Int J Cardiovasc Imaging (2008) 24:895–904
DOI 10.1007/s10554-008-9327-z

ORIGINAL PAPER

Accuracy of quantitative coronary angiography with computed tomography and its dependency on plaque composition

Plaque composition and accuracy of cardiac CT

Lars Husmann · Oliver Gaemperli · Tiziano Schepis · Hans Scheffel · Ines Valenta · Tobias Hoefflinghaus · Paul Stolzmann · Lotus Desbiolles · Bernhard A. Herzog · Sebastian Leschka · Borut Marincek · Hatem Alkadhi · Philipp A. Kaufmann

Received: 14 April 2008 / Accepted: 4 June 2008 / Published online: 19 June 2008

Abstract *Objective*: To determine the impact of plaque composition on accuracy of quantitative 64-slice computed tomography coronary angiography (CTCA). *Methods*: The institutional review board approved this study; written informed consent was obtained from all patients. One hundred consecutive patients (42 women, mean age 64.6 ± 9.4 years, age range 39–87 years) underwent CTCA and invasive quantitative coronary angiography (QCA) to determine (a) the diagnostic accuracy of CTCA for the detection of significant stenosis (diameter reduction of ≥50%), and (b) the accuracy of stenosis grading. In CTCA stenosis severity was graded in 10% steps and evaluated separately for calcified and non-calcified coronary lesions using Pearson-linear-regression analysis, Bland/Altman-analysis (BA), and Mann-Whitney-U-test. *Results*: In 60/100 patients 139 significant coronary artery stenoses were identified with QCA. On a per-segment analysis, sensitivity of CTCA was 75.5%, and specificity was 96.6% (positive predictive value: 72.9%, negative predictive value: 97.0%). Quantification of stenosis grading correlated moderately between methods ($r = 0.60$; $P < 0.001$), with an overestimation by CTCA of 5.5% (BA limits-of-agreement −29 to 39%). BA limits-of-agreement were greater in calcified lesions (−29.2 to 45.6%; mean error 8.2%) than in non-calcified lesions (−25.9 to 30.2%; mean error 2.2%) and differed significantly ($P < 0.05$). *Conclusions*: Diagnostic accuracy of CTCA is high, however agreement for quantitative lesion severity assessment between CTCA and QCA is moderate for calcified but superior for non-calcified lesions.

Keywords Plaque composition · Quantitative coronary angiography · 64-Slice computed tomography

L. Husmann · O. Gaemperli · T. Schepis · I. Valenta · T. Hoefflinghaus · B. A. Herzog · P. A. Kaufmann (✉)
Cardiovascular Center, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland
e-mail: pak@usz.ch

H. Scheffel · P. Stolzmann · L. Desbiolles · S. Leschka · B. Marincek · H. Alkadhi
Institute of Diagnostic Radiology, University Hospital Zurich, Zurich, Switzerland

P. A. Kaufmann
Zurich Center for Integrative Human Physiology (ZIHP), University of Zurich, Zurich, Switzerland

Abbreviations

CA	Coronary angiography
CAD	Coronary artery disease
CTCA	Computed tomography coronary angiography
QCA	Quantitative coronary angiography

Introduction

Sixty-four-slice computed tomography (CT) is a reliable noninvasive tool to document or rule out hemodynamically significant coronary artery lesions on a qualitative basis [1–10]. For clinical decision-making further evaluation of lesion severity by visual grading of invasive coronary angiography (CA) or quantitative analysis of CA (QCA) is warranted [11]. Earlier studies have shown that the quantification of coronary artery stenoses with CT is affected by large limits of agreement compared to the clinical reference standard QCA [2, 3, 12–14]. Plaque composition has been suspected to affect the accuracy of quantitative CT coronary angiography (CTCA) [15], but its relative impact remains unknown.

The purpose of our study was to determine the impact of plaque composition on accuracy of quantitative 64-slice CTCA.

Methods

Patients

Between January 2005 and July 2006, 113 consecutive patients (43 women, 70 men; mean age 64.7 ± 9.0 years; age range 39–87 years) were scheduled for QCA and CTCA. The patients were suspected of having coronary artery disease (CAD) (n = 84) or had a history of known CAD with recurrent angina (n = 29). Exclusion criteria for CTCA were allergy to iodinated contrast agent, renal insufficiency (creatinine levels >150 μmol/l), non-sinus rhythm, and hemodynamic instability.

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

CT data acquisition and post-processing

All CT examinations were performed on a 64-slice CT scanner (Somatom Sensation 64, Siemens Medical Solutions, Forchheim, Germany). Intravenous metoprolol (5–20 mg) (Beloc, AstraZeneca, Zug, Switzerland) was administered prior to the CT examination to achieve a target heart rate <70 beats per minute (bpm), if necessary. In the presence of contraindications for beta-adrenoreceptor antagonists or when the maximum dose did not lower the heart rate satisfactorily, the scan was performed even at higher heart rates. In addition, all patients received a single dose of 2.5 mg isosorbiddinitrate sublingual (Isoket, Schwarz Pharma, Monheim, Germany) 2 min prior to the scan. The CTCA scan was started by continuously injecting a bolus of 80 ml of iodixanol (Visipaque 320, 320 mg/ml, GE Healthcare, Buckinghamshire, UK) followed by 30 ml saline solution into an antecubital vein via an 18-gauge catheter (injection rate 5 ml/s). Bolus tracking was performed with a region of interest (ROI) placed into the ascending aorta, and image acquisition was automatically started 5 s after the signal attenuation reached a predefined threshold of 100 Hounsfield units (HU). Scanning was performed from 1 cm below the level of the tracheal bifurcation to the diaphragm in a cranio-caudal direction using the following scanning parameters: detector collimation 32 × 0.6 mm, slice collimation 64 × 0.6 mm by means of a z-flying focal spot, gantry rotation time 330 ms, pitch 0.2, tube potential 120 kV, and tube current time product 650 effective mAs. The electrocardiogram (ECG) was digitally recorded during data acquisition and was stored with the unprocessed CT dataset.

CT image reconstruction and analysis

Synchronized to the ECG data, CT data sets were retrospectively reconstructed throughout the entire cardiac cycle in 5% steps of the R-R interval. When automatic positioning of the R-wave indicators by the software failed, manual repositioning of the indicators was performed. In case of irregular heart rates, the temporal variability in the reconstruction phase was compensated by manual ECG editing. In case of premature heart beats, the temporal window of the following heart beat was deleted, and the next diastolic window was filled with one to three temporal windows to avoid data gaps. The adaptive cardio volume approach was used for image reconstruction [16]. Reconstruction of axial images was performed with a slice thickness of 1.0 mm and an increment of 0.8 mm. All images were reconstructed using a medium-soft and a sharp tissue convolution kernel (B30f and B46f)[17] and were transferred to an external workstation (Leonardo, Siemens Medical Solutions).

For analysis of CTCA data, coronary arteries were segmented as suggested by the American Heart

Association [18]: The right coronary artery was defined to include segments 1–4, the left main and left anterior descending artery to include segments 5–10, and the left circumflex artery to include segments 11–15. The intermedial artery was designated as segment 16, if present. All segments with a diameter of at least 1.5 mm at their origin were included. Diameter measurements were performed with an electronic caliper tool. Segments distal to an occluded vessel were excluded from analysis.

First, one reader semi-quantitatively assessed the overall image quality in the best reconstruction interval on a 5-point scale, based on a previously published score [19, 20] (1, no artifacts; 2, mild artifacts; 3, moderate artifacts; 4, severe artifacts; 5 nonevaluative), and determined the reconstruction interval with the best image quality. Images in the best reconstruction interval were evaluated and classified by two independent readers using axial source images, multi-planar reformations, and thin-slab maximum intensity projections on a per-segment basis. Both readers assessed all coronary artery segments for the presence of hemodynamically significant stenoses, defined as narrowing of the coronary luminal diameter $\geq$50%. Furthermore, the degree of coronary stenosis was quantified, measuring vessel diameters with an electronic caliper tool on reconstructions perpendicularly oriented to the vessel course at the site of maximal luminal stenosis and in a reference vessel (results were rounded up or down to the nearest first decimal place before consensus reading). In case of multiple lesions in one segment, the segment was classified by the worst lesion. For any disagreement in data analysis between the two observers, consensus agreement was achieved; the mean was calculated, only if the difference in stenosis grading between both readers was 10%.

In addition, coronary lesions on CTCA images were grouped in calcified lesions (visually graded as totally calcified or predominantly calcified) and non-calcified lesions (visually graded as not calcified or predominantly non-calcified) by two experienced reader in consensus; calcifications were identified as previously described [2]. In order to determine the impact of plaque composition on stenosis grading by CTCA, all lesions not concordantly detected by both methods, all segments without stenosis, and all segments with total occlusions were excluded from analysis. Absolute differences of stenosis grade quantification were calculated in the calcified and in the non-calcified group.

Quantitative invasive coronary angiography

QCA was performed according to standard techniques, and multiple views were stored on a CD-ROM. The angiograms were quantitatively evaluated using QCA software (Xcelera, PhilipsMedical Systems, the Netherlands) by an independent and experienced interventional cardiologist blinded to the results from CT coronary angiography. Coronary artery segments were defined as mentioned above [18], and analysis was performed in all vessels with a luminal diameter of at least 1.5 mm, excluding those vessels distal to complete occlusions. Each vessel segment was scored as being significantly stenosed, defined as a diameter reduction of $\geq$50%.

Statistical analysis

Quantitative variables were expressed as mean $\pm$ standard deviation and categorical variables as frequencies, median (25th, 75th percentiles), or percentages.

All statistical analysis was performed using SPSS software (SPSS 12.0.1, Chicago, Ill, USA). The clustered nature of the data (i.e. the fact that there were not 1278 independent vessel segments but instead clusters of segments in 100 patients) was taken into account. Inter-observer agreements for assessment of significant coronary artery (patient-, vessel-, and segment-based) stenoses were interpreted by the guidelines of Landis and Koch [21] by using the clustered data.

Pearson correlation coefficient and Bland-Altman (BA) analysis were used to compare the quantification of lesion with QCA and CTCA and for the inter-observer agreement for the quantification of lesions. Differences of stenosis grade quantification in the calcified and in the non-calcified group were determined using Mann–Whitney-U-test. A P-value of <0.05 was considered to indicate statistical significance.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated from Chi-Square tests of contingency, and the 95% confidence intervals (CI) were calculated from binomial expression on a per-segment basis. Because of the interdependencies between different segments, the statistics were also calculated on a per-vessel basis

(presence of at least one significant coronary artery stenosis or absence of any significant stenosis in each vessel) and per-patient basis (presence of at least one significant coronary artery stenosis or absence of any significant stenosis in each patient). QCA was considered the standard of reference.

Results

Thirteen of 113 consecutive patients were excluded because either CA (n = 4) or CTCA (n = 9) were not performed. Three patients declined CA after normal findings in CTCA, one patient declined CA after an allergic reaction to iodinated contrast medium after CTCA. Four patients declined CTCA after normal findings in QCA, three patients were not examined because of atrial fibrillation, and 2 patients were not examined because of serum creatinine levels >150 μmol/l. CTCA and QCA were successfully performed within 5.2 ± 11.8 days (range: 0–85 days) in the remaining 100 patients. Fifty-eight patients (58%) were on oral beta-adrenoreceptor antagonists medication as part of their baseline medication, additional intravenous metoprolol was administered in 9 patients prior to the CT

Table 1 Patient demographics

Number of patients	100
Age in years (mean ± std (range))	64.6 ± 9.4 (39–87)
Female/male	42/58
BMI (mean ± std (range))	22.0 ± 3.5 (12.8–31.9)
Symptoms	
Angina pectoris	37/100
Atypical chest pain	20/100
Dyspnea	22/100
No symptoms (preoperative rule out of CAD)	21/100
Known CAD (1-, 2-, multi-vessel disease)	26 (7, 10, 9)
Previous percutaneous coronary intervention	26/100
Previous coronary bypass grafting	0/100
Previous myocardial infarction	18/100
Unknown CAD	74/100
LDL in mmol/l (mean ± std (range))	2.9 ± 1.2 (1.3–7.4)
HDL in mmol/l (mean ± std (range))	1.5 ± 0.6 (0.3–5.3)
Systolic blood pressure in mmHg (mean ± std (range))	134 ± 18 (101–188)
Diastolic blood pressure in mmHg (mean ± std (range))	88 ± 12 (45–110)
Diabetes	14/74 (18.9%)
Nicotine abuse	20/74 (27.0%)
Framingham risk score (mean ± std (range))	7.3 ± 3.4 (–3–17)
Framingham 10 year risk of CAD (in %)	12.0 ± 7.2 (1–40)
Low pretest probability (<5%)	5/74 (7%)
Intermediate pretest probability (5–12%)	41/74 (55%)
High pretest probability (≥13%)	28/74 (38%)
At CTCA scan	
Heart rate (mean ± std (range))	62.7 ± 9.1 (45–87)
Heart rate variability (mean ± std (range))	4.7 ± 6.2 (0.5–22.1)
Overall image quality (median (25th; 75th percentiles))	2 (1;3)
score 1, 2, 3, 4, 5	39, 32, 22, 7, 0/100
Best reconstruction interval (median (25th; 75th percentiles))	60 (60;65)
30, 35, 40, 55, 60, 65, 70%	4, 7, 5, 4, 52, 20, 8/100

Table 2 Reasons for exclusion of coronary segments

Segment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total
Missing segments	0	0	2	10	2	0	0	0	0	0	0	3	0	2	76	42	137 (8.5%)
Vessel diameter < 1.5 mm	0	1	6	9	0	0	0	1	8	20	0	31	1	15	4	0	96 (6.4%)
Motion artefacts	3	7	2	0	0	0	0	2	0	1	0	1	1	0	0	0	17 (1.0%)
Stents	2	2	1	0	0	4	7	5	0	0	1	2	5	2	0	0	31 (1.9%)
Segment distal to total occlusion	0	7	11	11	0	0	2	2	2	2	0	1	1	1	1	0	41 (2.6%)
Total	5	17	22	30	2	4	9	10	10	23	1	38	8	20	81	42	322 (20.1%)

examination. Baseline characteristics of the final study group are presented in Table 1.

A total of 1,278 coronary artery segments with a diameter ≥1.5 mm were evaluated (137 segments were missing because of anatomical variants, 96 segments had a diameter less than 1.5 mm at their origin). Seventeen segments were excluded due to severe motion artifacts, 31 segments were excluded because of previous stent implantations, and 41 segments were distal to an occluding stenosis; a segment-based analysis of reasons for segment exclusions is demonstrated in Table 2.

Diagnostic accuracy of CTCA in comparison to QCA

A total of 139 coronary artery stenoses with a luminal narrowing of more than 50% in diameter were identified with QCA in 60 patients (60%). Single-vessel disease was present in 28/100, 2-vessel disease in 21/100, and 3-vessel disease in 11/100. Significant coronary artery stenoses could be excluded in 40/100 patients.

CTCA correctly recognized 105 of the 139 significant stenoses (75.5%) detected with QCA. Thirty-nine false-positive (FP) and 34 false-negative (FN) ratings occurred with CTCA. The kappa value for coronary artery stenosis detection with CTCA was 0.88, 0.64, and 0.55 (patient-, vessel-, and segment-based) indicating a good inter-observer agreement.

Thus, on a per-segment analysis, overall sensitivity was 75.5% (105/139; 95% CI: 67.5–82.4), specificity was 96.6% (1100/1139; 95% CI: 95.4–97.6), PPV was 72.9% (105/144; 95% CI: 64.9–79.9), and NPV was 97.0% (1100/1134; 95% CI: 95.8–97.9); a further analysis for each segment is demonstrated in Table 3.

On a per-vessel analysis, sensitivity was 89.3% (92/103; 95% CI: 81.7–94.6), specificity was 95.3% (283/297; 95% CI: 92.2–97.4), PPV was 86.8% (92/106; 95% CI: 78.8–92.6), and NPV was 96.3% (283/294; 95% CI: 93.4–98.1).

On a per-patient analysis, sensitivity was 95.0% (57/60; 95% CI: 86.1–98.9), specificity was 97.5% (39/40; 95% CI: 86.8–99.9), PPV was 98.3% (57/58;

Table 3 Segment-based analysis of diagnostic accuracy of CTCA

Segment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total
TP [n]	18	6	1	7	0	16	17	5	6	1	14	5	8	0	1	0	105
FP [n]	5	4	0	0	0	10	3	3	2	2	4	0	2	3	0	1	39
TN [n]	71	72	74	62	97	68	68	82	75	74	76	51	79	77	18	56	1100
FN [n]	1	1	3	1	1	2	3	0	7	0	5	6	3	0	0	1	34
Sensitivity [%]	94.7	85.7	25.0	87.5	0	88.9	85.0	100	46.2	100	73.7	45.5	72.7	n.a.	100	0	75.5
Specificity [%]	93.4	94.7	100	100	100	87.2	95.8	96.5	97.4	97.4	95.0	100	97.5	96.3	100	98.2	96.6
NPV [%]	98.6	98.6	96.1	98.4	98.9	97.1	95.8	100	91.5	100	93.8	89.5	96.3	100	100	98.2	97.0
PPV [%]	78.3	60.0	100	100	n.a.	61.5	85.0	62.5	75	33.3	77.8	100	80.0	0	100	0	72.9

TP: true positive; FP: false positive; TN true negative; FN: false negative; PPV: positive predictive value; NPV: negative predictive value; n.a.: not applicable

95% CI: 90.8–99.9), and NPV was 92.9% (39/42; 95% CI: 80.5–98.5).

Impact of plaque composition on stenosis quantification

Inter-observer agreement for quantification of the stenosis severity by CTCA revealed an overestimation of one reader of 0.5% (BA limits of agreement: −44.2 to 45.2%). After exclusion of all lesions not detected by one of the methods, all segments without stenosis, and all segments with total occlusions, a significant positive correlation was found between quantified grades of stenosis measured with QCA and CTCA ($r = 0.60$; $P < 0.001$) (Fig. 1a), with an absolute mean difference of 14.0 ± 11.1% (range: 0–46%) and an overestimation from CTCA of 5.5% (BA limits of agreement: −28.5 to 39.4%) (Fig. 1b).

In the group with non-calcified lesions, a significant positive correlation was found between quantified grades of stenosis measured with QCA and CTCA ($r = 0.73$; $P < 0.001$) (Fig. 2a), with an absolute mean difference of 11.1 ± 9.1% (range: 0–38%) and an overestimation from CTCA of 2.2% (BA limits of agreement: −25.9 to 30.2%) (Fig. 2b). In the group with calcified lesions, a significant positive correlation was found between quantified grades of stenosis measured with QCA and CTCA ($r = 0.48$; $P < 0.001$) (Fig. 2c), with an absolute mean difference of 16.3 ± 12.2% (range: 0–46%) and an overestimation from CTCA of 8.2% (BA limits of agreement: −29.2 to 45.6%) (Fig. 2d). The absolute differences between QCA and CTCA were found to be significantly larger for calcified versus non-calcified lesions ($P < 0.05$).

Discussion

The quantification of coronary lesion severity has important therapeutic consequences in clinical routine [11]. Our study adds to the previous knowledge on CTCA and on quantification of coronary artery stenoses with CT [2, 3, 12–14] the following results, that the limits of agreement for quantitative assessment of coronary artery stenosis with 64-slice CT compared to QCA are wide, and correlation between QCA and quantitative CTCA is higher for non-calcified lesions than for calcified lesions.

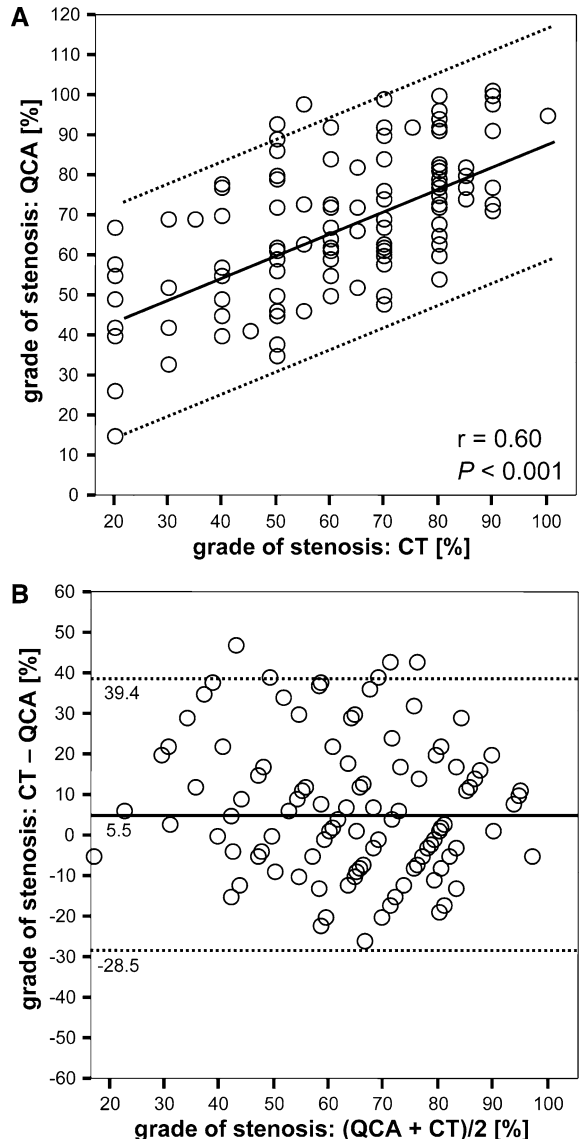

Fig. 1 (**a**) Linear regression with 95% individual prediction interval (dashed lines) of 113 quantified coronary stenoses detected with both methods (total occlusions were excluded). A significant positive correlation between quantified grades of stenosis measured with QCA (y-axis) and CTCA (*x*-axis) was detected ($r = 0.60$; $P < 0.001$). (**b**) Difference of the grades of 113 quantified coronary stenoses detected with both methods, plotted against the mean grades of stenosis as measured with QCA and CTCA. The solid line describes an overestimation of 5.5% of CTCA. Dashed lines represent BA limits of agreement (−28.5 to 39.4%)

Diagnostic accuracy of CTCA in comparison to QCA

A high diagnostic performance of 64-slice CTCA has been demonstrated by many investigators. Variations

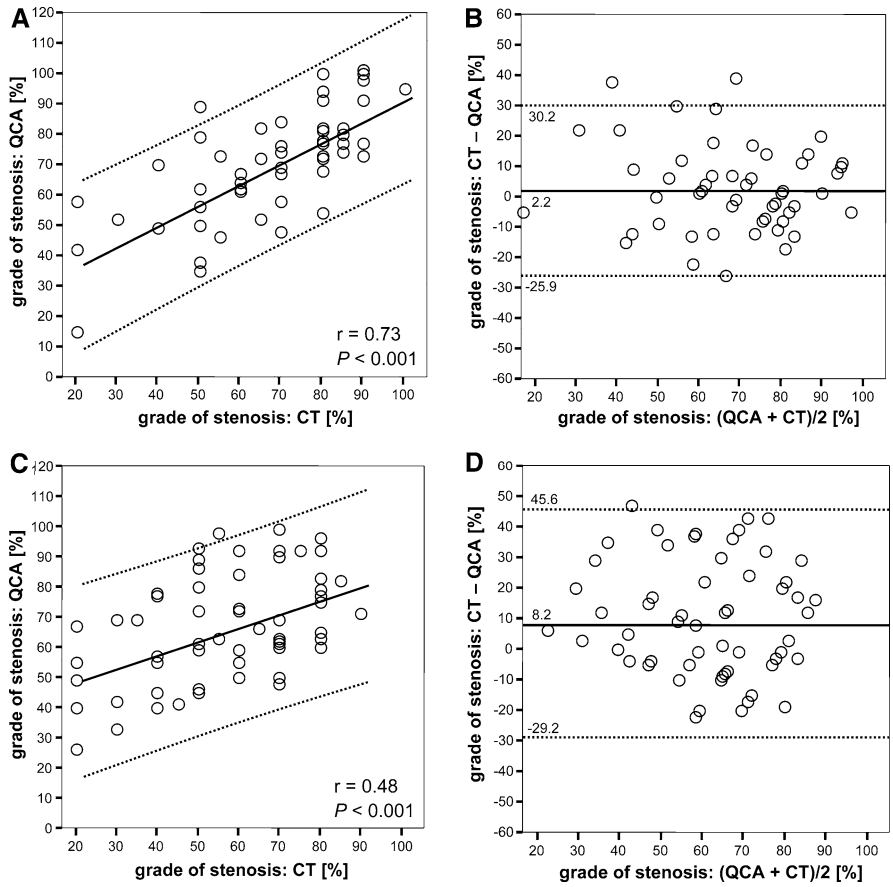

Fig. 2 Impact of plaque composition on stenosis grade quantification. (**a**) Linear regression with 95% individual prediction interval (dashed lines) of all non-calcified (n = 52) quantified coronary stenoses detected with both methods (total occlusions were excluded). A significant positive correlation between quantified grades of stenosis measured with QCA (*y*-axis) and CTCA (*x*-axis) (r = 0.73; $P < 0.001$) was detected. (**b**) Difference of the grades of stenosis in 52 non-calcified coronary stenoses, plotted against the mean grades of stenosis as measured with QCA and CTCA. The solid line describes an overestimation of 2.2% of CTCA. Dashed lines represent BA limits of agreement (−25.9 to 30.2%). (**c**) Linear regression with 95% individual prediction interval (dashed lines) of all calcified (n = 61) quantified coronary stenoses detected with both methods (total occlusions were excluded). A significant positive correlation between quantified grades of stenosis measured with QCA (*y*-axis) and CTCA (*x*-axis) (r = 0.48; $P < 0.001$) was detected. (**d**) Difference of the grades of stenosis in 61 calcified coronary stenoses, plotted against the mean grades of stenosis as measured with QCA and CTCA. The solid line describes an overestimation of 8.2% of CTCA. Dashed lines represent BA limits of agreement (−29.2 to 45.6%)

in diagnostic performance between different study groups [1–3, 5, 6, 8–10] are due to several factors. A high prevalence of CAD in a patient population favours a high PPV and lower NPV. Compared to other groups we had a relatively low prevalence of CAD (60%), explaining a relatively low NPV and a very high PPV in our group (patient-based analysis). Sensitivity and specificity on the other hand are influenced by factors such as image quality and coronary calcifications, which renders an interstudy comparison difficult. In our study a relatively low sensitivity and a high specificity were demonstrated compared to other studies. We can only speculate that this was due to the use of a sharp tissue-convolution kernel for the assessment of calcified coronary lesions, leading to more precise evaluation of calcified lesions [22] and less false positive, but possibly also to more false negative ratings.

Quantification of stenosis and impact of plaque composition and vessel opacification

Only few authors have assessed the quantitative grading of coronary stenosis, demonstrating large

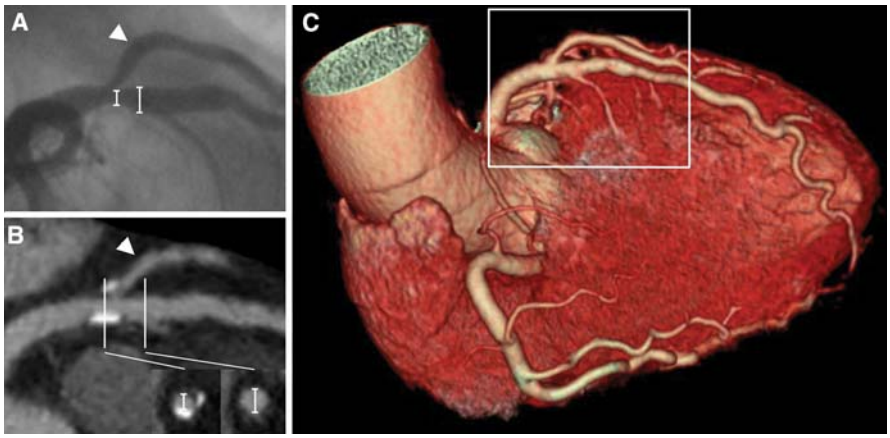

Fig. 3 Demonstration of an overestimation of a calcified stenosis with CTCA in a 70-year-old female patient (**a**) With QCA a 50% diameter stenosis in the mid LAD was diagnosed; because the origin of the first diagonal branch (white arrow head) was just proximal to stenosis, quantification was performed only in relation to the distal reference vessel (white indicators). (**b**) With CTCA (using a sharp tissue convolution kernel: B46f) a 60% diameter stenosis was diagnosed, on planes, perpendicular to the course of the vessel (white lines and corresponding inlays). (**c**) The volume rendered reconstruction of the heart after removal of the left atrial appendage demonstrates the location of the region of interest (white square)

limits of agreement with 16-slice CTCA (−23 to 25%, [13]; −30 to 25%, [12]) and 64-slice CTCA (−26 to 29%, [3]; −24 to 36%, [23]).

This is in line with results of our study, also displaying large limits of agreement of −29 to 39%. With 64-slice CT, authors found CTCA to slightly overestimate the degree of coronary stenosis [3, 23], not taking into account the composition of the plaques. We could demonstrate for the first time that CTCA quantifies calcified stenoses with a larger overestimation and with larger limits of agreement, compared to non-calcified stenoses.

However, the large limits of agreement for stenosis grading between CTCA and QCA demonstrated in our study are most likely also due to limitations inherit of the two methods:

Limitations of QCA

QCA depicts coronary anatomy from planar two-dimensional projections of the lumen. Theoretically, two orthogonal angiograms should accurately reflect the severity of most lesions. However, adequate orthogonal views are frequently unobtainable in QCA because of foreshortening, overlapping side branches, or disease at bifurcation sites. Furthermore, certain complex luminal shapes cannot be accurately depicted with any arbitrary angle of view [24]. This is underlined by several studies which revealed major discrepancies between the apparent angiographic severity of lesions and postmortem histology [25, 26], and between the apparent severity of lesions and their physiological effects [27, 28].

Limitations of CTCA

64-slice CT allows three-dimensional image reconstructions at any desirable plane [29], overcoming the mentioned shortcomings of planar two-dimensional projections with QCA. On the other hand the temporal and especially the spatial resolution of CTCA are inferior to QCA, leading to unclear definition of lesion margins and possible consecutive quantification errors (Fig. 3).

Therefore, limitations of both CTCA and QCA render the exact quantification of coronary lesions cumbersome, and are most likely accountable for large limits of agreement in a direct comparison of both methods.

Limitations of the study

First, 60% of the study patients had significant coronary stenosis indicating an increased probability for CAD which may have resulted in an overestimation of the ability of CTCA to detect stenosis. Therefore, patient selection bias may possibly limit the transfer of these results to patient populations

with a low to intermediate likelihood of CAD. Second, our study was performed using 64-slice CT and not using most recent dual-source CT scanner technology [30].

Conclusions

Diagnostic accuracy of CTCA is high, however agreement for quantitative lesion severity assessment between CTCA and QCA is moderate for calcified but superior for non-calcified lesions.

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