Imaging of coronary atherosclerosis and vulnerable plaque

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CHAPTER 5

Diagnostic Performance of Non-Invasive Multidetector Computed Tomography Coronary Angiography to Detect Coronary Artery Disease using Different Endpoints; Detection of Significant Stenosis versus Detection of Atherosclerosis

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Eur Heart J. 2011 Mar;32(5):637-4

ABSTRACT

Background: The positive predictive value of multidetector computed tomography angiography (CTA) for detecting significant stenosis remains limited. Possibly CTA may be more accurate in the evaluation of atherosclerosis rather than in the evaluation of stenosis severity. However, a comprehensive assessment of the diagnostic performance of CTA in comparison to both conventional coronary angiography (CCA) and intravascular ultrasound (IVUS) is lacking. Therefore, the aim of the study was to systematically investigate the diagnostic performance of CTA for 2 endpoints, namely detecting significant stenosis (using CCA as the reference standard) versus detecting the presence of atherosclerosis (using IVUS as reference of standard).

Methods: A total of 100 patients underwent CTA followed by both CCA and IVUS. Only those segments in which IVUS imaging was performed were included for CTA and QCA analysis. On CTA, each segment was evaluated for significant stenosis (defined as ≥50% luminal narrowing), on CCA significant stenosis was defined as a stenosis ≥50%. Secondly, on CTA, each segment was evaluated for atherosclerotic plaque, atherosclerosis on IVUS was defined as a plaque burden of ≥40% on cross-sectional area.

Results: CTA correctly ruled out significant stenosis in 53 of 53 (100%) patients. However, 9 patients (19%) were incorrectly diagnosed as having significant lesions on CTA resulting in sensitivity, specificity, positive and negative predictive values of 100%, 85%, 81% and 100%. CTA correctly ruled out the presence of atherosclerosis in 7 patients (100%) and correctly identified the presence of atherosclerosis in 93 patients (100%). No patients were incorrectly classified, resulting in sensitivity, specificity, positive and negative predictive values of 100%.

Conclusion: The present study is the first to confirm using both CCA and IVUS that the diagnostic performance of CTA is superior in the evaluation of the presence or the absence of atherosclerosis when compared with the evaluation of significant stenosis.

INTRODUCTION

With the introduction of multidetector computed tomography angiography (CTA) technology, non-invasive imaging of coronary anatomy has become possible. The technique has developed rapidly and is increasingly used for the evaluation of coronary artery disease (CAD), although the precise role of CTA in the assessment of CAD has not been adequately defined yet. On the basis of the high specificity and the high negative predictive value, CTA has an excellent ability of ruling out significant CAD.[1-3]

However, relatively low positive predictive values have been reported and frequently the presence of a significant stenosis that is observed on CTA is not confirmed on conventional coronary angiography (CCA).[4] This discrepancy between CTA and CCA has been attributed to the inferior spatial and temporal resolution of CTA when compared with CCA and at present it seems that the technique remains inferior to CCA. However, one could also question the use of CCA as a reference standard. In contrast to the luminographic approach of CCA, CTA is a cross-sectional or tomographic imaging technique. As a result, CTA allows direct visualization of the coronary vessel wall and thus the presence of coronary atherosclerosis. It is anticipated that precisely this information will become increasingly important in the evaluation and subsequent management of patients with CAD.[5] Possibly the true strength of coronary CTA may therefore lie in the evaluation of atherosclerosis rather than evaluation of significant stenosis.

Thus far diagnostic accuracy studies have only evaluated the performance of CTA using invasive CCA as the standard of reference.[1 3 4] Nonetheless, it is conceivable that CTA may perform better when compared with IVUS (using atherosclerosis as endpoint) than when compared with CCA (using significant stenosis as endpoint). However, thus far no studies have addressed this issue by combing these endpoints in a large cohort of patients. Such a comprehensive evaluation would provide valuable information to further understand how CTA should be used in clinical practice. Therefore, the purpose of this study was to provide a systematic evaluation concerning both the diagnostic accuracy for the detection of significant stenosis (using CCA as the reference standard) and the diagnostic accuracy for the detection of atherosclerosis (using IVUS as the reference standard) in a large cohort of patients.

METHODS

Patients and study protocol

The study group consisted of 106 patients without known CAD who were clinically referred for coronary CTA because of chest pain or elevated risk profile. On the basis of imaging results and clinical presentation patients were referred for CCA in combination with IVUS of 1 - 3 vessels and enrolled in the present study. Contra-indications for CTA were 1) (supra) ventricular arrhythmias, 2) renal insufficiency (glomerular filtration rate <30 ml/min), 3) known allergy to iodine contrast material, 4) severe claustrophobia, 5) pregnancy. Exclusion

criteria for IVUS were severe vessel tortuousness, severe stenosis or vessel occlusion. In each patient, the presence of CAD risk factors including diabetes, systemic hypertension, hypercholesterolemia, positive family history, smoking and obesity, were recorded. Patients were classified as having a low, intermediate or high pre-test likelihood of CAD using the method described by Diamond and Forrester.[6] The study protocol was approved by the institutional ethics committee, and informed consent was obtained in all patients.

Multidetector computed tomography angiography

Data acquisition

Beta-blocking medication (metoprolol 50 or 100 mg, single oral dose, 1 hour prior to examination) was administered in case of a heart rate ≥65 beats/min and in the absence of contra-indications. CTA was performed using either a 64-detector row helical scanner (Aquilion 64, Toshiba Medical Systems, Toshiba Medical Systems, Otawara, Japan) or a 320-detector row volumetric scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan). For the 64-row contrast-enhanced scan, collimation was 64 x 0.5 mm, tube voltage 100 - 135 kV and tube current 250 - 350 mA, depending on body posture. Non-ionic contrast material (Iomeron 400, Bracco, Milan, Italy) was administered with an amount of 80 - 110 ml followed by a saline flush with a flow rate of 5 ml/s. Data acquisition was performed during an inspiratory breath hold of ~ 8 - 10 seconds. Datasets were reconstructed from the retrospectively gated raw data, the best phase was reconstructed with an interval of 0.3 mm. Using a single test slice reconstructed throughout the various phases of the heart cycle, other suitable R-R intervals were examined for additional reconstructions.

For the 320-row contrast-enhanced scan the heart was imaged in a single heartbeat, using prospective triggering with exposure interval depending on the heart rate. Scan parameters were: 350 ms gantry rotation time, 100 - 135 kV tube voltage, and a tube current of 400 - 580 mA, depending on body mass index (BMI). In total, 60 - 90 ml contrast material (Iomeron 400) was administered with a flow rate of 5 - 6 ml/s followed by a saline flush. Automatic peak enhancement detection in the left ventricle was used for timing of the bolus using a threshold of +180 Hounsfield Units. Data acquisition was performed during an inspiratory breath hold of ~ 4 - 6 seconds. Subsequently, data sets were reconstructed and transferred to a remote workstation as previously described.[7]

Data analysis

CTA scans were evaluated using dedicated software (Vitrea 2.0 or Vitrea FX 1.0, Vital images, Minnetonka, MN, USA). CTA examinations were evaluated by two experienced readers (blinded to CCA and IVUS results). Disagreement between readers was resolved in consensus. Three-dimensional rendered reconstructions were used to obtain general information on the anatomy of the coronary arteries. Coronary arteries were subsequently divided into 17 segments according to a modified American Heart Association classification.[8] First, to evaluate the presence of significant stenosis, each segment was evaluated

for the presence of luminal narrowing using axial and/or orthogonal images and curved multiplanar reconstructions. Atherosclerotic lesions were deemed significant stenosis if resulting in ≥50% luminal narrowing. Lesions below this threshold were considered to be non-significant. Second, to evaluate the presence of atherosclerosis, each segment was evaluated for the presence of any atherosclerotic plaque on axial and/or orthogonal images and curved multiplanar reconstructions. Structures >1 mm^2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen, were defined as atherosclerotic plaque.[9]

Conventional and quantitative coronary angiography (QCA)

CCA was performed according to standard protocols. QCA analysis was performed on a segmental basis by an observer unaware of CTA and IVUS findings with the use of QCA-CMS version 6.0 (Medis, Leiden, The Netherlands). QCA was performed only in those segments with plaque. Plaque on invasive CCA was defined as any evidence of luminal narrowing of any degree, clinically significant or not, or evidence of calcification on angiogram before or after contrast injection.[10] The tip of the catheter was used for calibration and for each segment examined both with CTA and IVUS, the reference diameter and minimum luminal diameter were measured and percentage diameter stenosis was reported. Measurements were performed on at least two orthogonal projections and the highest percentage diameter stenosis was used for further analysis. Significant stenosis was defined as ≥50% luminal narrowing.

Intravascular ultrasound

Image acquisition

IVUS examinations were acquired during CCA in 219 of the 300 available vessels with the use of a dedicated IVUS-console (Volcano Corporation, Rancho Cordova, CA, USA). IVUS was performed with a 20 MHz, 2.9 F phased-array IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, CA, USA), which was introduced distally in the coronary artery under fluoroscopic guidance, after administration of nitrates locally. A motorized automated pullback with a continuous speed of 0.5 mm/s was used until the catheter reached the guiding catheter. Cine runs before and after contrast injections were performed to confirm the position of the IVUS catheter. Images were stored on CD-ROM or DVD for offline analysis.

Image analysis

IVUS analysis was performed by two blinded observers. Lumen and external elastic membrane (EEM) contours were manually traced to determine lumen area and EEM area (QCU-CMS, version 4.5, Leiden, the Netherlands). In each segment, the site with minimum lumen area (mm^2) was identified. Additionally, cross-sectional area measurements of EEM, lumen area and percentage plaque burden (plaque and media area / EEM area multiplied by 100) were performed. The measurements were performed in accordance with the

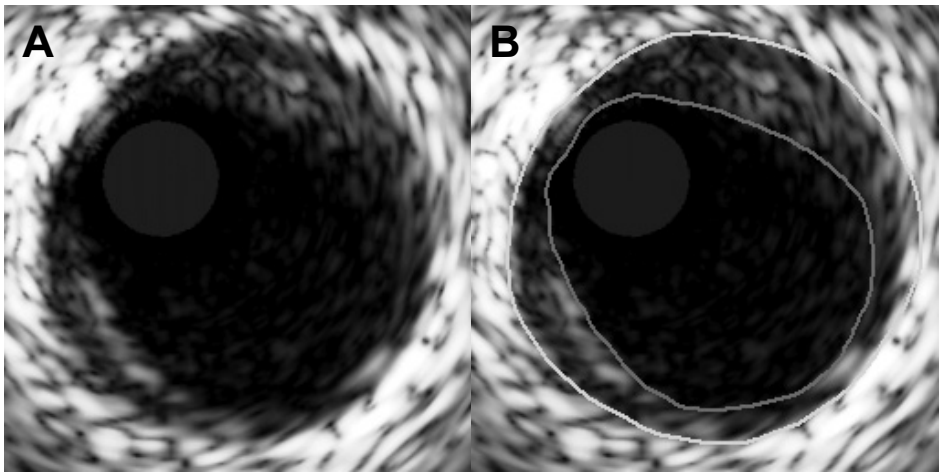

Figure 1. Example of intravascular ultrasound IVUS) cross-sectional image without (A) and with border detection (B). Cross-sectional image of coronary atherosclerosis with vessel border (green) and lumen (red) border tracing demonstrated in panel B. The IVUS image corresponds to a plaque burden of 41%.

IVUS guidelines of the American College of Cardiology.[11] The presence of visually evident atherosclerosis on IVUS was defined as a plaque burden of ≥40% cross-sectional area on at least three consecutive frames.[12] An example of an IVUS cross-sectional image with a plaque burden of ≥40% is demonstrated in Figure 1.

Statistical analysis

Only those segments in which IVUS imaging was performed were included for CTA and QCA analysis. First, the diagnostic accuracy (sensitivity, specificity, positive and negative predictive values including 95% confidence intervals) of CTA for the detection of significant stenosis (luminal narrowing ≥50% on CCA) was calculated on segmental, vessel and patient basis. CCA was the standard of reference for detection of significant stenosis and a segment, vessel or patient was classified as true positive if a significant stenosis was identified correctly by CTA. Second, the diagnostic accuracy (sensitivity, specificity, positive and negative predictive values including 95% confidence intervals) of CTA for the detection of atherosclerosis (plaque burden ≥40% on cross-sectional area on IVUS) was calculated on segmental, vessel and patient basis. IVUS was the standard of reference for the detection of atherosclerosis and a segment, vessel, or patient was classified as true positive if the presence of atherosclerosis was identified correctly by CTA. In the analysis on a vessel basis, the left main was considered part of the left anterior descending artery (LAD) and the intermediate branch was considered part of the left circumflex artery (LCx). Initially, the diagnostic accuracy was determined excluding segments of non-diagnostic image quality. In a subsequent analysis, non-diagnostic segments were included in the analysis and were considered positive for stenosis and atherosclerosis. Differences between the diagnostic accuracy for the two different endpoints were considered significant at the

0.05 level if 95% confidence intervals did not overlap. Continuous values were expressed as means (± standard deviation) if normally distributed and compared with the two-tailed t-test for independent samples. If not normally distributed, values were expressed as medians and interquartile range (IQR) and compared with the 2-tailed Mann-Whitney test. A p-value of <0.05 was considered statistically significant.

To account for possible clustering of coronary artery segments and vessels within patients, the generalized estimating equation (GEE) method was applied for stenosis and atherosclerosis evaluation. When compared to QCA, CTA was scored as significant stenosis present (luminal narrowing ≥50% and non-diagnostic segments) or absent (luminal narrowing <50%). When compared to IVUS, CTA was scored as atherosclerosis present (including non-diagnostic segments) or absent. First, regular binary logistic regression analysis was performed to evaluate the predictive value of CTA for the presence of significant stenosis on QCA and the predictive value of CTA for presence of atherosclerosis on IVUS. Second, to adjust for clustering of segments within patient, GEE analyses were

Table 1. Patient characteristics of the study.

Gender (male/female)	64/36
Age (years)	57 ± 11
Risk factors for CAD (%)	
Diabetes	29 (29%)
Hypertension	60 (60%)
Hypercholesterolaemia	62 (62%)
Positive family history	44 (44%)
Current smoking	47 (47%)
Obese (BMI ≥30 kg/m^2)	21 (21%)
Symptoms (%)	
Typical angina	27 (27%)
Atypical angina	27 (27%)
Non-anginal chest pain	46 (46%)
Pre-test likelihood (%)	
Low	24 (24%)
Intermediate	57 (57%)
High	19 (19%)
Prevalence segments with ≥50% luminal narrowing on QCA	58 (11%)
Prevalence segments with ≥40% plaque burden on IVUS	329 (65%)

BMI; body mass index, QCA; quantitative coronary angiography; IVUS, intravascular ultrasound

performed with proc GENMOD with a binominal distribution for the outcome variable, the link function specified as logit, and patients as separate subjects. In both analyses the parameters of estimation and the standard error were virtually identical, suggesting that

no clustering within patients was present. Statistical analysis was performed using SPSS 14.0 software (SPSS Inc., Chicago. Illinois, USA).

RESULTS

Patient characteristics

In the study population of 106 patients, overall image quality on CTA was reduced in 6 patients (6%). Reasons for reduced image quality were the presence of motion artifacts, increased noise due to a high BMI, elevated heart rate and breathing. Accordingly, these patients were not included in the analysis. Patient characteristics of the remaining 100 patients are presented in Table 1. The average age of the patient group was 57 ± 11 years and 64 were male (64%). The majority of patients (57%) had an intermediate pre-test likelihood for CAD. The average interval between CTA and CCA including IVUS was 61 ± 73 days. In total, in 528 segments both CTA and invasive data (CCA and IVUS analysis) were available (right coronary artery = 72, left anterior descending coronary artery = 87, left circumflex coronary artery = 60). Image quality was insufficient in 18 segments (3%) because of small vessel size (n= 8), a high BMI resulting in increased noise (n=3) and motion artifacts (n=7) and these segments were excluded. For this study estimated mean radiation dose for the 320-row CTA was 3.2 ± 1.1 mSv if scanned full dose at 75% of R-R interval. In patients who were scanned full dose at 65-85% of R-R interval, estimated mean radiation dose was 7.1 ± 1.7 mSv. For the 64-row CTA the estimated mean radiation dose was 18.1 ± 5.9 mSv in patients scanned for the full R-R interval, retrospectively gated.

Diagnostic accuracy of CTA for the detection of significant stenosis

The diagnostic accuracy of CTA (with 95% confidence intervals) for the detection of significant stenosis on a segment, vessel and patient basis excluding and including non-diagnostic segments is presented in Table 2. When excluding non-diagnostic segments, the presence of stenosis was correctly ruled out by CTA in 435 of 452 segments, without significant stenosis on CCA, whereas 57 of the 58 segments were correctly classified as having a significant stenosis. However, CTA overestimated a total of 17 lesions deemed non-significant on CCA and underestimated 1 lesion which was significant on CCA. On a segmental basis, this resulted in a sensitivity and specificity of respectively 98% and 96%, and positive and negative predictive values of 77% and 99%, respectively. On a vessel basis, a total of 47 vessels out of the 219 vessels were identified as significant stenosis on CCA. CTA correctly identified all the 47 vessels as significant (100%). In the remaining 172 vessels, CTA correctly identified 158 vessels as non-significant (92%). However, 14 vessels were overestimated as significant CAD by CTA. On a vessel basis, this resulted in a sensitivity and specificity of respectively 100% and 92%, and positive and negative predictive values of 77% and 100%, respectively. On a patient basis, CTA correctly ruled out significant CAD in 53 of 62 (85%) patients without significant stenosis on CCA. Additionally, CTA

Table 2. Diagnostic accuracy for the detection of significant stenosis, excluding and including non-diagnostic segments.

	Segmental Analysis	Vessel Analysis	Patient Analysis
Excluding non-diagnostic segments			
Sensitivity	57/58 (98%, 95%-100%)	47/47 (100%)	38/38 (100%)
Specificity	435/452 (96%, 94%-97%)	158/172 (92%, 88%-96%)	53/62 (85%, 78%-93%)
PPV	57/74 (77%, 69%-85%)	47/61 (77%, 67%-88%)	38/47 (81%, 71%-90%)
NPV	435/436 (99.7%, 99%-100%)	158/158 (100%)	53/53 (100%)
Diagnostic Accuracy	492/510 (96%, 95%-98%)	205/219 (94%, 90%-97%)	91/100 (92%, 86%-96%)
Including non-diagnostic segments			
Sensitivity	60/61 (98%, 95%-100%)	47/47 (100%)	38/38 (100%)
Specificity	435/467 (93%, 91%-95%)	149/172 (87%, 82%-92%)	53/62 (85%, 78%-93%)
PPV	60/92 (65%, 55%-75%)	47/70 (67%, 56%-78%)	38/47 (81%, 71%-90%)
NPV	435/436 (99.7%, 99%-100%)	149/149 (100%)	53/53 (100%)
Diagnostic Accuracy	495/528 (94%, 92%-96%)	196/219 (90%, 85%-94%)	91/100 (92%, 86%-96%)

Accuracy and 95% confidence intervals of CTA to detect significant stenosis using CCA as the standard of reference [segmental (n=510), vessel (n=219) and patient (n=100) analysis], excluding and including non-diagnostic segments.
PPV; positive predictive value, NPV; negative predictive value.

correctly identified 38 of 38 patients (100%) with one or more significant lesions. However, nine patients (19%) were incorrectly classified as having significant lesions on CTA.

Diagnostic accuracy of CTA for the detection of atherosclerosis

The diagnostic accuracy of CTA (with 95% confidence intervals) for the detection of atherosclerosis on a segment, vessel and patient basis, excluding and including non-diagnostic segments is presented in Table 3. In the 510 evaluated segments, median minimal lumen area was 6.7 mm^2 (IQR 4.5 - 10.1 mm^2), median EEM area was 14.0 mm^2 (IQR 10.0 - 20.0 mm^2) and median percentage plaque burden was 42% (IQR 34 - 50%). When excluding non-diagnostic segments, 329 segments with atherosclerosis were detected by IVUS, of which 326 were correctly identified by CTA (sensitivity 99%). CTA incorrectly classified three segments as without atherosclerosis. In addition, of the 181 segments considered without atherosclerosis by IVUS, atherosclerosis was correctly excluded in 179 segments by CTA (specificity 99%) and two segments were incorrectly classified as positive for atherosclerosis. On a vessel basis, 172 vessels out of 173 vessels which were deemed positive for atherosclerosis by IVUS were correctly identified by CTA (99%). Moreover, CTA correctly ruled out presence of atherosclerosis in the 45 out of 46 vessels deemed negative for atherosclerosis by IVUS. Thus, CTA overestimated only one vessel as positive and underestimated one vessel as negative for atherosclerosis. On a vessel basis, this resulted in a sensitivity and specificity of respectively, 99% and 98% and a positive and negative predictive value of 99% and 98%, respectively. On a patient basis CTA correctly ruled out the presence of atherosclerosis in 7 patients (100%), and correctly identified the presence

Table 3. Diagnostic accuracy for the detection of atherosclerosis, excluding and including non-diagnostic segments.

	Segmental Analysis	Vessel Analysis	Patient Analysis
Excluding non-diagnostic segments			
Sensitivity	326/329 (99%, 98%-100%)	172/173 (99%, 98%-100%)	93/93 (100%)
Specificity	179/181 (99%, 97%-100%)	45/46 (98%, 94%-100%)	7/7 (100%)
PPV	326/328 (99%, 99%-100%)	172/173 (99%, 98%-100%)	93/93 (100%)
NPV	179/182 (98%, 97%-100%)	45/46 (98%, 94%-100%)	7/7 (100%)
Diagnostic Accuracy	505/510 (99%, 98%-99.8%)	217/219 (99%, 98%-100%)	100/100 (100%)
Including non-diagnostic segments			
Sensitivity	343/346 (99%, 98%-100%)	172/173 (99%, 98%-100%)	93/93 (100%)
Specificity	179/182 (98%, 97%-100%)	45/46 (98%, 94%-100%)	7/7 (100%)
PPV	343/346 (99%, 98%-100%)	172/173 (99%, 98%-100%)	93/93 (100%)
NPV	179/182 (98% (97%-100%)	45/46 (98 %, 94%-100%)	7/7 (100%)
Diagnostic Accuracy	522/528 (99%, (98%-99.7%)	217/219 (98%, 99%-100%)	100/100 (100%)

Accuracy and 95% confidence intervals of CTA for the detection of atherosclerosis, with IVUS as the standard of reference [segmental (n=510), vessel (n=219) and patient (n=100) analysis], excluding and including non-diagnostic segments.
PPV; positive predictive value, NPV; negative predictive value.

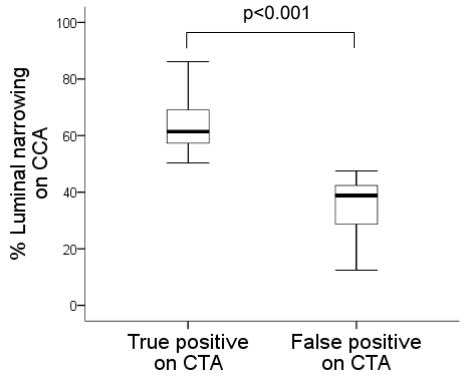

Figure 2A. Difference in percentage luminal narrowing between true and false positives for detection of significant stenosis on multidetector computed tomography angiography (CTA). Box plot graph illustrating the difference in percentage luminal narrowing on conventional coronary angiography (CCA) between true positive (median = 61%) and false positive (median = 39%) lesions for significant stenosis on CTA.

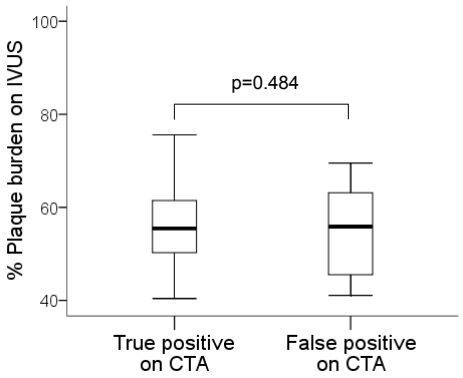

Figure 2B. Difference in percentage plaque burden between true and false positives for significant stenosis on multidetector computed tomography angiography (CTA).
Boxplot illustrating the difference in percentage plaque burden on intravascular ultrasound (IVUS) between lesions true positive (median = 56%) and false positive (median = 56%) for significant stenosis on CTA.

of atherosclerosis in 93 patients (100%) resulting in sensitivity, specificity, positive and negative predictive values of 100%.

Quantitative analysis of CCA and IVUS characteristics of lesions with correct and incorrect diagnosis of significant stenosis on CTA

To explore the differences between lesions correctly identified as a significant stenosis by CTA (true positives) and lesions incorrectly identified as significant lesions by CTA (false positives), CCA, and IVUS characteristics were compared. As demonstrated in Figure 2A, percentage luminal narrowing on CCA was significantly higher in true positives when compared with false positives (61% (IQR 57 - 70%) versus 39% (IQR 28 - 43%) p<0.001).

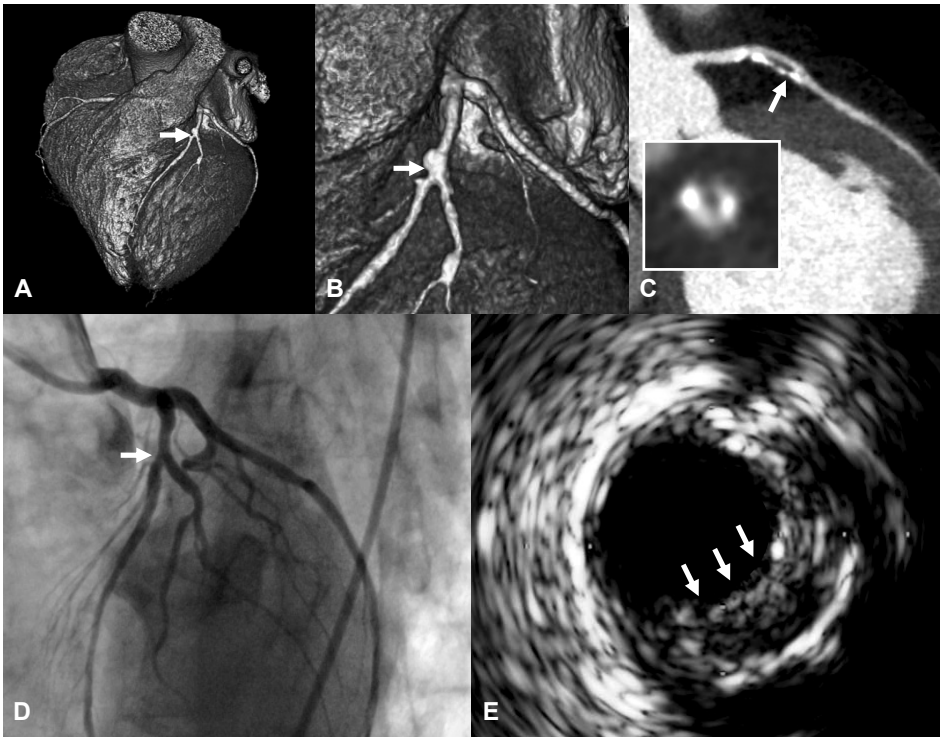

Figure 3. Case example of a 65 year old male with extensive coronary artery disease (CAD) as demonstrated by 320-row multidetector computed tomography angiography (CTA) and intravascular ultrasound (IVUS) while conventional coronary angiography (CCA) showed no significant CAD. (A) 3D volume rendered reconstruction providing an overview of the left anterior descending coronary artery (LAD) showing signs of extensive atherosclerosis in the mid LAD (arrow). (B) An enlargement of the mid LAD demonstrating presence of extensive calcifications. (C) Multiplanar reconstruction of the LAD demonstrating the presence of diffuse atherosclerosis in the mid LAD (arrow) with luminal narrowing, enlargement showing cross-sectional view of the LAD with calcified and non-calcified elements. (D) CCA demonstrating no signs of significant luminal narrowing in the LAD. (E) IVUS cross-sectional image of the mid LAD confirming the presence of extensive atherosclerosis with calcifications (arrows) and a plaque burden of ≥40%.

However, minimal lumen area on IVUS was not significantly different between true positives and false positives (3.9 mm^2 (IQR 3.0 - 5.6 mm^2) versus 4.1 mm^2 (IQR 3.6 - 7.6 mm^2), p=0.136). More importantly, plaque burden on IVUS was not significantly different between true and false positives (56% (IQR 50 - 62%) versus 56% (IQR 46 - 63%), p=0.484) implying that substantial atherosclerosis is present in lesions that are falsely classified as positive for stenosis on CTA despite the absence of significant luminal narrowing (Figure 2B). A case example of a patient with stenosis on CTA in the absence of significant stenosis on CCA is provided in Figure 3.

DISCUSSION

The present study is the first to perform a comprehensive evaluation of the diagnostic performance of CTA. We systematically investigated the diagnostic accuracy of CTA for the detection of significant stenosis (with CCA as the reference standard) as well as for the detection of atherosclerosis (using IVUS as the reference standard) in a large patient population. In the current study, regarding the accuracy of CTA to detect significant stenosis, a negative predictive value of 100% and a diagnostic accuracy of 92% were observed on a patient level. Importantly, no patients with significant stenosis were missed. Nevertheless, nine patients (9% of the total population) were incorrectly classified as having a significant stenosis resulting in a limited positive predictive value of 81%. However, when the definition of disease was changed from significant stenosis (gold standard CCA) to the presence of atherosclerosis (gold standard IVUS), the performance of CTA improved and an excellent diagnostic accuracy was observed. Further exploration of lesions incorrectly classified as having significant stenosis on CTA confirmed the presence of substantial plaque burden in these segments. The findings of the present study demonstrate that CTA may be superior in the evaluation of the presence or the absence of visually evident atherosclerosis on IVUS when compared with the evaluation of significant stenosis. Accordingly, CTA may therefore perform better in the assessment of atherosclerosis rather than the evaluation of stenosis severity. Conceivably, precisely this information on atherosclerosis, which cannot be derived from CCA, may become increasingly important in the definition and subsequent management of CAD.[5]

The present observations regarding the diagnostic accuracy for detection of significant stenosis are in line with the previous literature using 64-row CTA.[1 3] Recently in a multicentre trial, the diagnostic performance of 64-row CTA was investigated in 230 symptomatic patients with suspected CAD, reporting a sensitivity and specificity of 95% and 83% on a patient basis, respectively.[1] However, while in this study the negative predictive value (on a patient basis) was high (99%), a relatively low positive predictive value of 64% was reported. Indeed, due to limitations in spatial resolution it has been established that CTA cannot precisely grade the severity of stenosis and frequently overestimates the degree of luminal narrowing. Similarly, in the present study, 17 segments were incorrectly identified as having significant stenosis leading to a positive predictive value for detecting significant

stenosis of only 77% on segmental basis and 81% on patient basis. Therefore, while CTA remains an excellent tool for ruling out the presence of significant stenosis, a substantial proportion of lesions are overestimated, thereby resulting in incorrect diagnosis.

Importantly, when changing the definition of CAD from the presence of significant stenosis to the presence of atherosclerosis, the overestimated lesions were no longer false positive studies. Comparison with IVUS revealed that in all of these patients despite the absence of significant luminal narrowing, substantial plaque burden was present. Accordingly, CTA had excellent diagnostic accuracy for the detection of atherosclerosis when compared with IVUS. Importantly, no patients with visually evident atherosclerosis (as determined on IVUS) were missed nor was the presence of atherosclerosis incorrectly diagnosed. On a segmental and vessel level, only slightly lower values were observed. Accurate assessment of atherosclerosis with CTA has previously been demonstrated in several investigations. When compared with histology, a good correlation for detecting and characterizing atherosclerotic plaque was reported.[13] In vivo, Leber et al observed a sensitivity and specificity for 16-row CTA of respectively 85% and 92% to detect coronary lesions as determined on IVUS.[9] Evaluation of the characteristics of lesions missed on CTA revealed that particularly small plaques located in distal segments were not identified. In contrast, larger and proximally located plaques, which may be considered more clinically relevant, were accurately detected.

Clinical implications

At present, CCA is the gold standard for detecting severely stenotic lesions and remains the basis for referral for surgical and catheter-based revascularization. However, CCA has a tendency to underestimate total atherosclerotic plaque burden (partly due to positive remodeling) and more detailed characterization of atherosclerosis is not feasible at present. Currently, the gold standard for assessing and quantifying coronary artery plaque burden is IVUS. Nevertheless, the use of this invasive technique is restricted to patients with a high likelihood of having significant lesions requiring intervention. In contrast, non-invasive CTA will typically be used in lower likelihood patients and thus to evaluate the presence of CAD in more early stages. This technique has been proved very useful in the clinical setting and particularly due to the high negative predictive value it can accurately rule out the presence of significant disease in the majority of patients with a low to intermediate pre-test risk profile. While the technique accurately rules out the presence of significant stenosis, the limited positive predictive value (potentially resulting in unnecessary invasive procedures) has been a cause of concern. However in this regard, two issues are important to acknowledge. First, as demonstrated in the current study, coronary segments false positive for significant stenosis may not necessarily be false positive for atherosclerosis. Accordingly, these findings may still be considered relevant for risk stratification and initiation of anti-atherosclerotic measures. Second, regardless of the actual severity of the detected lesion, functional testing remains essential to determine the haemodynamical consequences of the lesion.[14] The presence and extent of ischaemia rather than an estimate of luminal narrowing should invariably serve as the

basis for further referral for CCA and possible revascularization. Considering these issues, it is conceivable that the emphasis of CTA, which traditionally has been on the evaluation of significant stenosis, may shift towards the evaluation of atherosclerosis.

As demonstrated in our systematic comparison of CTA with both CCA and IVUS, the diagnostic accuracy of CTA for detecting the presence of atherosclerosis was superior over the detection of significant stenosis. In fact, the ability of CTA to accurately exclude the presence of atherosclerosis may be considered superior over other non-invasive techniques. Importantly, supporting data are emerging that patients without any evidence of atherosclerotic plaques on CTA have excellent prognosis that is maintained over a relatively long period of time.[15 16] In these patients, CTA may obviate the need for further testing and unnecessary aggressive therapy. In contrast, patients with atherosclerotic plaques on CTA have been shown to have worse outcome. These patients may thus benefit from intensified treatment, while further evaluation with functional testing remains essential to determine the need for revascularization. On the basis of these and the current observations, it is conceivable therefore that shifting the use of CTA from mere stenosis assessment towards evaluation of atherosclerosis may have several advantages for clinical management and may allow improved risk stratification.

Limitations

In the current study, only patients with sufficient CTA image quality for the evaluation of both the presence of significant stenosis and atherosclerosis were included. In addition, a verification bias could be present, as in a limited number of cases patients were referred for CCA on the basis of CTA findings. Moreover, in the present study, no nitroglycerine was administered before the CT scan. Furthermore, concerns have been raised about CTA radiation dose, especially with respect to the long term effects. However, the recent introduction of single heart beat imaging (320-row CTA), dose modulation and particularly prospective triggering have drastically reduced patient radiation dose. Future research will most likely focus on further decreasing radiation exposure while maintaining good image quality.

Conclusion

The present study is the first to perform a comprehensive evaluation of the diagnostic accuracy of CTA for the detection of significant stenosis and for the presence of atherosclerosis. In this regard, the diagnostic accuracy of CTA for the detection of the presence of atherosclerosis was superior over the detection of significant stenosis. Possibly, the emphasis of CTA should shift towards the evaluation of atherosclerosis rather than mere stenosis severity.

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