Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

Schuijf, J.D.

Chapter 14

Relationship between Non-Invasive Coronary Angiography with Multi-Slice Computed Tomography and Myocardial Perfusion Imaging

Joanne D. Schuijf, William Wijns, J. Wouter Jukema, Douwe E. Atsma,
Albert de Roos, Hildo J. Lamb, Marcel P. M. Stokkel,
Petra Dibbets-Schneider, Isabel Decramer, Pieter De Bondt,
Ernst E. van der Wall, Piet K. Vanhoenacker, Jeroen J. Bax

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Abstract

Background

Multi-slice computed tomography (MSCT) detects atherosclerosis, whereas myocardial perfusion imaging (MPI) detects ischemia; how these 2 techniques compare in patients with an intermediate likelihood of CAD is unknown. Aim of the study was to perform a head-to-head comparison between MSCT and MPI in patients with an intermediate likelihood of coronary artery disease (CAD), and to compare non-invasive findings to invasive coronary angiography.

Methods

114 patients, mainly with intermediate likelihood of CAD, underwent both MSCT and MPI. MSCT studies were classified as having no CAD, non-obstructive (<50% luminal narrowing) CAD or obstructive CAD. MPI examinations were classified as showing normal or abnormal (reversible and/or fixed defects). In a subset of 58 patients, invasive coronary angiography was performed.

Results

Based on the MSCT data, 41 (36%) patients were classified as having no CAD, of which 90% had normal MPI. A total of 33 (29%) patients showed non-obstructive CAD, whereas at least 1 significant (≥50% luminal narrowing) lesion was observed in the remaining 40 (35%) patients. Only 45% of patients with an abnormal MSCT had abnormal MPI; even in patients with obstructive CAD on MSCT, 50% still had a normal MPI. In the subset of patients undergoing invasive angiography, the agreement with MSCT was excellent (90%).

Conclusions

MPI and MSCT provide different and complementary information on CAD, namely detection of atherosclerosis versus detection of ischemia. As compared to invasive angiography, MSCT has a high accuracy for detecting CAD in patients with an intermediate likelihood of CAD.

Introduction

In the evaluation of patients with suspected coronary artery disease (CAD), the role of non-invasive imaging has increased exponentially over the past decades. Particularly in patients with an intermediate pre-test likelihood of CAD, non-invasive imaging plays an important role in risk stratification and selection of further treatment strategies. Traditionally, the detection of CAD by non-invasive imaging was based on assessment of the hemodynamic significance of the stenoses through visualization of inducible ischemia. For this purpose, myocardial perfusion imaging (MPI) with gated single photon emission computed tomography (SPECT) has been used extensively [1].
More recently, multi-slice computed tomography (MSCT) has been proposed as an alternative imaging modality for evaluation of patients with suspected CAD. With the recently introduced 64-slice MSCT, high sensitivity and specificity for the detection of significant (≥50% luminal narrowing) stenoses have been reported [2-7]. However, since MSCT visualizes coronary artery stenoses directly rather than the hemodynamic significance of the lesions, it is important to recognize that, unlike MPI, the technique identifies atherosclerosis rather than ischemia.
Thus far, data regarding the diagnostic accuracy of MSCT have been obtained in populations undergoing invasive coronary angiography because of a high likelihood of CAD. In contrast, its value in patients with a lower likelihood of CAD remains to be established, despite the fact that this population represents the target population for non-invasive diagnostic imaging. Moreover, the relative merits MPI and MSCT in patients with an intermediate likelihood of CAD remain to be established. Accordingly, the aim of the present study was to perform a head-to-head comparison between MSCT and MPI in patients with mainly an intermediate likelihood of CAD, including women. In addition, the non-invasive findings were compared to invasive coronary angiography in a subset of patients.

Methods

Patients and Study protocol

The study group consisted of 114 consecutive patients who presented to the outpatient clinic (Leiden, the Netherlands and Aalst, Belgium) for the evaluation of chest pain without history of CAD in whom non-invasive imaging with gated SPECT was clinically indicated. In addition to MPI, patients underwent non-invasive coronary angiography with MSCT within one month. Exclusion criteria were 1) known allergy to iodinated contrast agent, 2) renal insufficiency (serum creatinine >120 mmol/L), 3) atrial fibrillation, 4) pregnancy, and 5) known CAD, defined as history of myocardial infarction or coronary revascularization and/or presence of one or more angiographically documented coronary stenosis ≥50% luminal diameter [8;9]. For each patient, the baseline clinical characteristics (type of symptoms and risk factors) were recorded [10]. Pre-test likelihood of CAD was determined according to the Diamond and Forrester method using percent cut-offs of <13.4%, >87.2% and in-between for respectively low, high and intermediate pre-test likelihood [11]. The study protocol was approved by the ethics committee and informed consent was obtained.

MSCT coronary angiography

In the first 28 patients, data acquisition was performed using a 16-slice MSCT scanner (Aquilion 16, Toshiba Medical Systems, Japan) with a collimation of 16 x 0.5 as previously described [9]. In the remaining 86 patients, imaging was performed using a 64-slice MSCT scanner (Aquilion 64, Toshiba Medical Systems, Japan or Sensation 64, Siemens, Germany). Accordingly, data were acquired with a collimation of either 64 x 0.5 mm or 32 x 2 x 0.6 mm and a tube rotation time of 400 or 330 ms, respectively. For the Aquilion 64, the tube current was 300 mA at 120 kV for patients with normal posture. In case of patients with higher body mass indexes, tube current was increased to 350 or 400 mA at 135 kV. For the Siemens 64, tube currents up to 550 ms at 120 kV were available. During 16-slice MSCT, non-ionic contrast material was administered in the antecubital vein with an amount of 130 to 140 ml, depending on the total scan time, and a flow rate of 4 ml/sec (Xenetix 300 ®) followed by a saline flush. Similarly, for 64-slice MSCT, 80 to 110 ml, again depending on the total scan time, was administered with a flow rate of 5 ml/sec (Iomeron 400 ®) resulting in comparable contrast doses for 16- and 64-slice MSCT. Subsequently, data sets were reconstructed and transferred to a remote workstation as previously described [9]. Briefly, images were initially reconstructed at 75% of the cardiac cycle. In case of motion artefacts, a representative single slice was reconstructed throughout the cardiac cycle in steps of 20 ms to determine the most optimal additional reconstruction phases.

MSCT examinations were evaluated on a patient level and vessel level by an experienced operator blinded to the gated MPI data for the presence of significant (≥50% luminal narrowing) stenoses. For this purpose, both the original axial dataset as well as curved multiplanar reconstructions were used. The MSCT studies, or coronary arteries, without significant or obstructive stenoses were further classified as completely normal or as having non-obstructive CAD, when atherosclerotic lesions <50% of luminal diameter were present.

Stress-rest gated myocardial perfusion imaging

In all patients, stress-rest MPI (using either technetium-99m tetrofosmin or technetium-99m sestamibi) was performed with symptom-limited bicycle exercise or pharmacological (dipyridamole, adenosine or dobutamine) stress [12]. Data were acquired with either a dual-head SPECT camera (Vertex Epic ADAC Pegasus, n=27) or a triple-head SPECT camera (GCA 9300/HG, Toshiba Corp., Tokyo, Japan, n=87) 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 [13;14]. Perfusion defects were identified on the stress images (segmental tracer activity less than 75% of maximum) and divided into ischemia (reversible defects, with ≥10% increase in tracer uptake on the resting images) or scar tissue (irreversible defects). 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. The gated images were used to assess regional wall motion to improve differentiation between perfusion abnormalities and attenuation artifacts [15].

Conventional coronary angiography

A total of 58 patients were referred for conventional coronary angiography based on clinical presentation and/or imaging findings at the discretion of the referring cardiologist. Conventional coronary angiography was performed according to standard clinical protocols. Coronary angiograms were evaluated by two experienced observers blinded to the MSCT data using the same classification as used for the MSCT studies (normal, significant stenoses defined as ≥50% luminal narrowing or non-obstructive atherosclerosis).

Statistical analysis

Continuous variables were described by mean ± SD. Comparisons between patient groups were performed using 1-way ANOVA for continuous variables and the Chi-Square test with Yates' correction for categorical variables. A P-value <0.05 was considered statistically significant.

Results

Patient characteristics

In total 114 patients (64 male, 50 female, average age 60 ± 11 years) were enrolled and underwent both MSCT and stress-rest gated SPECT within 1 month of each other. Patient characteristics are

Table 1. Clinical characteristics of the study population (n=114).

	n (%)
Gender (M/F)	64/50
Age (years)	60 ± 11
Risk factors for CAD	
Diabetes Mellitus	24 (21%)
Hypertension	53 (46%)
Hypercholesterolemia	53 (46%)
Positive family history	36 (32%)
Current smoking	33 (29%)
Obese (BMI ≥ 30 kg/m^2)	16 (14%)
Symptoms	
Asymptomatic	10 (9%)
Dyspnoea	1 (1%)
Non-anginal chest pain	5 (4%)
Atypical angina pectoris	88 (77%)
Typical angina pectoris	10 (9%)
Pre-test likelihood of CAD	
Low	7 (6%)
Intermediate	97 (85%)
High	10 (9%)

Abbreviations: BMI: body mass index, CAD: coronary artery disease.

described in detail in Table 1. Pre-test likelihood of CAD according to Diamond and Forrester was low, intermediate and high in respectively 7 (6%), 97 (85%) and 10 (9%) patients. For men, these percentages were respectively 3%, 84%, and 13%. In women, pre-test likelihood was low in 10%, intermediate in 86% and high in 4% of women. Based on clinical presentation and/or imaging results, 58 patients (38 men, 20 women, average age 63 ± 10 years) were referred for invasive coronary angiography. Clinical parameters of these patients are provided in Table 2. In this subset, pre-test likelihood of CAD was low, intermediate or high in 1 (2%), 48 (83%) and 9 (15%) of patients, respectively.

Table 2. Clinical characteristics of patients referred for invasive angiography (n=58).

	n (%)
Gender (M/F)	38/20
Age (years)	63 ± 10
Risk factors for CAD	
Diabetes Mellitus	17 (29%)
Hypertension	36 (62%)
Hypercholesterolemia	34 (59%)
Positive family history	18 (31%)
Current smoking	23 (40%)
Obese (BMI ≥ 30 kg/m2)	10 (17%)
Symptoms	
Asymptomatic	3 (5%)
Dyspnea	1 (2%)
Non-anginal chest pain	1 (2%)
Atypical angina pectoris	44 (76%)
Typical angina pectoris	9 (15%)
Pre-test likelihood of CAD	
Low	1 (2%)
Intermediate	48 (83%)
High	9 (15%)

Abbreviations: BMI: body mass index, CAD: coronary artery disease.

MSCT coronary angiography

Average heart rate during MSCT data acquisition was 66 ± 15 beats per minute. Based on the MSCT images, 41 (36%) patients were classified as having no CAD. A total of 33 (29%) patients showed non-obstructive CAD, whereas at least one significant ≥50% luminal narrowing was observed in the remaining 40 (35%) patients. Analysis on a vessel basis resulted in 342 coronary arteries, of which 157 (%) were normal. CAD was identified in the remaining 185 coronary arteries with at least 1 significant lesion in 62 (18%) coronary arteries.

Stress-rest gated myocardial perfusion imaging

In the majority of patients, stress was performed with symptom-limited bicycle exercise (n=72; 63%). In those patients, at least 85% of maximum age-predicted heart rate was achieved if no stress-induced symptoms or changes in ECG or blood pressure occurred. In the remaining patients, pharmacological stress was applied using adenosine (n=30; 26%), dobutamine (n=7; 7%) or dipyridamole (n=5; 3%). Normal myocardial perfusion in both stress and rest images was observed in 77 (68%) patients. In the remaining 37 patients, reversible and fixed defects were observed in 28 and 12 patients, respectively; 3 patients showed both fixed and reversible defects. On a vascular territory basis, 284 (83%) territories showed normal myocardial perfusion, whereas reversible and fixed defects were observed in 38 (11%) and 20 (6%) vascular territories, respectively.

Conventional coronary angiography

Out of 58 patients undergoing invasive coronary angiography, no abnormalities were seen in 9 (16%) patients, whereas 22 (38%) patients showed non-obstructive CAD. In the remaining 27 (47%) patients, at least 1 significant narrowing was detected.

Relation between findings on MSCT angiography and myocardial perfusion imaging

Patient based analysis

As demonstrated in Figure 1, the majority of patients with a normal MSCT study showed normal perfusion on MPI (n=37, 90%). In patients with an abnormal MSCT study (with either obstructive or non-obstructive CAD), 40 (55%) patients had a normal MPI, whereas 33 (45%) had an abnormal MPI.

In Figure 2, the distribution of MPI results among patients with either obstructive or non-obstructive CAD on MSCT is depicted. In patients with obstructive CAD on MSCT, abnormal perfusion was observed in 20 (50%) patients. Of these patients, respectively 7 and 15 patients showed fixed or reversible defects. The majority of patients (n=20, 61%) with non-obstructive CAD on MSCT had normal perfusion on MPI. In the remaining 13 (39%) patients, reversible defects were observed in 11 with only 2 patients showing fixed defects. An example of a patient with abnormal MSCT but normal MPI is provided in Figure 3.

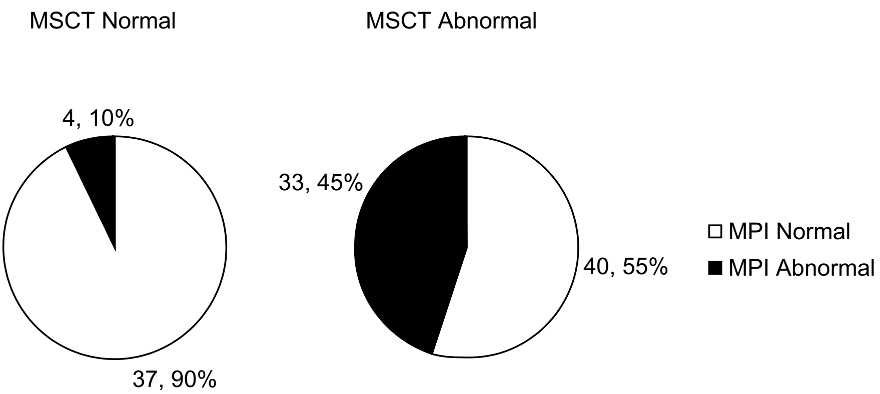

Figure 1. Pie-charts depicting the relation between MSCT and MPI results. Of note, the MSCT abnormal population includes both patients with non-obstructive and obstructive CAD.

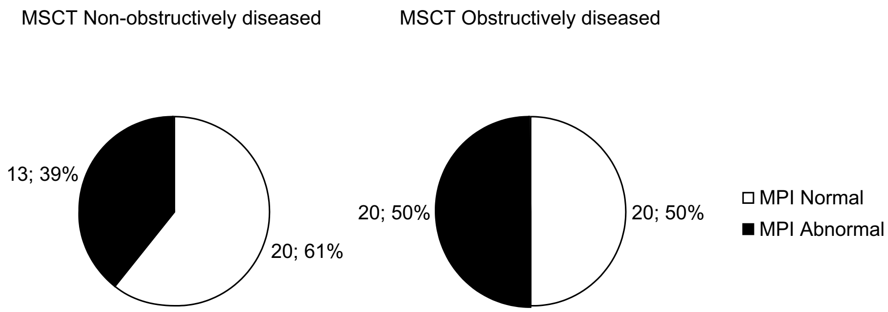

Figure 2. Pie-charts depicting the relation between MSCT and MPI results.

In a separate analysis depicted in Table 3, results were compared between data obtained with 16-slice and 64-slice MSCT, indicating no significant differences in distribution of normal and abnormal MPI examinations for the different MSCT categories.

Vessel based analysis

In total, 342 coronary arteries and related perfusion territories were evaluated. The majority of the 157 normal coronary arteries on MSCT showed normal MPI as well, (n=142, 90%). Also, in 143 of 185 (77%) vascular territories corresponding to coronary arteries with abnormal MSCT, normal perfusion was demonstrated. In coronary arteries showing non-obstructive CAD on MSCT, normal MPI was obtained in 104 of 123 (85%) corresponding vascular territories. Finally, 24 of 62 (39%) coronary arteries with obstructive CAD on MSCT showed abnormal myocardial perfusion.

Comparison of MSCT and MPI to conventional coronary angiography in 58 patients

Table 3. Comparison of 16-slice versus 64-slice MSCT.

	16-slice MSCT	64-slice MSCT	P-value*
MPI Abnormal/MPI Normal			
MSCT Normal	2/8	2/29	NS
MSCT Non-obstructively diseased	5/3	8/17	NS
MSCT Obstructively diseased	7/3	13/17	NS

*Chi-square analysis with Yates' correction.

The relation between findings on MSCT, MPI and conventional coronary angiography is illustrated in the flowcharts in Figure 4. All patients with normal MSCT (n=9) had normal coronary arteries on conventional coronary angiography; the majority of these patients (n=7, 78%) also had a normal MPI; all patients with normal MSCT, normal invasive angiography but abnormal MPI had a mild fixed defect suggestive of attenuation artefacts.

An abnormal MSCT was noted in 49 patients (with 16 non-obstructive and 33 obstructive CAD) and invasive coronary angiography confirmed CAD in all patients. Interestingly, only 29 (59%) patients had an abnormal MPI.

Non-obstructive CAD on MSCT was observed in 16 (28%) patients, and all had non-obstructive CAD on invasive angiography; of note, 6 (38%) patients had a normal MPI and 10 (62%) had an abnormal MPI.

Obstructive CAD (at least one significant stenosis) on MSCT was noted in 33 (57%) patients, with 27 (82%) having obstructive CAD on invasive coronary angiography. An abnormal MPI was present in 16 (59%) patients, whereas 11 (41%) patients had a normal MPI. Of interest, 2 of these patients had 3-vessel disease. In a separate analysis, data obtained with 16-slice MSCT were compared to 64-slice data. With 16-slice MSCT, 19 of 21 (90%) patients were correctly diagnosed as compared to invasive coronary angiography, whereas correct diagnosis was obtained in 33 of 37 (89%) patients studied with 64-slice MSCT (P=NS).

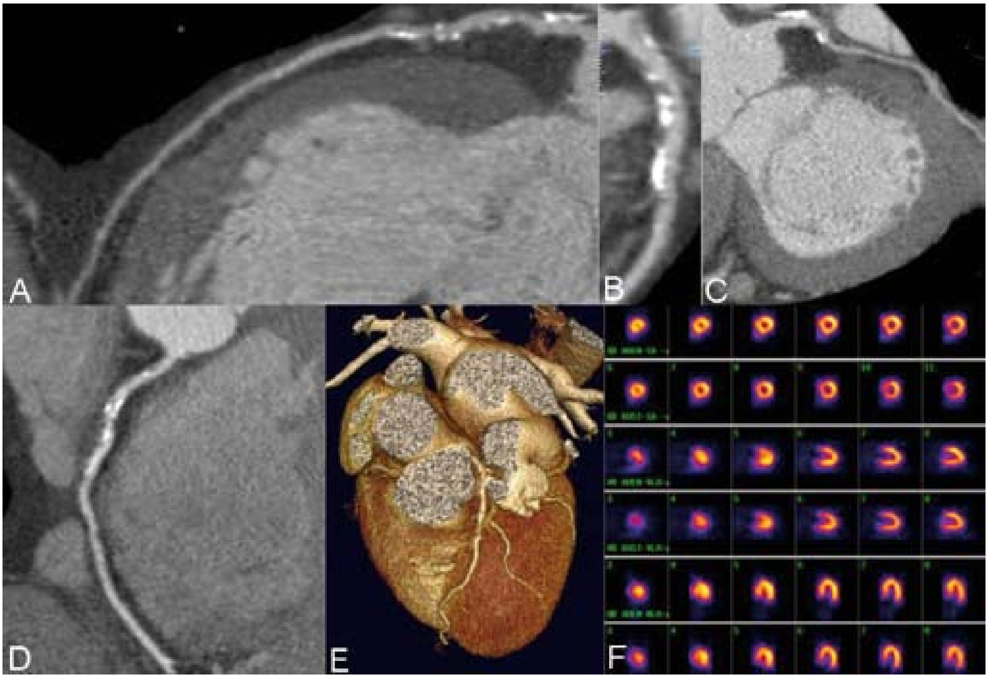

Figure 3. Discrepancy between MSCT and MPI: Example of a 69-year-old male patient with an abnormal MSCT but no perfusion abnormalities on MPI. In Panels A, C, and D, curved multiplanar MSCT reconstructions of respectively the left anterior descending coronary artery, the left circumflex coronary artery and the right coronary artery are provided. Panel B is an enlargement of the proximal part of the left anterior descending coronary artery perpendicular to Panel A, whereas a 3D volume rendered reconstruction is provided in Panel E. In all 3 coronary arteries, the presence of diffuse atherosclerosis can be observed. In Panel F, however, short-axis (upper two rows), vertical long-axis (middle two rows) and horizontal long-axis (lower two rows) MPI images during exercise (first, third and fifth rows) and rest (second, fourth and sixth rows) demonstrate homogeneous myocardial perfusion without perfusion defects.

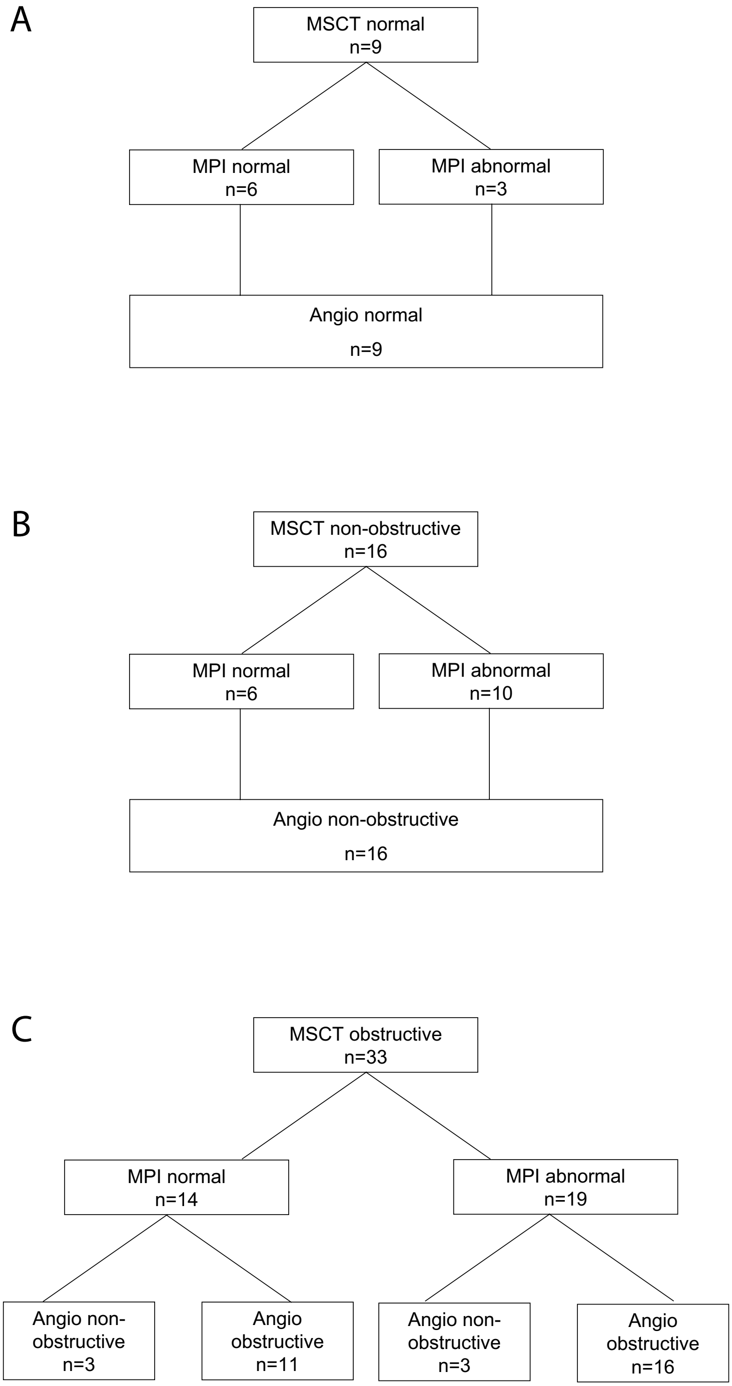

Figure 4. Flow charts describing the relation between findings on MSCT, MPI and invasive coronary angiography.

Discussion

This head-to-head comparison between non-invasive coronary angiography with MSCT and functional imaging by MPI in a large population with an intermediate likelihood of CAD, reveals several findings. Firstly, 55% of patients with an abnormal MSCT had normal MPI, indicating that only half of the observed lesions on MSCT may be of hemodynamic significance. Even in patients with obstructive CAD on MSCT, 50% had a normal MPI.

Conversely, patients with a normal MPI frequently (52%) exhibited an abnormal MSCT, indicating that a normal MPI does not exclude the presence of coronary atherosclerosis. In the subgroup of patients undergoing coronary angiography, similar results were obtained. These findings highlight the discrepancy between the 2 tests, namely that atherosclerosis is not synonymous to ischemia, but also emphasize the complementary information that both tests provide.

Finally, this is a first attempt to apply MSCT in patients with an intermediate likelihood of CAD, including 44% of women. The MSCT findings correlated well with invasive coronary angiography, suggesting that the high accuracy of MSCT demonstrated previously in patients with a high likelihood of CAD also applies to patients with an intermediate likelihood of CAD.

Obstructive CAD versus hemodynamic significance

In the current study, a normal MPI was obtained in 55% of patients with an abnormal MSCT. Moreover, 50% of patients with obstructive CAD on MSCT had a normal MPI. The findings are in line with preliminary results by Hacker et al [16] who compared MSCT and MPI in 25 patients with known or suspected CAD. These authors showed that only 8 of 17 (47%) significant stenoses on MSCT were associated with abnormal perfusion on MPI.

These observations confirm that the severity of focal stenosis severity in itself is not sufficient to predict the hemodynamic significance of the coronary plaque burden. In our study, vessel based analysis shows indeed that only 39% of obstructed vessels have abnormal MPI while 15% of non obstructive vessels show perfusion abnormalities. In the latter situation, the additive effect of multiple mild stenoses in series eventually causes the perfusion defect [17]. Similarly discrepant results have been reported when comparing invasive angiography with non-invasive imaging or invasive fractional flow reserve measurements. Salm et al [18] showed that MPI was normal in 50% of angiographically significant lesions. In particular lesions with an intermediate stenosis severity (defined as a percent diameter stenosis between 40% and 70%) vary in hemodynamic significance [18-20]. To some extent, these discrepancies may be attributable to imperfect allocation of perfusion defects to corresponding coronary arteries due to individual variations in coronary anatomy. Still, analysis on a vessel basis further emphasizes that only a moderate proportion of anatomically significant stenoses are of hemodynamic significance and result in abnormal perfusion in the corresponding vascular territory.

Atherosclerosis versus MPI findings

Alternatively, CAD was completely absent in only 48% of patients with normal MPI of which 52% had atherosclerosis on MSCT and 26% already exhibited obstructive CAD on MSCT. Thus, a normal MPI does not exclude CAD and non-invasive coronary angiography with MSCT allows detection of CAD at a much earlier stage than MPI. The relation between atherosclerosis detected by coronary calcifications and MPI was explored recently by Berman et al [21] in 1195 patients without known CAD who underwent electron beam computed tomography. The authors showed a poor relation between the presence of atherosclerosis on electron beam computed tomography and MPI results. Similar to the current results, a large proportion of patients with a normal MPI had atherosclerosis according to coronary artery calcium scoring, indicating again that a normal MPI does not exclude the presence of CAD.

Clinical implications

The current observations have important clinical implications. With the introduction of MSCT and comparison to MPI, a paradigm-shift occurs in the definition of CAD, displacing the emphasis from inducible ischemia to atherosclerosis. Based on the discrepancy between MSCT and MPI, one can argue that MSCT could be used as the first-line test. A normal MSCT excludes CAD and the patient can be reassured. Alternatively, in the presence of atherosclerosis on MSCT, additional information is needed to define the hemodynamic significance of the observed lesions. This additional information could be provided by sequential MSCT and nuclear myocardial perfusion imaging using either PET or SPECT. Patients with an abnormal MSCT but normal MPI have CAD. In those, aggressive medical therapy and risk factor modification should be considered (targeted primary prevention), whereas patients with an abnormal MSCT and an abnormal MPI should be referred for invasive angiography with potential revascularization.

MSCT in patients with an intermediate likelihood of CAD

As emphasized in a recent meta-analysis [22], the available MSCT studies have been performed in patients with known CAD or a high likelihood of CAD; in particular, pooling of 24 MSCT studies revealed a prevalence of significant stenoses on MSCT and invasive angiography of 65%. Pooled data from six 64-slice MSCT studies (including 363 patients) showed a sensitivity of 96% and a specificity of 92% to detect or exclude significant CAD [2-7]. The current study was performed in patients with predominantly intermediate likelihood of CAD, yet the agreement between MSCT and invasive angiography remains excellent. All patients with normal MSCT had normal coronary arteries on invasive angiography, and all patients with (obstructive or non-obstructive) CAD on MSCT had CAD on invasive angiography. Only 6 of 33 (18%) patients with a significant stenosis on MSCT did not have a significant stenosis on invasive coronary angiography by visual estimation.

These observations suggest that MSCT may be as accurate in patients with an intermediate likelihood as in patients with a high likelihood of CAD, although larger studies are clearly needed to confirm this finding.

Limitations

In the present study, MSCT and MPI protocols were not uniform in all patients. For MSCT, scanners from 2 generations as well as manufacturers were used, while for MPI different tracers and stressors were applied. This however, reflects the daily clinical routine and confers generalized applicability to our observations. Also, comparison of results obtained with either 16-slice or 64-slice MSCT did not show any significant differences.

Conventional coronary angiography was performed in approximately half of the patients included in the study and stenotic segments were not analyzed by quantitative angiography. However, the angiography was performed as considered clinically indicated and according to standard practice. Finally, despite the introduction of 64-slice MSCT, the technique still suffers from several important limitations, including limited diagnostic accuracy in case of extensive calcifications or elevated heart rates. Also, combination of MSCT with MPI and (potentially) conventional coronary angiography will result in a considerable radiation exposure.

Conclusions

MSCT and MPI provide different information on CAD, namely atherosclerosis versus ischemia. How both techniques should be integrated in the clinical setting is not entirely clear yet, but the discrepant results provided by the 2 techniques underscore that MSCT and MPI provide complementary information.

Also, our study demonstrates that MSCT may be as accurate in men and women with an intermediate likelihood of CAD as was previously reported in patients with a high likelihood of CAD.

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