronary arteries on MSCT may be reassured and in general do not require further testing. Nevertheless, in a substantial number of patients MSCT will reveal the presence of atherosclerotic disease. However, previous comparisons demonstrated that only half of patients with stenosis of 50% or greater showed abnormal perfusion, resulting in a low positive predictive value of merely 50%.4, 5 Accordingly, with the expanding use of MSCT, clinicians will be increasingly confronted with patients having an obstructive lesion detected on MSCT but without information on the hemodynamic relevance. To determine further management, additional evaluation with functional imaging techniques remains necessary in these patients. However, if the likelihood of ischemia on MPI can be estimated more accurately based on MSCT results, a more appropriate selection of further testing and management can be achieved. Possibly, knowledge of the extent, composition, and location of atherosclerotic disease, as can be derived from MSCT, may enhance prediction of the presence of ischemia over the mere assessment of the degree of stenosis.

Extent and composition of atherosclerosis

In addition to the presence of a single stenotic lesion in the coronary arteries, previous studies have reported that diffuse atherosclerosis also contributes to ischemia.[13, 14] By measuring coronary flow reserve, de Bruyne et al. demonstrated that diffuse atherosclerotic disease can cause a decline in coronary flow despite the absence of obstructive CAD.[13] These findings suggest that the severity of perfusion abnormalities not only depends on the presence of obstructive disease but is also influenced by the atherosclerotic burden in the coronary artery. The current study is in line with these observations, suggesting that more extensive atherosclerotic plaque burden indicates a higher likelihood for ischemia. Moreover, the present results parallel previous studies comparing MPI with coronary calcium scoring.[15, 16] He et al. studied the relationship between the presence of stress-induced ischemia on MPI and coronary artery calcium (CAC) and demonstrated in approximately 4000 asymptomatic patients that CAC was predictive of ischemia on MPI.[16] However, only a minority of patients (22%) with an abnormal CAC had abnormal perfusion on MPI. Similarly, Berman et al. established that the frequency of abnormal perfusion was related to the magnitude of CAC abnormality.[17] However, patients with normal MPI results frequently had extensive atherosclerosis on the basis of CAC criteria, indicating that a normal MPI did not exclude the presence of CAD. Conversely, the presence of CAC did not necessarily result in perfusion abnormalities on MPI. Therefore, although a relation exists between the extent of

atherosclerosis and ischemia, the extent alone may not be a strong predictor of ischemia. Importantly, to improve agreement of MSCT and MPI, integration of the extent of CAD with other variables of atherosclerosis identified on MSCT can refine identification of patients with ischemic MPI.

In the present study, extent of mixed and calcified plaque independently predicted the presence of ischemia on MPI. Indeed, mixed and calcified lesions are thought to typically represent the more advanced stages of atherosclerosis and thus linked with larger plaque volume and a higher extent of ischemia. Additionally, plaque composition on MSCT has previously been linked to abnormal perfusion on SPECT by Lin et al. in 163 patients.[18] The authors demonstrated that the presence of mixed plaques was found to be the strongest independent predictor of abnormal perfusion (OR 1.6, p=0.01). The current and previous studies indicate that an association between extent and composition of atherosclerosis and a higher likelihood of ischemia may exist. Accordingly, plaque extent and composition should be taken into consideration when evaluating and reporting coronary MSCT angiograms. However, the exact underlying mechanisms remain largely unknown and should be further investigated.

Location of atherosclerosis

Location of atherosclerotic disease has been shown to influence myocardial perfusion. In general, the more proximal the location of stenosis, the more severe and extensive the corresponding perfusion abnormality will be. Conversely, the effect of distal lesions on myocardial perfusion will be limited as a smaller amount of myocardium is involved. In the current study, location of atherosclerotic disease in the LM and/or proximal LAD was demonstrated to be a predictor for the presence of ischemia on MPI. Similarly, previous studies have shown that patients with angiographically observed atherosclerotic disease in the LM and/or proximal LAD are at higher risk for events. Califf et al. developed the jeopardy score (an angiographic risk stratification score) which, in addition to severity of disease, incorporated location of atherosclerotic disease to estimate the amount of myocardium at risk.[19] As more proximally located lesions were associated with a higher occurrence of events, the jeopardy score demonstrated to allow improved risk stratification as compared to other angiographic scoring techniques. Interestingly, Lin et al. adapted this scoring technique for MSCT angiography; the MSCT segment-at-risk score.[18] Using this method, individuals with reversible defects could be more accurately identified.

Clinical implications

Recently, MSCT cardiac imaging has been increasingly applied for the evaluation of patients presenting with suspected CAD. The reported high negative predictive values of almost 100% precipitate MSCT as a particularly effective technique for ruling out the presence

of obstructive CAD. Accordingly, if patients show normal coronary arteries on MSCT angiography further testing is not required, whereas if atherosclerotic disease has been verified on MSCT, unfortunately no information is provided on the hemodynamical relevance. As a result, the decision which patient requires further functional testing or direct invasive evaluation with potential revascularization currently remains largely dependent on individual interpretation of the coronary arteries on MSCT angiography combined with pre-test likelihood and clinical judgment. Preferably, more information than merely presence of luminal narrowing is required from this technique. In our study several MSCT variables of atherosclerosis were identified which were associated with a higher likelihood of ischemia. Moreover, integration of all MSCT variables of atherosclerosis significantly improved prediction of the presence of ischemia on MPI. Possibly, these results may allow a more refined and individualized assessment of patients undergoing MSCT angiography and provide the basis for the development of an algorithm to improve identification of patients requiring more aggressive therapy or intervention.

However it is important to realize that in the current study, MSCT and MPI data were acquired in two different institutions with slightly different image acquisition protocols, which may have influenced our findings.

Conclusion

The results of the current study demonstrate that in addition to the presence of obstructive CAD, anatomical MSCT variables describing plaque extent, composition and location of atherosclerosis are independent predictors for the presence of ischemia on MPI.

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