Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

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Chapter 8

Do Risk Factors influence Diagnostic Accuracy of Non-Invasive Coronary Angiography with Multi-Slice Computed Tomography?

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Abstract

Background

Multi-Slice Computed Tomography (MSCT) is a relatively new non-invasive imaging modality in the evaluation of patients with suspected coronary artery disease (CAD). Whether diagnostic accuracy is influenced by gender or risk factors for CAD is currently unknown and was evaluated in the present study.

Methods

In 197 patients (171 men, mean age 60 ± 11 years) 16-slice MSCT was performed and compared to invasive coronary angiography at 2 different centers (Leiden and Rotterdam, the Netherlands). Diagnostic accuracy for the detection of ≥50% luminal narrowing was calculated for all patients combined as well as for patients with known versus suspected CAD. In addition, diagnostic accuracy was determined in men versus women and in different subsets of patients, based on the presence of risk factors for CAD including hypertension, type 2 diabetes mellitus, hypercholesterolemia, and obesity. Only segments with a diameter ≥2.0 mm were evaluated, whereas smaller segments as well as stents were excluded from the analysis.

Results

Overall, a sensitivity and specificity of 99% and 86% on a patient level were demonstrated, with corresponding positive and negative predictive values of respectively 95% and 96%. Similar values were observed in the different subsets of patients, with no statistical differences.

Discussion

These findings confirm the high diagnostic accuracy of MSCT, regardless of gender or risk factors.

Introduction

Over the past few years, Multi-Slice Computed Tomography (MSCT) has emerged as a promising modality for non-invasive evaluation of coronary anatomy [1,2]. Moreover, with the introduction of 16- and 64-slice scanners, the non-invasive diagnosis of significant CAD has improved substantially. Reported sensitivities and specificities are in the range of 70% to 98% and 86% to 98% respectively, with an average sensitivity and specificity of 88% and 96% respectively [3]. In addition, more complete coverage of the coronary tree has been achieved, with a substantial reduction in the number of non-diagnostic segments [3]. Accordingly, routine evaluation for CAD has become realistic and the expectation is that (in the near future) MSCT may replace invasive angiography to rule out CAD. For this purpose, the technique should primarily be implemented in the clinical work-up of patients with *suspected* CAD rather than *known* CAD. Considering the fact that the majority of these patients will present with atypical or even no complaints but with an elevated risk of CAD due to the presence of multiple risk factors, information on the accuracy of MSCT in these various clinical conditions is highly needed. However, despite the overwhelming number of reported studies thus far, it is unknown whether diagnostic accuracy is influenced by gender or risk factors. The purpose of the present study therefore, was to evaluate the influence of gender and risk factors for CAD on the diagnostic accuracy of 16-slice MSCT in a large cohort of patients.

Methods

Study population

A total of 201 patients, presenting with known or suspected CAD (based on symptoms and/or multiple risk factors for CAD) and scheduled for invasive coronary angiography for diagnostic purposes were included at 2 different centers (Rotterdam and Leiden, the Netherlands). The following exclusion criteria were applied: renal insufficiency (serum creatinine >120 µmol/L [1.35 mg/dL]) or other contraindications to the administration of iodinated contrast, pregnancy, acute coronary syndromes and (supra-)ventricular arrhythmias. For all patients, the presence of coronary risk factors was documented according to the following criteria:

1. **Type 2 Diabetes** was defined as 1. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl (11.1 mmol/l) or 2. Fasting plasma glucose level ≥126 mg/dl (7.0 mmol/l)[4].
2. **Hypertension** was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, and/or use of anti-hypertensive medication [5].
3. **Obesity** was defined as a body mass index (BMI) ≥30 kg/m [2,5,6].
4. **Hypercholesterolemia** was defined as total serum cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or use of a lipid-lowering agent [5,7].
5. **Smoking.**
6. **A positive family history** was defined as having relatives of first or second degree with premature (younger than 55 years of age) cardiovascular disease.

The study protocol was approved by the local ethics committees, and informed consent was obtained from all patients.

MSCT; Data acquisition

All studies were performed with a 16-detector row system. In Rotterdam, a Sensation 16 (Siemens, Germany) was used, whereas in Leiden, data were acquired with an Aquilion 16 system (Toshiba, Japan). If the heart rate was 65 beats/min or higher, additional beta-blockers (metoprolol, 100 mg, single dose, 1 hour prior to scan) were provided if tolerated. Scan parameters of the Sensation 16 system were the following: collimation 16 x 0.75 mm, tube rotation 420 ms, table feed 3 mm/rotation, and tube voltage 120 kV, while the tube current was 400 to 450 mAs [8]. A bolus of 100 ml contrast (Visipaque 320, Amersham Health, Forchheim, United Kingdom) was injected intravenously at a flow rate of 4 ml/s. Scan parameters of the Aquilion 16 were: collimation 16 x 0.5 mm, tube rotation, 400 or 500 ms, table feed 3-4 mm/rotation, and tube voltage 120 kV at 250mA. The total contrast dose for the scan ranged from 120 to 150 ml depending on the total scan time, with an injection rate of 4 ml/s through the antecubital vein (Xenetix 300®, Guerbet, Aulnay S. Bois, France), followed by a saline flush of 40 ml [9]. Both systems used an automated bolus tracking system for timing of the helical scan. Images were obtained during a single breath hold of approximately 20-25 seconds, while the ECG was recorded simultaneously to allow retrospective gating of the data.
Images were reconstructed in cardiac phase containing the fewest motion artifacts, typically during the mid-to-end diastolic phase. However, other reconstruction windows were obtained when necessary. Reconstructed images were then transferred to a remote workstation for evaluation.

MSCT; Data evaluation

MSCT angiograms were independently evaluated for the presence of significant (≥50% narrowing of luminal diameter) by 2 observers (blinded to all other data). In addition to the original axial slices, thin-slab maximum intensity projections and multiplanar reconstructions were used to estimate the degree of luminal narrowing. Segments with coronary stents or side-branches with a diameter smaller than 2.0 mm were excluded from the analysis. In case of previous bypass grafting, only native segments distal to the anastomosis of a patent bypass graft were evaluated.

Conventional coronary angiography

Conventional coronary angiography was performed according to standard clinical protocols within 1 month of the MSCT examination. To obtain vascular access, the femoral approach with the Seldinger technique was applied. Angiograms were evaluated by consensus reading of 2 experienced observers without knowledge of the MSCT data.

Stress electrocardiography

In a subset of patients, stress-testing, by means of a 12-lead ECG at rest and during stress, was performed within 3 months of MSCT and conventional coronary angiography. Patients with revascularization in the period between the stress-ECG and MSCT/conventional coronary angiography were excluded, resulting in 44 eligible patients. Electrocardiographic findings during peak stress were graded as normal or abnormal based on the presence of ≥1.0-mm ST-segment changes (horizontal or downslope) measured at 80 ms after the J point in 2 contiguous leads during peak stress or immediately after recovery.

Data evaluation and statistical analysis

Sensitivity, specificity, positive and negative predictive values with corresponding 95% confidence intervals (CI) for the detection of ≥50% luminal narrowing were calculated. Data were analyzed on a patient, vessel and segmental level. In addition, diagnostic accuracy was compared between men and women and the data were analyzed according to the presence of risk factors for CAD. A p-value <0.05 was considered to indicate statistical significance.

Table 1. Characteristics of the study population (n=197).

Characteristic	value (%)
Gender (M/F)	171/26
Age (yrs)	60 ± 11
Heart rate during acquisition	61 ± 10
Beta blocker medication	181 (92%)
Previous PCI/ CABG	59(30%)/23 (12%)
Risk factors for CAD	
Diabetes type 2	54 (27%)
Hypertension	106 (54%)
Smoking	83 (42%)
Hypercholesterolemia	143 (73%)
Family with CAD	90 (46%)
Obesity	44 (22%)
Vessel disease	
0-vessel	34 (17%)
1-vessel	57 (29%)
2-vessel	56 (28%)
3-vessel	50 (25%)

Data are presented as absolute values (%).

Results

Clinical features

In total, 201 patients were evaluated with MSCT, of which 128 in Rotterdam [8] and 73 in Leiden [9]. A subset of patients has been included in previous studies [8;9]. MSCT was performed successfully in all but 2 patients. In those 2 patients, the examination could not be evaluated due to technical issues. In 2 other patients, all 3 vessels were stented and these patients were excluded from the analysis as well. Main clinical features of the remaining 197 patients are presented in Table 1.

Coronary angiography in all patients

Based on invasive coronary angiography, significant CAD (defined by the presence of significant stenoses or previous revascularization) was present in 163 patients (1-vessel disease in 57 patients, 2-vessel disease in 56, and 3-vessel disease in 50).

A total of 2015 segments were available for analysis. Of these segments, 92 (5%) were of low image quality but were included in the analysis. A total of 21 (1%) segments were excluded from the analysis. Causes of poor image quality or uninterpretability were predominantly calcifications, motion artifacts, and low contrast-to-noise ratio.

Table 2. Diagnostic accuracy of MSCT in the entire study population (n=197).

	Segmental basis	Vessel basis	Patient basis
Excluded	1%	1%	0%
Evaluation possible with low confidence	5%	2%	8%
Sens (%, 95% CI)	90, 87-93	92, 89-95	99, 97-100
Spec (%, 95% CI)	96, 95-97	93, 91-95	86, 76-96
PPV (%, 95% CI)	82, 78-86	87, 83-91	95, 92-98
NPV (%, 95% CI)	98, 97-99	96, 94-98	96, 90-100

NPV: negative predictive value; PPV: positive predictive value; sens: sensitivity; spec: specificity.

Significant stenoses were correctly identified in 303 segments, while the presence of significant stenosis was correctly ruled out in 1591 of 1658 segments, resulting in a sensitivity and specificity of 90% (95% CI 87-93%) and 96% (95% CI 95-97%). In only 2 of 147 (1%) patients, the presence of one or more significant stenoses was missed on MSCT (resulting in a sensitivity of 99% on a patient level, 95% CI 97-100%), while the absence was correctly identified in 43 of 50 (86%, 95% CI 76-96%) patients without significant stenoses. On a vessel basis, a sensitivity and specificity of respectively 92% (95% CI 89-95%) and 93% (95% CI 91-95%) were obtained.

Data are summarized in Table 2.

Influence of gender

In total, 26 (13%) of included patients were female. Similar diagnostic accuracy was observed in men and women (Table 3). Sensitivity and specificity (on a segmental basis) were respectively 90% (95% CI 79-100%) and 97% (95% CI 95-99%) in women and 90% (95% CI 87-93%) and 96% (95% CI 95-97%) in men (sensitivity and specificity not significant versus women).

Table 3. Influence of gender on the diagnostic accuracy of MSCT.

	Females (n=26)	Males (n=171)
Patient basis		
Sens (%, 95% CI)	100	98, 96-100
Spec (%, 95% CI)	90, 71-100	85, 74-96
PPV(%, 95% CI)	94, 83-100	96, 93-99
NPV (95% CI)	100	94, 86-100
Segmental basis		
Sens (%, 95% CI)	90, 79-100	90, 87-93
Spec (%, 95% CI)	97, 95-99	96, 95-97
PPV (%, 95% CI)	79, 65-94	82, 78-86
NPV (95% CI)	99, 98-100	98, 97-99

NPV: negative predictive value; PPV: positive predictive value; sens: sensitivity; spec: specificity.

Diagnostic accuracy in the presence of different risk factors for CAD

Next, the diagnostic accuracy of MSCT was explored in the presence of different risk factors (type 2 diabetes n=54, hypertension n=106, hypercholesterolemia n=143, obesity n=44, positive family history n=90, and smoking n=83). Results are summarized in Table 4. No statistical differences were observed between the different groups.

Comparison of patients with suspected and known CAD

Based on clinical evaluation (ECG, history etc) the presence of significant CAD was already known in 75 (38%) patients, whereas it was suspected (based on the presence of symptoms and/or multiple risk factors for CAD) in the remaining 122 (62%). In the former, sensitivity and specificity on a segmental basis were respectively 97% (95% CI 93-100%) and 99% (95% CI 98-100%). In the latter, these values were respectively 89% (95% CI 85-93%, $p<0.05$ versus known CAD) and 95% (95% CI 94-96%, $p<0.05$ versus known CAD). Thus, a slightly higher sensitivity/specificity on a segmental basis was

observed in patients with known CAD as compared to patients with suspected CAD. However, no differences were observed when analysis was performed on a patient level (see Table 5).

Comparison of coronary angiography with stress-electrocardiography

In 44 patients (36 male, 8 female, average age 61 ± 11 years), stress-ECGs were available to evaluate the presence of inducible ischemia. In one patient, the presence of left bundle branch block precluded ECG interpretation. In the remaining 43 patients, stress ECG was abnormal in 10 patients. In all but 1 patient (90%), MSCT confirmed the presence of one or more significant lesions. In 33 patients, no ischemia was detected during stress-ECG testing. Nevertheless, in 18 (55%) of these patients at least 1 or more significant lesion was demonstrated during MSCT. In 4 of these patients with a normal stress-ECG, left main or 3 vessel disease was observed.

Table 4. Influence of coronary risk factors on the diagnostic accuracy of MSCT.

	Risk factor DM type 2 (n=54)	Obesity (n=44)	Hypercholesterolemia (n=143)	Hypertension (n=106)	Family (n=90)	Smoking (n=83)
Segmental basis						
Excluded	2.7%	1.3%	1.4%	0.6%	0.9%	1.8%
Evaluation possible with low confidence	3.2%	5.7%	5.3%	4.6%	4.6%	3.2%
Sens (%, 95% CI)	89, 82-96	92, 85-99	94, 91-97	91, 87-95	90, 85-95	91, 86-96
Spec (%, 95% CI)	95, 93-97	98, 97-99	96, 95-97	96, 95-97	98, 97-99	97, 96-98
PPV (%, 95% CI)	80, 72-88	85, 77-93	82, 77-88	82, 76-88	89, 84-94	82, 75-89
NPV (%, 95% CI)	98, 97-99	99, 98-100	99, 98-100	98, 97-99	98, 97-99	99, 98-100
Patient basis						
Sens (%, 95% CI)	100	97, 91-100	98, 95-100	98,95-100	98, 95-100	100
Spec (%, 95% CI)	100	90, 71-100	86, 76-96	92, 81-100	92, 82-100	81,66-96
PPV (%, 95% CI)	100	97, 91-100	95,91-99	98,95-100	97, 93-100	92, 85-99
NPV (%, 95% CI)	100	90, 71-100	95,88-100	92, 81-100	96, 88-100	100

NPV: negative predictive value; PPV: positive predictive value; sens: sensitivity; spec: specificity.

Discussion

The results of the present study demonstrate the clinical value of MSCT in the assessment of patients presenting with chest pain. In line with previous reported results, a sensitivity and specificity of respectively 90% and 96% on a segmental level was observed in the entire study population. Similar to other studies, the diagnostic accuracy of MSCT for the detection of significant CAD differed between analyses on a patient and segmental level [10]. Whereas specificity and negative predictive values were high on a segmental based analysis (respectively 96% and 98%), these values tended to slightly decrease (86% and 96%) when analyzed on a patient basis. In contrast, sensitivity and positive predictive value increased from 90% and 82% to 99% and 95%, respectively. To a large extent, this observation may be attributed to the high prevalence of CAD in the present population, which was 83% with one in 4 patients having 3-vessel disease.

Table 5. Diagnostic accuracy of MSCT in patients with known versus suspected CAD.

	Suspected CAD (n=122)	Known CAD (n=75)
Patient basis		
Sens (%, 95% CI)	100	95, 88-100
Spec (%, 95% CI)	88, 73-100	85, 73-97
PPV (%, 95% CI)	98, 95-100	89, 80-98
NPV (%, 95% CI)	100	93, 84-100
Segmental basis		
Sens (%, 95% CI)	89, 85-93	97, 93-100
Spec (%, 95% CI)	95, 94-96	99, 98-100
PPV (%, 95% CI)	79, 74-84	93, 88-98
NPV (%, 95% CI)	98, 97-99	100

NPV: negative predictive value; PPV: positive predictive value; sens: sensitivity; spec: specificity.

Gender

In the current study, no gender differences in diagnostic accuracy were observed. Particularly in women, a non-invasive modality to visualize the coronary arteries may be of benefit, since obstructive CAD is less likely to be demonstrated than in age-matched men, despite the presence of symptoms [11]. Indeed, no abnormalities are observed in almost half of all women referred for invasive coronary angiography as compared to 17% in men [12]. However, similar to previous studies using MSCT, women contributed only to a small portion (13%) of the present study population. Clearly, larger cohorts of women need to be studied in order to provide consistent evidence that the technique is not limited in women.

Known CAD, suspected CAD and risk factors

In addition, diagnostic accuracy was compared between patients with suspected and known CAD (according to clinical presentation). Although the majority of studies involving the diagnostic accuracy of MSCT have thus far been confined to predominantly populations with known CAD, the use of the technique will eventually shift towards early evaluation of patients with an intermediate likelihood of CAD. Thus, it is important to establish whether diagnostic accuracy is not affected by knowledge of previous CAD. In the present study, a comparable diagnostic accuracy was observed between patients with suspected and known CAD, suggesting that the MSCT can indeed be of value for early diagnosis of CAD in patients presenting with first complaints or elevated risk profiles. Indeed, these are precisely the patient populations in which MSCT will play an increasingly important role in clinical management. Since in these patients, certain risk factors such as hypertension or type 2 diabetes mellitus are highly prevalent, it has become increasingly important to establish the influence of these clinical conditions on diagnostic performance. At present however only limited data on the performance of MSCT in the presence of these risk factors for CAD are available. Thus far, two studies have previously reported on the feasibility of MSCT in either patients with type 2 diabetes mellitus [13] and hypertension [14]. No effect of either risk factor on the diagnostic accuracy of MSCT was demonstrated and reported sensitivity/specificity were 95%/95% and 93%/96% in respectively patients with type 2 diabetes and patients with hypertension. However, only a limited number of patients were included in both studies. Still, results were very similar to the present findings, which further underline that the diagnostic accuracy of MSCT is not affected by the presence of risk factors. A slightly higher percentage uninterpretable segments however, was in the present study observed in patients with type 2 diabetes (2.7%) as compared to the entire study population (1%). To some extent this phenomenon may be attributed to the more generalized diffuse atherosclerosis that is known to be present in patients with type 2 diabetes, resulting in an increased incidence of (extensive) calcifications, which in turn may affect image quality [15]. Nevertheless, diagnostic accuracy was not different in patients with type 2 diabetes.

Obesity is another risk factor that may influence image quality due to a decreased signal to noise ratio in these patients. Indeed, the largest number of segments with low image quality was observed in patients with a BMI over 30. The percentage of uninterpretable segments however, was similar to the general study group, with no differences in diagnostic accuracy either. As expected, other risk factors such as a positive family history for CAD, smoking and hypercholesterolemia, were found to influence neither image quality nor diagnostic accuracy.

Stress-testing

Finally, results of MSCT were compared in a subset of patients to first-line stress-testing by means of stress-electrocardiography. Although the observation of ischemia on stress-electrocardiography and the presence of significant lesions on MSCT correlated well (90%), correlation between the absence of ischemia versus no significant lesions visible during anatomical testing was considerably

lower (46%). Obstructive CAD was identified in approximately half of patients with a normal stress-ECG, with 4 patients having even left main or 3-vessel disease. Nonetheless, the majority of observed lesions with normal stress-ECG may have represented stenoses without hemodynamic relevance. Comparable findings were reported by Hacker et al, who compared MSCT to myocardial perfusion scintigraphy (MPS) in 25 patients. Similarly, only 47% of lesions on MSCT were associated with ischemia during MPS [16]. Thus, the presence of ischemia, as it appears to concern only a moderate portion of significant lesions, cannot be predicted based on the findings obtained with MSCT. Accordingly, functional testing remains essential in case of an abnormal MSCT examination to determine further management (medical therapy versus revascularization).

Limitations

First, patients were evaluated with two different MSCT systems, while presently no data are available on the relative performance of systems of different manufacturers. Also, to what extent subtle differences in image acquisition or evaluation protocols between both centers may have influenced the results is unknown. Only patients with a high suspicion for CAD and thus referred for invasive coronary angiography were included in the present study, and as a result the prevalence of CAD was high (83%). Accordingly, validation of MSCT in the presence of coronary risk factors is still needed in populations with a lower CAD prevalence, as these populations represent the target population for non-invasive anatomical imaging. Finally, an important limitation is the fact that only segments with a diameter of ≥ 2.0 mm were included, while also stented segments were excluded. With 4- and 16-slice MSCT, evaluation of segments with a small diameter still pose significant problems, which is even worse in the presence of calcifications. Inclusion of segments <2.0 mm would likely have resulted in reduced overall percentage interpretable segments as well as a lower diagnostic performance. However, segments less than 2.0 mm can frequently not be surgically revascularized, and were therefore not included in the present study.

In addition, MSCT has several disadvantages in general. First the radiation dose of a single MSCT examination still ranges between 8 to 12 mSv, which compares unfavorably to conventional coronary angiography. Regarding clinical management, another important limitation exists, which is the fact that no information on the hemodynamical importance of the observed lesions can be derived from MSCT, as also observed in the present study. As a result, the implementation of MSCT may potentially lead to an increased number of patients that are referred to conventional coronary angiography, rather than the desired decrease in referral for angiography. Accordingly, the anatomical MSCT data of patients with a positive examination should ideally be integrated with functional information in order to determine clinical management more precisely.

Conclusion

These findings confirm the high diagnostic accuracy of MSCT, regardless of gender or risk factors. Also, accuracy was comparable between patients with known and suspected CAD, suggesting that

the technique may be of value in the early diagnosis of CAD. As both image quality and diagnostic performance of the technique will continue to improve with the latest generation of 64-slice scanners, cardiologists will become increasingly confident to use the technique as a first-line imaging modality. Nevertheless, comparison between stress-testing and MSCT showed a considerable discrepancy between functional and anatomical findings. Future research therefore should not merely focus on the diagnostic accuracy of MSCT but rather on how to relate this new modality to other available, first-line techniques in order to allow most optimal integration of MSCT in daily clinical cardiology.

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