Imaging of coronary atherosclerosis with multi-slice computed tomography

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Chapter 3

Gender Influence on the Diagnostic Accuracy of 64-Slice Multislice Computed Tomography Coronary Angiography for Detection of Obstructive Coronary Artery Disease

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Abstract

Aims: To compare the diagnostic accuracy of 64-slice multi-slice computed tomography (MSCT) coronary angiography between female and male patients using conventional coronary angiography as the reference standard.

Methods: 103 consecutive patients (51 men, 52 women, mean age 60±10 years) with known and suspected coronary artery disease underwent 64-slice MSCT. Main outcome measure was diagnostic accuracy of 64-slice MSCT to detect obstructive (≥50% luminal narrowing) stenoses in men and women.

Results: One male and two female patients were excluded from the analysis due to non-diagnostic MSCT scans as a result of elevated heart rate and breathing during the scan. Accordingly, on segmental level, 728 of 762 coronary segments were of sufficient quality in women (96% (95% CI 95%-97%)) and 704 of 723 segments were interpretable in men (97% (95% CI 96%-98%)). In the remaining 100 patients included in the further analyses, the sensitivity and specificity on a segmental level in women and men was 85% (95% CI 75%-95%) versus 85% (95% CI 78%-92%) and 99% (95% CI 98%-100%) versus 99% (95% CI 98%-100%), respectively. On a patient level, the sensitivity in women and men was 95% (95% CI 87%-100%) versus 100%, specificity 93% (95% CI 83%-100%) versus 89% (95% CI 74%-100%), positive predictive value 91% (95% CI 79%-100%) versus 94% (95% CI 86%-100%), and negative predictive value 96% (95% CI 89%-100%) versus 100%, respectively.

Conclusions: The findings of the study confirm the high diagnostic accuracy of 64-slice MSCT coronary angiography in both male and female patients.

Introduction

Coronary artery disease (CAD) is the leading cause of mortality in the western world. Although in men mortality due to CAD appears to be declining, an increase has recently been observed in women.[1-3] Unfortunately, accurate diagnosis of CAD may be more challenging in women as compared to men. Limited exercise capacity is frequently encountered in women, resulting in inconclusive exercise electrocardiography results. In addition higher false positive rates may be observed.[2] As a result, a considerable proportion of women are unnecessarily referred for conventional invasive coronary angiography, and obstructive CAD is absent in nearly half of women undergoing invasive coronary angiography.[2]

Multi-slice computed tomography (MSCT) coronary angiography allows direct non-invasive visualization of coronary arteries and accurate detection of obstructive lesions as compared to invasive coronary angiography. Indeed, the reported mean sensitivity and specificity of 64-slice MSCT is 87% and 96%, respectively.[4] In particular, the negative predictive value was extremely high (approaching 100%) allowing reliable exclusion of CAD. Nevertheless, to date substantial under-representation of women has been observed in MSCT diagnostic accuracy studies, with approximately only 20% of included patients being female.[4,5]

Accordingly, the purpose of the study was to compare the diagnostic accuracy of current 64-slice MSCT coronary angiography between males and females using conventional coronary angiography as the reference standard.

Methods

Study population

A total of respectively 51 and 52 consecutive male and female patients presenting with known and suspected CAD (based on chest pain complaints and presence of risk factors of CAD) and scheduled for conventional invasive coronary angiography were included in the study. The aim of the study inclusion was to reach a 50% distribution of both genders in the total patient population. The median interval between conventional and MSCT coronary angiography was 4 (0-8) weeks. No intervening changes in the clinical condition of the patients occurred between the two examinations. Only patients with sinus rhythm and without contraindications to iodinated contrast medium were included in the study. All patients gave informed consent, which was approved by local ethics committee.

MSCT data acquisition

All MSCT coronary angiography examinations were performed with an Aquilion 64 system (Toshiba, Tokyo, Japan). If the heart rate was ≥65 beats/min oral beta-blockers (metoprolol, 50 or 100 mg, single dose, one hour prior to the examination) were provided if tolerated. The following parameters were used for 64-slice MSCT coronary angiography: collimation 64x0.5 mm, tube rotation time 400, 450 or 500 ms depending on the heart rate, tube current 300 or 350 mA, tube voltage 120 kV. Non-ionic contrast material was administered in the antecubital vein with an amount of 90 to 100 ml, depending on the total scan time, and a flow rate of 5 ml/sec (Iomeron 400, Bracco Altana Pharma, Konstanz, Germany), followed by a saline solution flush of 50 ml. Automated bolus-tracking in the aortic root was used for timing of the scan. All images were acquired during a single inspiratory breath hold of approximately 10 s, with simultaneous registration of the patient's electrocardiogram. With the aid of a segmental reconstruction algorithm, data of one, two or three consecutive heartbeats were used to generate a single image.

Images were reconstructed in the cardiac phase showing least motion artefacts. Typically this was an end-diastolic phase, however additional reconstructions were made throughout the entire cardiac cycle, if needed. Reconstructed images were transferred to a remote workstation for post-processing.

MSCT data analysis

MSCT angiograms were evaluated in consensus by two experienced observers, who were unaware of the results of conventional coronary angiography. The presence of obstructive lesions (≥50% luminal narrowing) was evaluated by scrolling through axial images, followed by visual assessment of curved multiplanar reconstructions in at least two orthogonal planes. Patients were excluded from the analysis of diagnostic accuracy of MSCT coronary angiography in case of 1. an uninterpretable proximal or mid segment or 2. more than two uninterpretable segments in the vessel. However, these patients were included in the analysis of interpretability. Coronary stents were included in the analysis and restenosis was defined as reduced or complete absence of contrast within the stent as well as reduced or absent contrast runoff distally.

Conventional invasive coronary angiography

Conventional invasive coronary angiography was performed according to the standard protocols. Coronary angiograms were visually assessed by one experienced observer who was unaware of the results of MSCT coronary angiography. Each coronary segment as defined by the American Heart Association/American College of Cardiology modified 17 segment model was evaluated in two orthogonal views for the presence of ≥50% diameter stenosis.

Statistical analysis

Continuous variables are expressed as mean (standard deviation) and compared between the two groups by t-test for independent samples. When not normally distributed, continuous data are expressed as median (interquartile range) and compared between the two groups by non-parametric Mann-Whitney test. Categorical variables are expressed as absolute numbers (percentages) and compared between the two groups by Chi-square test or Fisher's exact test for sparse data. The sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and diagnostic odds ratio were calculated based on the rates of true positive, true negative, false positive and false negative test results.[6] The interpretability and diagnostic accuracy to detect stenoses of ≥50% were compared between the two groups using the 95% confidence intervals (95% CI). Conventional coronary angiography served as the reference standard. Diagnostic accuracy was evaluated on segmental, vessel and patient basis. A vessel or patient was assigned as correct positive if at least one obstructive lesion in the vessel or patient were detected correctly. Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, Il, USA). P-values <0.05 were considered as statistically significant. The study conforms to the criteria as set in the STARD initiative.[7]

Results

Patient characteristics

An elevated heart rate and breathing during the scan rendered examinations of one male and two female patients non-diagnostic and as a consequence these patients were excluded from the MSCT diagnostic accuracy analysis. However, these patients were included in the evaluation of interpretability of the study results. The clinical characteristics of the remaining 100 patients included in the study of diagnostic accuracy (50 men and 50 women, mean age 60±10 years) are presented in Table 1. In total, 36 (36%) patients presented with a previous history of CAD (myocardial infarction and/or percutaneous coronary intervention), the remaining 64 (64%) patients presented with suspected CAD. Women showed a higher prevalence of family history of CAD and lower overall Agatston calcium score than men.

Table 1. Characteristics of the study population

	Total population (n=100)	Women (n=50)	Men (n=50)
Age (mean±SD)	60±10	60±10	60±11
History of CAD:			
Previous PCI	34 (34%)	17 (34%)	17 (34%)
Previous MI	31 (31%)	16 (32%)	15 (30%)
Risk factors for CAD:			
Type 2 diabetes mellitus	21 (21%)	9 (18%)	12 (24%)
Hypercholesterolemia	62 (62%)	28 (56%)	34 (68%)
Arterial hypertension	58 (58%)	31 (62%)	27 (54%)
Family history of CAD*	46 (46%)	29 (58%)	17 (34%)
Smoking	46 (46%)	25 (50%)	21 (42%)
Obesity	21 (21%)	8 (16%)	13 (26%)
Medications:			
ACEI	44 (44%)	21 (42%)	23 (46%)
Beta-blockers	61 (61%)	31 (62%)	30 (60%)
Aspirin	64 (64%)	32 (64%)	32 (64%)
Statins	55 (55%)	23 (46%)	32 (64%)
No. of diseased vessels:			
0	46 (46%)	28 (56%)	18 (36%)
1	20 (20%)	9 (18%)	11 (22%)
2	24 (24%)	11 (22%)	13 (26%)
3	10 (10%)	2 (4%)	8 (16%)
MSCT:			
Total Agatston calcium score (median, 25^{th}-75^{th} percentile)†	216 (7-530)	78 (0-321)	387 (155-715)

* p=0.016 between women and men.

† p<0.0001 between women and men.

Data are absolute numbers (%), unless otherwise indicated.

ACEI, angiotensin converting enzyme inhibitors; CAD, coronary artery disease; MI, myocardial infarction; MSCT, multi-slice computed tomography; PCI, percutaneous coronary intervention.

MSCT coronary angiography

All patients

On the basis of conventional invasive coronary angiography, obstructive lesions were present in 54 (54%) patients (one vessel disease was observed in 20 patients, two vessel disease – in 24 patients, three vessel disease – in ten patients) (Table 1).

Table 2. Diagnostic accuracy of 64-slice MSCT in the entire study population

	Segmental basis	Vessel basis	Patient basis
Interpretable	1432/1485 (96, 95-97)	400/412 (97, 95-99)	100/103 (97, 94-100)
Sensitivity	122/143 (85, 80-91)	90/100 (90, 84-96)	53/54 (98, 95-100)
Specificity	1276/1289 (99, 98-100)	290/300 (97, 95-99)	42/46 (91, 83-99)
PPV	122/135 (90, 85-95)	90/100 (90, 84-96)	53/57 (93, 86-100)
NPV	1276/1297 (98, 97-99)	290/300 (97, 95-99)	42/43 (98, 94-100)
Positive LR (LR, 95% CI)	84.59 (49.04-145.91)	27 (14.63-49.84)	11.29 (4.42-28.81)
Negative LR (LR, 95% CI)	0.15 (0.10-0.22)	0.1 (0.06-0.19)	0.02 (0.00-0.14)
Diagnostic OR (OR, 95% CI)	570.23 (279.91-1160.87)	261 (106.1-642.09)	556.5 (71.37-3921.83)

Data are absolute values used to calculate percentages unless otherwise indicated. Data in parentheses are the percentages with 95% confidence intervals unless otherwise indicated.
CI, confidence intervals; LR, likelihood ratio; MSCT, multi-slice computed tomography; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

The results of diagnostic accuracy to detect obstructive lesions with 64-slice MSCT are depicted in Table 2. After exclusion of 13 segments due to small vessel size and 40 segments due to motion artefacts, 1432 coronary segments (38 segments with stents) were included in the analysis. Of 143 obstructive lesions detected on conventional invasive coronary angiography, 122 were correctly identified on MSCT, and disease was correctly ruled-out in 1276 segments out of 1289, resulting in sensitivity of 85% (95% CI 80%-91%), specificity of 99% (95% CI 98%-100%), positive likelihood ratio of 84.59 (95% CI 49.04-145.91), negative likelihood ratio of 0.15 (95% CI 0.10-0.22), and diagnostic odds ratio of 570.23 (95% CI 279.91-1160.87). In total, 12 coronary vessels were excluded from the analysis. In the included vessels, the overall sensitivity was 90% (95% CI 84%-96%) and the specificity was 97% (95% CI 95%-99%). All but one patients with obstructive CAD on conventional invasive coronary angiography and included in the analysis were correctly identified by MSCT to have at least one obstructive lesion, resulting in sensitivity of 98% (95% CI 95%-100%). Four patients were identified as false positive, resulting in specificity of 91% (95% CI 83%-99%).

Women versus men

An example of obstructive CAD on 64-slice MSCT in a female patient is provided in Figure 1. After exclusion of 6 segments due to small vessel size and 28 segments due to motion artefacts, 728 (96%) coronary segments (18 segments with stents) were included in the female population. In the male population, 7 segments were excluded due to small vessel size and 12 segments due to motion artefacts, resulting in 704 (97%) segments included in the study (20 segments containing stents). As can be derived from Table 3, no significant differences were observed between the number of interpretable segments in men and women. Moreover, similar diagnostic accuracy was found on a segmental, vessel and patient basis. On a segmental basis, the sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio to detect obstructive stenoses in women were 85% (95% CI 75%-95%), 99% (95% CI 98%-100%), 82.98 (95% CI 39.34-174.99), 0.15 (95% CI 0.07-0.29), and 563.12 (95% CI 191.21-1659.22), respectively, and 85% (95% CI 78%-92%), 99% (95% CI 98%-100%), 86.54 (95% CI 38.86-192.72), 0.15 (95% CI 0.09-0.24), and 581.46 (95% CI 220.59-1524.5), respectively, in men, not significantly different between the two patient populations. No significant differences were observed between the number of interpretable vessels and patients in women and men. When shifting to vessel and patient level, both in men and women the sensitivity increased, while specificity decreased slightly. No significant influence of gender was observed (sensitivity, specificity, positive and negative likelihood ratios in women 95% (95% CI 87%-100%), 93% (95% CI 83%-100%), 13.36 (95% CI 3.50-50.97), and 0.05 (95% CI 0.01-0.33)), respectively, and 100%, 89% (95% CI 74%-100%), 9 (95% CI 2.44-33.24), and 0 (95% CI 0-0.09)), respectively, in men).

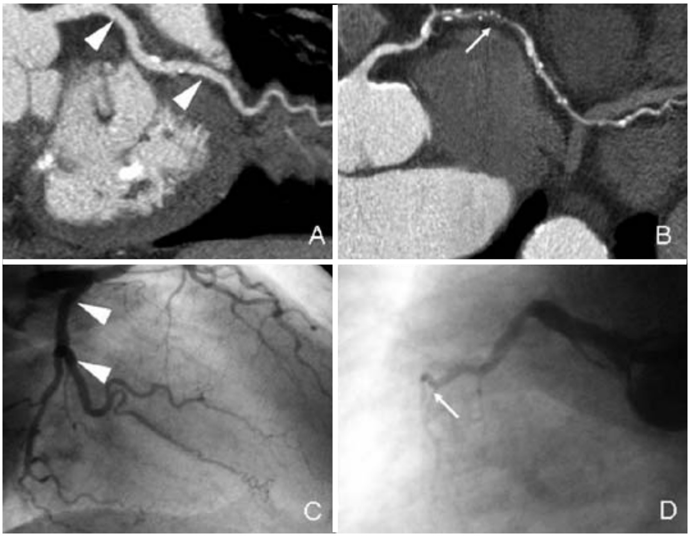

Figure 1. An example of a woman with obstructive coronary artery disease demonstrated with 64-slice multi-slice computed tomography (MSCT) coronary angiography. (A) Multiplanar reconstruction (MPR) of the left circumflex coronary artery (arrowheads) with minimal irregularities of the artery wall. (B) MPR of the right coronary artery showing occlusion in the middle part of the vessel (arrow). The distal part of the artery is filled through collaterals. (C, D) The findings were confirmed by conventional coronary angiography (arrowheads and arrow).

Table 3. Diagnostic accuracy of 64-slice MSCT in women versus men

	Women	Men
Segmental basis:		
Interpretable	728/762 (96, 95-97)	704/723 (97, 96-98)
Sensitivity	41/48 (85, 75-95)	81/95 (85, 78-92)
Specificity	673/680 (99, 98-100)	603/609 (99, 98-100)
PPV	41/48 (85, 75-95)	81/87 (93, 88-98)
NPV	673/680 (99, 98-100)	603/617 (98, 97-99)
Positive LR (LR, 95% CI)	82.98 (39.34-174.99)	86.54 (38.86-192.72)
Negative LR (LR, 95% CI)	0.15 (0.07-0.29)	0.15 (0.09-0.24)
Diagnostic OR (OR, 95% CI)	563.12 (191.21-1659.22)	581.46 (220.59-1524.5)
Vessel basis:		
Interpretable	200/208 (96, 93-99)	200/204 (98, 96-100)
Sensitivity	34/37 (92, 83-100)	56/63 (89, 81-97)
Specificity	158/163 (97, 94-100)	132/137 (96, 93-99)
PPV	34/39 (87, 76-98)	56/61 (92, 85-99)
NPV	158/161 (98, 96-100)	132/139 (95, 91-99)
Positive LR (LR, 95% CI)	29.96 (12.57-71.38)	24.36 (10.26-57.83)
Negative LR (LR, 95% CI)	0.08 (0.03-0.25)	0.12 (0.06-0.23)
Diagnostic OR (OR, 95% CI)	358.13 (84.76-1494.5)	211.2 (65.48-679.41)
Patient basis:		
Interpretable	50/52 (96, 91-100)	50/51 (98, 94-100)
Sensitivity	21/22 (95, 87-100)	32/32 (100, NA)
Specificity	26/28 (93, 83-100)	16/18 (89, 74-100)
PPV	21/23 (91, 79-100)	32/34 (94, 86-100)
NPV	26/27 (96, 89-100)	16/16 (100, NA)
Positive LR (LR, 95% CI)	13.36 (3.50-50.97)	9 (2.44-33.24)
Negative LR (LR, 95% CI)	0.05 (0.01-0.33)	0 (0-0.09)
Diagnostic OR (OR, 95% CI)	273 (27.14-2464.86)	NA

Data are absolute values used to calculate percentages unless otherwise indicated. Data in parentheses are the percentages with 95% confidence intervals unless otherwise indicated.
CI, confidence intervals; LR, likelihood ratio; MSCT, multi-slice computed tomography; NA, not applicable; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

Discussion

The present study demonstrated a high diagnostic accuracy of 64-slice MSCT coronary angiography in both men and women with no significant differences in accuracy between women and men on a segmental, vessel and patient basis.

On a segmental level, the sensitivity in the whole study population was 85% with specificity as high as 99%, while only 4% of coronary segments were excluded from the analysis. These findings are in line with the previously published data of the study populations composed of mainly male patients.[4,8-14] Indeed, in previous studies of patients with similar CAD prevalence (>50%) as compared to the present study, the reported sensitivity on a segmental level ranged between 85% to 99% and the specificity varied from 94% to 98%.[8-14] Moreover, in a recently published meta-analysis including 9 studies and 544 patients, the mean sensitivity and specificity of 64-slice MSCT coronary angiography to detect obstructive lesions were 87% and 96%, respectively.[4] When shifting to a patient level however, the sensitivity increased to 98% with a slight decrease in specificity to 91% while importantly the negative predictive value remained high (98%). In clinical practice, a patient based analysis is even more relevant, since selection (or exclusion) of patients for further invasive diagnostic studies followed by therapeutic interventions are based on the latter.

No significant differences in the diagnostic accuracy of MSCT coronary angiography were demonstrated between women and men with similar age and clinical presentation. Importantly, non-invasive angiography by MSCT may be particularly beneficial in women, since previous studies have shown that absence of obstructive CAD on conventional coronary angiography is demonstrated in approximately half of symptomatic women as compared to only 17% in age-matched men.[2,15,16] Similarly, the ability to predict CAD based on clinical symptoms appears to be limited in women of all age groups. Indeed, the observed disease prevalence on conventional coronary angiography in 55-65 year old women has been shown to be half of expected based on the likelihood of CAD determined by the Diamond and Forrester method.[2] Moreover, traditional non-invasive tests may be suboptimal in women in the detection of CAD as compared to men. Indeed, for exercise electrocardiography a lower sensitivity and specificity of 60% and 70% has been shown in women as compared to men, in whom sensitivity and specificity are approximately 80%.[2] Similarly, the sensitivity and specificity of stress myocardial perfusion imaging in women are 81% and 66%, respectively.[2,17] Accordingly, non-invasive coronary angiography with MSCT, which allows direct visualization and exclusion of coronary artery stenoses with high accuracy, may be a useful tool in the clinical work-up of women with suspected CAD. Importantly, in case of a normal MSCT scan, the likelihood of obstructive stenoses in the epicardial coronary arteries is extremely low, since the negative predictive value of the technique exceeds 95%. Accordingly, the technique allows accurate rule-out of obstructive CAD in women.

Study limitations

Several limitations of the study should be acknowledged. Only patients scheduled for conventional coronary angiography were included in the study, resulting in high disease prevalence (44% in women and 64% in men). Therefore, the findings of the study need to be validated in population with lower disease prevalence.

In addition, MSCT has several important limitations in general. First, the radiation dose of 64-slice MSCT is 12 to 15 mSv with an estimated radiation dose even higher in women.[18] Another important limitation of MSCT coronary angiography is that it does not provide information on functional significance of the detected stenoses and functional testing remains necessary in case of observed stenoses.

Conclusion

The findings of the present study confirm the high diagnostic accuracy of current non-invasive 64-slice MSCT coronary angiography in male as well as in female patients.

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