

Automated quantification of coronary plaque with computed tomography: comparison with intravascular ultrasound using a dedicated registration algorithm for fusion-based quantification

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Aims

Previous studies have used semi-automated approaches for coronary plaque quantification on multi-detector row computed tomography (CT), while an automated quantitative approach using a dedicated registration algorithm is currently lacking. Accordingly, the study aimed to demonstrate the feasibility and accuracy of automated coronary plaque quantification on cardiac CT using dedicated software with a novel 3D coregistration algorithm of CT and intravascular ultrasound (IVUS) data sets.

Methods and results

Patients who had undergone CT and IVUS were enrolled. Automated lumen and vessel wall contour detection was performed for both imaging modalities. Dedicated automated quantitative software (QCT) with a unique registration algorithm was used to fuse a complete IVUS run with a CT angiography volume using true anatomical markers. At the level of the minimal lumen area (MLA), percentage lumen area stenosis, plaque burden, and degree of remodelling were obtained on CT. Additionally, mean plaque burden was assessed for the whole coronary plaque. At the identical level within the coronary artery, the same variables were derived from IVUS. Fifty-one patients (40 men, 58 ± 11 years, 103 coronary arteries) with 146 lesions were evaluated. Quantitative computed tomography and IVUS showed good correlation for MLA ($n = 146$, $r = 0.75$, $P < 0.001$). At the level of the MLA, both techniques were well-correlated for lumen area stenosis ($n = 146$, $r = 0.79$, $P < 0.001$) and plaque burden ($n = 146$, $r = 0.70$, $P < 0.001$). Mean plaque burden ($n = 146$, $r = 0.64$, $P < 0.001$) and remodelling index ($n = 146$, $r = 0.56$, $P < 0.001$) showed significant correlations between QCT and IVUS.

Conclusion

Automated quantification of coronary plaque on CT is feasible using dedicated quantitative software with a novel 3D registration algorithm.

Keywords

Automated quantification • Computed tomography • Coronary plaque • Intravascular ultrasound • Registration

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Introduction

Multi-detector row computed tomography (CT) permits non-invasive evaluation of coronary artery disease (CAD) with excellent image quality and diagnostic accuracy when compared with invasive coronary angiography.^{1–3} The degree of coronary luminal narrowing is commonly used to guide diagnosis and therapeutic interventions in clinical cardiology.^{3–5} However, CT imaging is not restricted to coronary luminography as it provides additional information on the coronary atherosclerotic plaque itself, including plaque morphology, plaque burden, and the degree of plaque remodelling. However, one of the current drawbacks of CT imaging remains the fact that coronary plaque characteristics are most commonly evaluated by a visual approach, which is observer dependent and requires substantial reading experience.

Automated quantification of coronary plaque characteristics would be preferred to further improve the diagnostic accuracy, reproducibility, and time-efficiency of cardiac CT imaging. At present, however, the feasibility of automated quantification of coronary luminal narrowing using cardiac CT has only been demonstrated in a small number of studies.^{6,7} Earlier attempts that aimed to measure other coronary plaque characteristics have used either manually based or semi-automated techniques, rather than automated dedicated quantitative algorithms.^{8–10} Moreover, in these previous studies, a visual approach was used

to match coronary lesions on the different imaging techniques which may introduce inaccuracies.

Recently, dedicated automated quantitative computed tomography (QCT) software with a unique 3D registration algorithm has been developed to enable accurate matching of imaging modalities along the longitudinal and transversal axes of coronary arteries. The novel 3D registration algorithm allows fusion of cardiac imaging techniques using a *slice-by-slice comparison* of each location along the longitudinal and transversal axes of the coronary arteries and may improve detection and quantification of coronary plaques on cardiac CT when compared with previous quantitative CT studies using a visual approach.

At present, no study has evaluated the feasibility of automated coronary plaque quantification on cardiac CT using an automated 3D registration algorithm of CT and intravascular ultrasound (IVUS) data sets. Accordingly, the current study aimed to demonstrate the feasibility and accuracy of automated quantification of coronary plaque on cardiac CT using dedicated software with a novel 3D registration algorithm of CT and IVUS data sets.

Methods

Patient population and study protocol

The patient population consisted of patients who had undergone cardiac CT imaging and conventional invasive coronary angiography with IVUS within a period of 4 months. Clinical data were prospectively entered in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center). A total of 80 consecutive patients with known ($n = 32$) or suspected (48) coronary atherosclerosis who were referred for cardiac CT were selected. From these 80 patients, 51 patients were referred within a period of 4 months for invasive coronary angiography in combination with IVUS because of patient's clinical symptoms and/or imaging results to further evaluate the extent and severity of CAD. Accordingly, 29 patients who were not referred to invasive coronary angiography with IVUS ($n = 18$) or did not undergo invasive coronary angiography along with IVUS ($n = 11$) were excluded from further analyses. A flow chart of the patient inclusion is provided in Figure 1.

In each of the 51 patients, IVUS was performed in one to three coronary arteries during invasive coronary angiography. Of the 153 coronary arteries, IVUS was performed in 103 coronary arteries, whereas IVUS studies were not acquired in 50 coronary arteries due to vessel tortuosity ($n = 15$), severe luminal narrowing ($n = 9$), (subtotal) vessel occlusion ($n = 11$), or time constraints ($n = 15$).

Conventional invasive coronary angiography with grey-scale intravascular ultrasound

Data acquisition and analysis

Invasive coronary angiography was performed according to the standard protocol.¹¹ Vascular access was obtained via the femoral artery using the Seldinger Technique with a 6 or 7F sheath. During invasive coronary angiography, IVUS examinations were performed in 103 coronary arteries using a dedicated IVUS-console (Volcano Corporation, Rancho, Cordova, CA, USA). After administration of intracoronary nitrates, IVUS runs were acquired using a 20 MHz, 2.9 F phases-array IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, CA, USA) which was positioned in the distal coronary segments. Consecutively, the IVUS catheter was pulled back towards the coronary ostium at a continuous speed of 0.5 mm/s using an

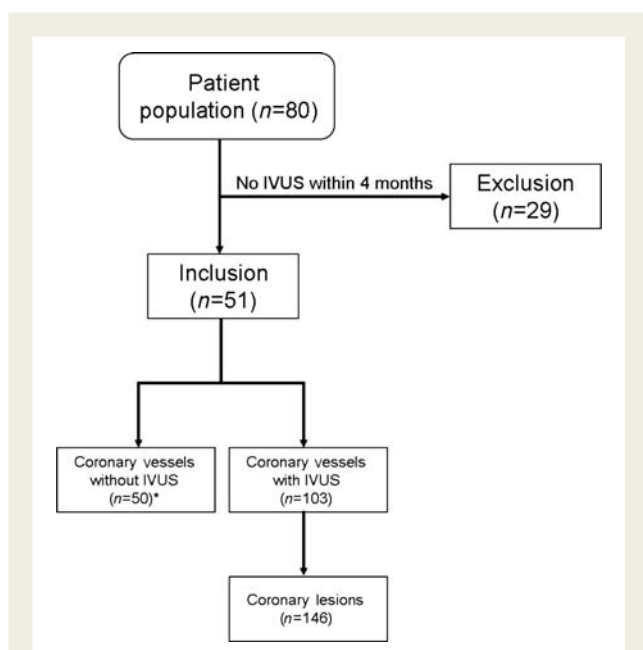


Figure 1 Flow chart of the patient inclusion. A total of 80 patients referred for cardiac computed tomography (CT) because of known or suspected coronary artery disease (CAD) were selected, of which 51 patients underwent invasive coronary angiography with intravascular ultrasound (IVUS). *IVUS examinations could not be performed in 50 coronary arteries due to vessel tortuosity ($n = 15$), severe luminal narrowing ($n = 9$), (subtotal) vessel occlusion ($n = 11$), or time constraints ($n = 15$).

automated pullback device. Images were acquired with a frame rate of 15 frames/s. Data sets were stored for offline post-processing analyses. Consecutively, lumen-intima and media-adventitia borders were obtained by dedicated post-processing software as described in the Supplementary material online, Appendix.

Computed tomography

Data acquisition and analysis

Cardiac CT imaging was performed using either a 64-detector row helical scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan) or a 320-detector row volumetric scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan). One hour prior to CT imaging, all patients with an elevated heart rate (≥ 65 b.p.m.) were given metoprolol 50 or 100 mg orally, unless contra-indicated. Additionally, patients received sublingual nitroglycerine (0.4 mg/dose, one dose per patient) directly before the CTA examination.

For the 64-detector and 320-detector row CT examination, patients underwent both a non-enhanced and contrast-enhanced scan. Prior to the contrast-enhanced helical scan, a non-enhanced electrocardiographic-triggered scan was performed to assess the coronary calcium score. The non-enhanced and contrast-enhanced scans were performed as previously described.^{6,12}

Reconstructed images were transferred to a remote dedicated workstation with post-processing software (Vitrea FX 1.0, Vital Images, Minnetonka, MN, USA). The non-enhanced scans were used to assess the total amount of coronary calcium according to the Agatston approach.¹³

Computed tomography angiography data sets were evaluated by an independent and experienced observer, who was blinded to the IVUS data. Prior to the automated quantitative analyses, image quality was evaluated using the following ordinal scale: (i) good image quality, (ii) moderate image quality, or (iii) poor image quality. Data sets with good quality showed no motion artefacts or increased image noise, whereas data sets were classified as moderate in case of motion artefacts or increased image noise. Non-diagnostic scans were classified as data sets with poor image quality. Furthermore, coronary lesions were classified by an independent and blinded observer as either non-calcified (no coronary calcium) or calcium-containing (any presence of coronary calcium) lesions.

Automated QCT angiography¹⁴ was performed by an independent observer who was blinded to IVUS data. A dedicated and extended version of the QAngio CT software (QAngio CT 1.1, Medis medical imaging systems, Leiden, the Netherlands) was used to perform quantitative CT analyses. On CT data sets, the dedicated software was able to detect both lumen and vessel wall contours which were used for automated quantitative measurements of coronary plaques, as depicted in Figure 2, upper panel. A detailed description of the lumen and vessel contour detection process is provided in the Supplementary material online, Appendix.

Registration and fusion-based quantification of coronary plaque

Dedicated quantitative software with a unique registration algorithm was developed for automated fusion of a complete pullback series of high-resolution IVUS images with CT angiography.¹⁵ The novel registration algorithm enabled an accurate matching of both imaging modalities along the longitudinal and transversal axes of the coronary arteries. Intravascular ultrasound images were fused on the corresponding slices within the CT data using a two-step 3D fusion process. First, the stack of IVUS images was mapped onto the longitudinal CT image along the centreline of the vessel by locating

corresponding anatomical landmarks. The anatomical landmarks (side-branches, coronary ostia, calcified plaques, and overlapping veins) were located and marked within both imaging modalities. Secondly, the individual IVUS images were translated and rotated until they fit best onto the corresponding cross-sections of the CT image (Figure 3). The fitting procedure was based on the location of the centre of the vessel in both images. In addition, the presence of anatomical landmarks (side-branches, calcified spots, and overlapping veins) in each image was used to identify the correct rotation of the IVUS image on top of the CT image. In between anatomical landmarks, IVUS images were aligned to the corresponding locations of the MPR volume of the CT data with the use of interpolation. For this reason, deviations within the motorized pullback speed of the IVUS catheter were corrected.

After both imaging modalities were aligned, fusion-based quantification of coronary lesions was performed using automated detected lumen and vessel wall contours as well as corresponding reference lines (Figure 2). In both modalities, the reference line represented an estimate of the normal proximal-to-distal tapering of the coronary artery. Reference lines were generated from proximal and distal non-diseased reference regions, in which the mean value of these regions was used to define a reference slope for both lumen and vessel wall contours. In the current study, proximal and distal reference regions were not positioned at coronary bifurcations. Importantly, the use of an average reference value results in a reduction in isolated discrepancies between sequential contours.

Per coronary lesion, fusion-based quantification was performed at the level of the minimal lumen area (MLA) and for the whole lesion, ranging from the proximal to distal lesion marker. At first, the level of the MLA and lesion markers was automatically identified within the coronary artery using the detected lumen contours on CT.

At the level of the MLA, plaque burden was calculated by the following equation: $(\text{vessel wall area} - \text{lumen area})/\text{vessel wall area} \times 100\%$. Using the same formula, the mean plaque burden was calculated for the whole coronary lesion. The percentage lumen area stenosis (%) was defined at the level of the MLA by: $1 - (\text{MLA}/\text{corresponding reference lumen area})$. In addition, at the level of the MLA, the degree of remodelling was calculated as reported previously.¹⁶ Positive remodelling was defined as a remodelling index ≥ 1.0 .¹⁶

Both MLA and lesion markers were automatically set on the same level within the IVUS run using the dedicated registration algorithm (Figures 2 and 3). Consecutively, the corresponding plaque variables on IVUS were automatically derived for each coronary lesion using the markers set at precisely the same level as used for cardiac CT.

Reproducibility of QCT for assessment of coronary plaque characteristics was evaluated in 10 randomly selected patients with 25 coronary lesions. To evaluate the reproducibility of QCT, automated lumen and vessel wall contour detection as well as plaque quantification were performed twice by the same observer. Quantification of coronary plaques was based on lesion as well as reference markers which were positioned at a similar level within the coronary artery in both CT data sets.

Statistical analysis

Continuous data were expressed as mean \pm standard deviation, and categorical data are presented as absolute numbers or percentages. Kolmogorov–Smirnov tests were used to evaluate the distribution of the data. When non-normally distributed, data were presented as medians and 25th and 75th percentiles. Comparison of both quantitative techniques was performed using Pearson's linear regression analysis (or spearman's rho correlation) and Bland–Altman analyses

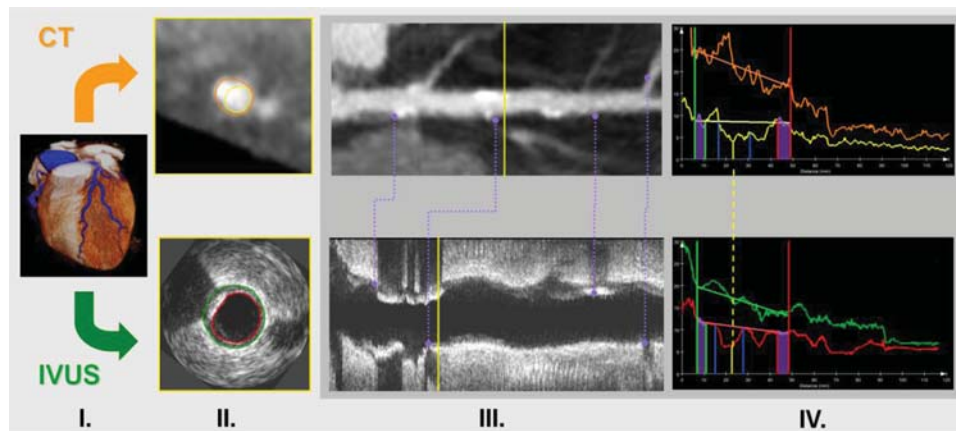


Figure 2 Schematic illustration of automated quantification of coronary plaque on multi-detector row computed tomography (CT) (QCT) in a direct comparison to quantitative intravascular ultrasound (IVUS). QCT was based on several consecutive processing phases, as depicted below. After the three-dimensional centerline was generated from the CT data set using a fast vessel-tracking algorithm (panel I), automated lumen and vessel wall contour detection was performed for both imaging modalities (panel II). Consecutively, dedicated quantitative software with a unique registration algorithm was used to fuse a complete pullback series of IVUS images with a computed tomography angiography (CTA) volume using true anatomical markers (panel III). Finally, fusion-based quantification of atherosclerotic lesions was based on the lumen and vessel wall contours as well as the corresponding reference lines (estimate of normal tapering of the coronary artery), as shown in panel IV. At the level of the minimal lumen area (MLA) (yellow lines), lumen area, lumen area stenosis, plaque burden, and remodelling index could be derived for both imaging techniques. Additionally, the mean plaque burden was derived for the whole coronary lesion, ranging from the proximal to distal lesion marker (blue markers).

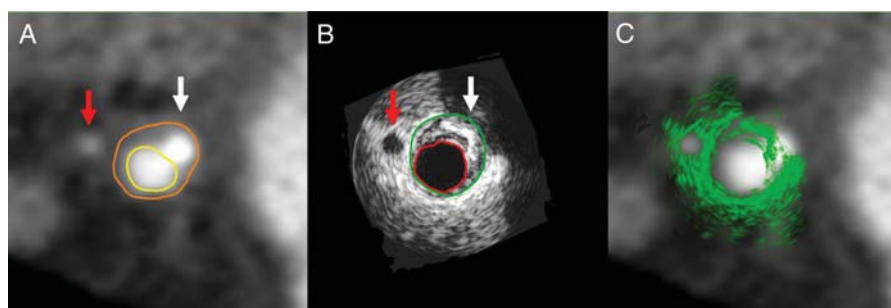


Figure 3 Dedicated quantitative software with a novel registration tool was used to merge a complete pullback IVUS run with a computed tomography angiography (CTA) volume. Fusion of both imaging modalities was based on the identification of true anatomical markers along the coronary artery. In this example, multi-detector row computed tomography (CT) (A) was aligned to the corresponding IVUS run (B) using a calcified spot (white arrow) and coronary side-branch (red arrow). Consecutively, the IVUS run (green colour) was projected on the corresponding CT image (C). The IVUS overlay in (C) was colour-coded in green to improve the visual appearance of the fusion process.

(GraphPad Prism software, version 5.01, GraphPad software Inc, San Diego, California, MA, USA). The 95% confidence intervals for the correlations were calculated using Fisher z-transformation.

Quantitative computed tomography and IVUS were compared on a lesion and vessel basis, in which lesion-based analysis was based on each coronary lesion, whereas vessel-based analysis was based on the most severe lesion per coronary vessel. Bland–Altman graphs showed the mean value of differences of each pair plotted against the average value of each pair, in which IVUS was subtracted from the QCT measurements.

In addition, in the lesion-based analysis, comparisons between both quantitative techniques were performed using generalized estimating equations in order to correct for the intra-patient correlation. The difference between QCT and IVUS was calculated for each quantitative parameter (MLA, lumen area stenosis, mean plaque burden, plaque burden at the MLA, and remodelling index) and was entered as dependent variable. The 95% confidence intervals for these analyses were calculated.

Furthermore, the accuracy of QCT for assessment of coronary plaque remodelling was assessed using a binary approach (using 1.0

as a cut-off) with IVUS as the reference method. For this analysis, corresponding sensitivity, specificity, negative, and positive predictive values were calculated. Additionally, the influence of image quality (good, moderate, or poor) on the performance of QCT was determined using Pearson's linear regression. Reproducibility of QCT was determined on a lesion basis (25 lesions) using intra-class correlation (ICC) analyses. Excellent agreement was defined as an ICC coefficient of >0.8 . All *P*-values were two-sided and a *P*-value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed with the use of statistical software (SPSS version 16.0, SPSS Inc., Chicago, IL, USA).

Results

Patient population

Baseline characteristics of the patient population are described in Table 1. Fifty-one patients (40 men, mean age 58.0 ± 10.6 years) who had undergone CT imaging and invasive coronary angiography with IVUS were enrolled. Patients had undergone either a 320-row volumetric ($n = 12$) or a 64-row helical scan ($n = 39$) to evaluate coronary atherosclerosis non-invasively. In the population consisting of 51 patients, IVUS studies were acquired in 103 coronary arteries in which a total of 146 non-stented coronary lesions were identified on both imaging modalities. The mean heart rate during cardiac CT imaging was 60.9 ± 11.0 b.p.m. Only the MLA data as derived from QCT and IVUS were non-normally distributed.

Table 1 Baseline characteristics of study population ($n = 51$)

Baseline characteristics	Values
Men	40 (78)
Age (years)	58.0 ± 10.6
Calcium score	595 ± 1386
Known CAD	11 (22)
Clinical presentation	
Atypical anginal complaints	31 (61)
Typical anginal complaints	20 (39)
Cardiovascular risk factors	
Diabetes	11 (22)
Systemic hypertension	32 (63)
Hypercholesterolaemia	28 (55)
Current smoking	23 (45)
Obesity	8 (16)
Positive family history	15 (29)
Medication	
Beta-blocker	27 (53)
Angiotensin converting enzyme/angiotensin II	18 (35)
Diuretic	13 (25)
Nitrate	11 (22)
Calcium antagonist	10 (20)

Data are represented as mean \pm standard deviation or as number (percentage). CAD, coronary artery disease.

Minimal lumen area and lumen area stenosis

On a lesion basis, good correlations were observed between QCT and IVUS for assessment of MLA ($n = 146$, $r = 0.75$, $P < 0.001$) (95% CI 0.67–0.81) (Figure 4A) and lumen area stenosis ($n = 146$, $r = 0.79$, $P < 0.001$) (95% CI 0.72–0.84) (Figure 5A). Lesions with a small MLA showed higher correlations between QCT and IVUS when compared with lesions with a large MLA. Similarly, vessel-based analysis showed good correlation between both quantitative techniques for assessment of MLA ($n = 103$, $r = 0.73$, $P < 0.001$) (95% CI 0.63–0.81) and lumen area stenosis ($n = 103$, $r = 0.82$, $P < 0.001$) (95% CI 0.75–0.88).

On a lesion basis, the mean bias between techniques for quantification of MLA was -3.0 mm² with 95% limits of agreement ranging from -7.5 to 1.4 mm² (Figure 4B). Quantitative computed tomography significantly underestimated the MLA when compared with IVUS [3.6 mm² (2.3–5.0) vs. 6.4 mm² (4.3–9.3); 95% confidence interval of the mean difference was -3.4 to -2.5 ; $P < 0.001$].

On a lesion basis, the mean bias was 9.8% for lumen area stenosis with 95% limits of agreement ranging from -13.9 to 33.6% (Figure 5B). The lumen area stenosis was significantly overestimated by QCT when compared with IVUS (44.4 ± 19.6 vs. 34.6 ± 17.8 %; 95% CI of the mean difference 7.9–11.7; $P < 0.001$).

Coronary plaque burden

Mean plaque burden ($n = 146$, $r = 0.64$, $P < 0.001$) (95% CI 0.53–0.73) showed a good correlation between QCT and IVUS on a lesion basis. On a vessel basis, QCT was correlated to IVUS for the assessment of mean plaque burden ($n = 103$, $r = 0.62$, $P < 0.001$) (95% CI 0.49–0.73). Bland–Altman analyses showed a mean bias for mean plaque burden of 12.3% with 95% limits of agreement ranging from -13.8 to 38.5%. Based on linear mixed models, the mean plaque burden was significantly overestimated with QCT when compared with IVUS (61.1 ± 16.1 vs. 48.8 ± 15.4 %; 95% CI of the mean difference 14.8–19.6; $P < 0.001$).

For plaque burden at the MLA, good correlations were found between QCT and IVUS on a lesion ($n = 146$, $r = 0.70$, $P < 0.001$) (95% CI 0.61–0.77) and vessel ($n = 103$, $r = 0.68$, $P < 0.001$) (95% CI 0.56–0.77) basis. For plaque burden at the MLA, Bland–Altman analyses showed mean bias of 17.2%, with 95% limits of agreement extending from -9.1 to 43.6%. Plaque burden at the MLA was significantly overestimated with QCT when compared with IVUS (69.4 ± 17.7 vs. 52.1 ± 16.8 %; 95% CI of the mean difference 9.7–15.0; $P < 0.001$) on a lesion basis.

Remodelling index

On a lesion basis, a significant correlation was observed between QCT and IVUS for assessment of remodelling index ($n = 146$, $r = 0.56$, $P < 0.001$) (95% CI 0.44–0.66). Both quantitative approaches showed an improved correlation on a vessel basis ($n = 103$, $r = 0.58$, $P < 0.001$) (95% CI 0.44–0.70). Bland–Altman analyses showed a mean bias of 0.05 with 95% limits of agreement ranging from -0.30 to 0.40. There was a trend towards overestimation of remodelling index by QCT when compared with IVUS with linear regression mixed models (0.94 ± 0.21

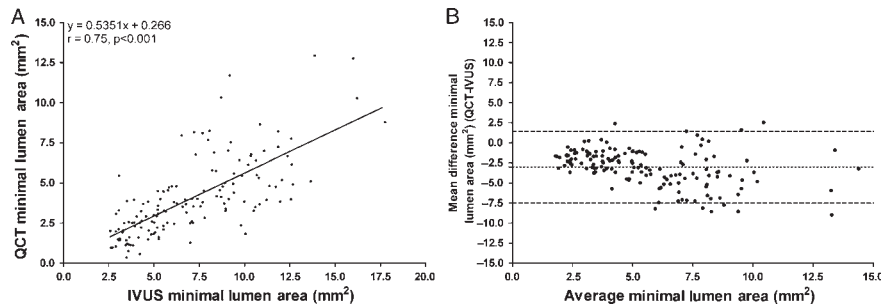


Figure 4 Quantitative computed tomography (QCT) was compared with quantitative coronary ultrasound (IVUS) for assessment of minimal lumen area (MLA). Linear regression (A) and Bland–Altman analyses (B) for MLA on a lesion basis ($n = 146$). The mean value of differences \pm standard deviation was -3.0 ± 2.3 mm² with 95% limits of agreement ranging from -7.5 to 1.4 mm².

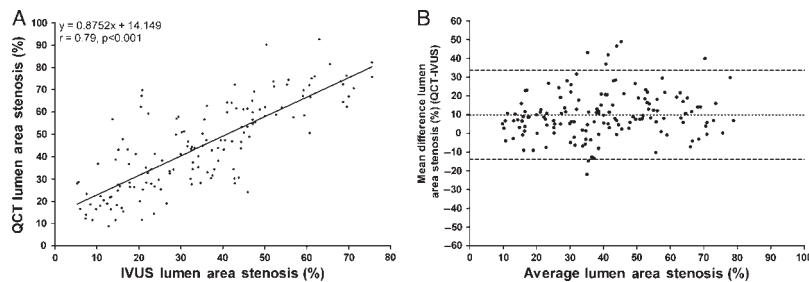


Figure 5 Quantitative computed tomography (QCT) was compared with quantitative coronary ultrasound (IVUS) for assessment of percentage lumen area stenosis. Linear regression (A) and Bland–Altman analyses (B) for percentage area stenosis on a lesion basis ($n = 146$). The mean value of differences \pm standard deviation was $9.8 \pm 12.1\%$ with 95% limits of agreement ranging from -13.9 to 33.6% .

vs. 0.90 ± 0.14 ; 95% CI of the mean difference 0.01–0.08; $P = 0.005$).

Additionally, the accuracy of QCT for assessment of coronary plaque remodelling was calculated using a binary approach on a vessel basis. In total, 20 coronary arteries showed positive remodelling on IVUS, of which 15 were classified similarly on QCT, yielding a sensitivity of 75% (95% CI 0.51–0.90). Of the 83 coronary vessels with negative plaque remodelling on IVUS, 66 were scored appropriately on QCT (specificity of 80%, 95% CI 0.69–0.87). Furthermore, the negative and positive predictive values were 93% (95% CI 0.85–0.97) and 47% (95% CI 0.31–0.64), respectively. Importantly, using IVUS as a reference method, the overall accuracy of QCT for assessment of plaque remodelling was modest (79%).

Influence of image quality on automated quantification

A sub-analysis was performed to evaluate the influence of image quality on the performance of QCT (Table 2). The image quality of CT data sets was classified as either good ($n = 49$), moderate ($n = 63$), or poor ($n = 34$). For the MLA, good correlations between both quantitative approaches were observed for data

sets with good ($r = 0.81$, $P < 0.001$) (95% CI 0.69–0.89) or moderate ($r = 0.75$, $P < 0.001$) (95% CI 0.62–0.84) quality, whereas they showed a moderate correlation for data sets with poor ($r = 0.68$, $P < 0.001$) (95% CI 0.44–0.83) quality. For the assessment of lumen area stenosis, QCT showed a slightly improved correlation with IVUS for data sets with good ($r = 0.84$, $P < 0.001$) (95% CI 0.73–0.91) and moderate ($r = 0.79$, $P < 0.001$) (95% CI 0.67–0.87) quality when compared with data sets with poor ($r = 0.78$, $P < 0.001$) (95% CI 0.60–0.89) image quality. Mean plaque burden showed a decreased correlation in data sets with suboptimal quality; good quality ($r = 0.70$, $P < 0.001$) (95% CI 0.52–0.82), moderate quality ($r = 0.65$, $P < 0.001$) (95% CI 0.48–0.77), and poor quality ($r = 0.60$, $P < 0.001$) (95% CI 0.32–0.78). However, the influence of image quality for the assessment of plaque burden at the MLA was minimal; IVUS and QCT were well-correlated for data sets with good ($r = 0.70$, $P < 0.001$) (95% CI 0.52–0.82), moderate ($r = 0.71$, $P < 0.001$) (95% CI 0.56–0.81), or poor ($r = 0.68$, $P < 0.001$) (95% CI 0.44–0.83) image quality. Additionally, image quality showed no effect on the assessment of plaque remodelling. Remodelling index showed significant but moderate correlations for data sets with good ($r = 0.42$, $P = 0.002$) (95% CI 0.16–0.63), moderate ($r = 0.62$, $P < 0.001$) (95% CI 0.44–0.75), and poor ($r = 0.55$, $P < 0.001$) (95% CI 0.26–0.75) quality.

Table 2 Influence of image quality on automated quantification of coronary plaque characteristics using quantitative computed tomography (QCT) in a direct comparison with quantitative coronary ultrasound (IVUS)

	Good quality (n = 49)	Moderate quality (n = 63)	Poor quality (n = 34)
MLA (mm ²)	0.81	0.75	0.68
Lumen area stenosis (%)	0.84	0.79	0.78
Mean plaque burden (%)	0.70	0.65	0.60
Plaque burden MLA (%)	0.70	0.71	0.68
Remodelling index	0.42	0.62	0.55

MLA, minimal lumen area. All correlations showed a $P < 0.05$; QCT and IVUS were compared on a lesion basis for data sets with good ($n = 49$), moderate ($n = 63$), or poor ($n = 34$) image quality. For each comparison, the corresponding Pearson's regression coefficients are shown.

Influence of coronary calcium

Coronary lesions were classified as either non-calcified (lesions with no coronary calcium) or calcium-containing (any presence of coronary calcium) lesions. Of the 146 coronary lesions, 76 (52%) lesions were classified as calcium-containing lesions, whereas the remaining 70 (48%) lesions were classified as non-calcified lesions. The correlation between QCT and IVUS was similar between non-calcified and calcium-containing lesions for assessment of MLA ($r = 0.70$, 95% CI 0.56–0.80; $r = 0.73$, 95% CI 0.60–0.82) and lumen area stenosis ($r = 0.77$, 95% CI 0.65–0.85; $r = 0.75$, 95% CI 0.63–0.83; both $P < 0.001$).

Furthermore, when compared with IVUS, QCT showed a smaller underestimation of MLA in calcium-containing lesions than in non-calcified lesions, as reflected by mean value of differences of -2.9 ± 2.2 and -3.1 ± 2.3 mm², respectively. In addition, the overestimation of lumen area stenosis on CT was higher in calcium-containing lesions than in non-calcified lesions (mean value of differences of $12.0 \pm 12.8\%$ and $7.4 \pm 11.0\%$, respectively).

Accordingly, no substantial differences in coronary plaque quantification were observed between QCT and IVUS, except for a small overestimation of lumen area stenosis by QCT in calcium-containing lesions.

Reproducibility of quantitative computed tomography

Reproducibility of QCT for coronary plaque quantification was evaluated in 10 randomly selected patients with 25 coronary lesions. On a lesion basis, QCT showed a good reproducibility for assessment of MLA (ICC 0.91, 95% CI 0.78–0.96) and lumen area stenosis (ICC 0.86, 95% CI 0.37–0.95). Furthermore, on a lesion basis, QCT was reproducible for the assessment of mean plaque burden (ICC 0.88, 95% CI 0.74–0.95) as well as plaque burden at the MLA (ICC 0.92, 95% CI 0.78–0.96). Finally, the

quantification of plaque remodelling showed good reproducibility with QCT, as reflected by an ICC of 0.84 (95% CI 0.63–0.93).

Discussion

The current study is the first study that has demonstrated the feasibility of automated quantification of coronary plaque on cardiac CT using dedicated quantitative software with a novel 3D registration algorithm of CT and IVUS data sets.

Automated QCT and IVUS were well-correlated for the assessment of MLA, lumen area stenosis, and plaque burden on a vessel and lesion basis. Coronary plaque remodelling showed a significant but moderate correlation between quantitative CT and IVUS on a vessel and lesion basis. When using a binary approach, the accuracy of QCT for assessment of coronary plaque remodelling was fair. Finally, MLA was significantly underestimated by QCT when compared with IVUS, whereas lumen area stenosis was significantly overestimated by QCT in comparison with IVUS.

Non-invasive imaging of coronary atherosclerosis with the use of cardiac CT provides important information for patient diagnosis, evaluation of therapeutic options as well as for risk stratification of patients for potential adverse cardiovascular events.^{1–3} Rapid developments in CT technology have led to an improvement in image quality and diagnostic accuracy for detection of coronary atherosclerosis.^{1–3} Despite its advances, one of the current drawbacks of cardiac CT represents the fact that evaluation of coronary atherosclerosis is most commonly based on a visual approach, which is observer dependent and requires substantial reading experience. A fully automated approach to quantify plaque characteristics would be preferred to further improve the diagnostic accuracy and reproducibility of cardiac CT. Moreover, automated quantification could potentially decrease the amount of post-processing time required for cardiac CT imaging. Accordingly, substantial effort has been invested in the development of quantitative strategies for CT.^{6–9,17–19}

Thus far, quantitative studies have used manually based or semi-automated algorithms for detection of lumen and vessel wall contours, rather than dedicated automated algorithms for contour detection. Furthermore, previous studies were hampered since comparisons between cardiac imaging techniques were based on visual assessment of coronary plaques as well as manual fusion of imaging modalities. The current study is the first study that allows comparison of cardiac CT and IVUS using a novel-dedicated quantitative algorithm, which allows automated detection of both lumen and outer vessel wall from CT data sets fused with IVUS data along its longitudinal and transversal axes. Additionally, the currently applied novel 3D registration algorithm represents a unique fusion imaging technique as it allows comparison between cardiac imaging techniques using a *slice-by-slice comparison* of each location along the transversal axis of the coronary arteries in both CT and IVUS images. The novel 3D registration algorithm allows improved detection of various (anatomical) landmarks in both longitudinal and transversal axes of the coronary arteries, which are used to obtain an accurate fusion between imaging modalities, and as a consequence, improved quantification of coronary plaque. Accordingly, a detailed fusion-based imaging view is

available, which permits a simultaneous quantification of the entire segmented coronary artery in both CT and IVUS.

At present, only a limited number of studies have aimed to quantify lumen area or lumen area stenosis using cardiac CT with variable results.^{8,18,20,21} Leber *et al.*⁸ evaluated the performance of cardiac CT for quantification of coronary lesions in 55 patients with stable CAD, of whom 18 patients underwent IVUS. Quantification of lumen area and lumen area stenosis was performed on cross-sectional reconstructions derived from cardiac CT images. Even though lumen area showed a good correlation with IVUS ($r = 0.81$, $P < 0.01$), lumen area stenosis showed only a modest correlation between quantitative CT and IVUS ($r = 0.61$, $P < 0.05$). Another study from Joshi *et al.*¹⁸ showed a modest correlation between IVUS and quantitative CT for assessment of lumen area ($r^2 = 0.41$, $P < 0.05$) in 48 patients with 67 coronary lesions. Accordingly, previous investigations which aimed to quantify lumen area stenosis or lumen area on cardiac CT showed a large variability. One of the potential explanations may be the fact that in these studies mostly semi-manual approaches were used, rather than dedicated quantitative algorithms. Moreover, a visual approach to match coronary lesions identified on CT with IVUS was used, which may have led to an inaccurate alignment of coronary plaques on both imaging modalities. In the current study, however, a novel registration algorithm was used permitting an accurate matching of lesions on both imaging modalities along the longitudinal and transversal axes of the coronary arteries. After both imaging modalities were aligned using true anatomical markers, fusion-based quantification showed a good correlation between CT and IVUS for MLA ($r = 0.75$, $P < 0.001$) and lumen area stenosis ($r = 0.79$, $P < 0.001$). Moreover, the quantification process itself was performed with the use of automated dedicated CT software, which represents a more robust approach for coronary plaque quantification when compared with manually based or semi-automated approaches. Furthermore, Bland–Altman analysis showed an underestimation of MLA (and overestimation of lumen area stenosis) as assessed with QCT when compared with IVUS. These findings may be related to the quantification of high-degree, heavily calcified lesions. In addition, QCT and IVUS showed a better correlation for lesions with a small MLA than lesions with a large MLA. This could be explained by the calculation of lumen areas, in which small changes in radius can result in considerable changes in MLA for a large radius.

Beyond coronary luminography, cardiac CT provides information on plaque burden and the degree of plaque remodelling.^{3,9} Previous studies have shown a good correlation between cardiac CT and IVUS for assessment of plaque volume. In these studies, the overall plaque volume was significantly underestimated with CT when compared with IVUS.^{9,22} Although the current study showed a good correlation for assessment of plaque burden with quantitative CT, a significant overestimation of plaque burden with cardiac CT was observed when compared with IVUS. The differences in study findings may be explained by the fact that the current population consisted of patients with advanced and heavily calcified lesions, which may have led to an overestimation of plaque burden with CT when compared with IVUS. In line with the current study, Bruining *et al.*¹⁹ showed a significant overestimation of plaque volume with quantitative

CT when compared with IVUS (222 ± 121 vs. 189 ± 93 mm³, $P < 0.05$). The study by Bruining *et al.*¹⁹ used a quantitative CT approach with limited manual interference to assess plaque volume. In 48 patients with clinical symptoms of CAD, a semi-automated vessel extraction software was used to derive the region of interest, in which lumen contours were detected with an automated edge-detection method. However, it is important to note that the study by Bruining *et al.*¹⁹ used manually drawn vessel wall contours, rather than automated detected vessel wall contours. Furthermore, in the study by Bruining *et al.*,¹⁹ the investigators were allowed to alter the window and level image settings during the quantification process, whereas the automated processing steps in the current study were independent from standard viewing settings. Accordingly, even though a significant overestimation of lumen area stenosis, mean plaque burden, plaque burden at the MLA, and remodelling index on CT was observed, the present study showed that coronary plaque quantification using an automated approach was highly reproducible, as indicated by a high ICC value for assessment of MLA, lumen area stenosis, mean plaque burden, plaque burden at the MLA, and remodelling index. This may represent an important advantage over previous quantification methods.^{9,23}

In addition, a sub-analysis was performed to determine the influence of image quality on the performance of automated quantitative CT. Although quantitative CT showed a slightly decreased performance in data sets with poor image quality for assessment of MLA and lumen area stenosis, no significant influence of image quality was observed for the quantification of plaque burden and remodelling index. Accordingly, these findings show the feasibility of automated quantification of coronary plaques in data sets with different image quality.

Finally, the study has evaluated the influence of coronary calcium on the accuracy of atherosclerotic plaque quantification using QCT. In line with previous observations,²¹ the current study showed that calcium-containing lesions showed a larger overestimation of lumen area stenosis when compared with non-calcified lesions. Although small differences between non-calcified and calcium-containing lesions were observed, the current study demonstrated that overall the QCT algorithm performed equally well in non-calcified and calcium-containing lesions.

Study limitations and clinical perspectives

Some limitations need to be considered. In the current study, the automated quantitative CT was only applied to non-stented coronary segments, whereas segments with coronary stents were excluded. Although a sub-analysis on stented segments would have provided additional information, the current study was only designed to demonstrate the feasibility of QCT for evaluation of coronary plaque. Moreover, IVUS was only performed in 103 (67%) coronary arteries as it could not be performed in 50 (33%) coronary arteries due to vessel tortuosity, severe luminal narrowing, (subtotal) vessel occlusion, or severe time constraints.

In addition, even though both quantitative techniques showed good correlations for coronary plaque characteristics, a significant bias for quantitative plaque parameters was observed. However, the bias between both quantitative imaging modalities was consistent as indicated by a high ICC coefficient in the reproducibility

analyses for assessment of MLA, lumen area stenosis, mean plaque burden, plaque burden at the MLA as well as remodelling index. Accordingly, the study showed the feasibility of QCT for automated coronary plaque quantification. Furthermore, the study showed only a moderate correlation between CT and IVUS for assessment of coronary plaque remodelling. However, when using a binary approach, the study showed a modest accuracy of QCT for assessment of plaque remodelling, indicating that quantitative CT allows assessment of coronary plaque remodelling. This is an important finding as outward remodelling of coronary lesions, which is commonly referred to as positive remodelling, represents one of the plaque characteristics that has been associated with an increased risk for plaque rupture and acute coronary syndromes.^{5,24} Finally, although QCT was reproducible for assessment of coronary plaque parameters, reproducibility was only tested in a limited number of patients.

In addition, the influence of coronary calcium on the accuracy of QCT was evaluated. The study demonstrated that QCT performed equally well in non-calcified and calcium-containing lesions when compared with IVUS. Although both techniques can be used for assessment of coronary calcium, IVUS represents a more accurate technique due to its superior spatial and temporal resolution. However, despite these potentials, IVUS studies are usually performed in only a limited number of patients (patients with a high likelihood of having a significant stenosis) due to the invasive nature of the technique. In contrast, cardiac CT allows non-invasive evaluation of plaque morphology in a wide variety of patients, predominantly patients with a low (or intermediate) pre-test likelihood of CAD, and an early stage of CAD. One of limitations of cardiac CT remains its relatively low positive predictive value which may be caused by the overestimation of heavily calcified lesions due to blooming artefacts. In the current study, the use of an automated quantitative algorithm may have resulted in only a small overestimation of calcium-containing lesions.

Conclusions

The current study demonstrated the feasibility of automated quantification of coronary plaque on cardiac CT using dedicated quantitative software with a novel 3D registration algorithm of CT and IVUS data sets. Both quantitative CT and IVUS showed good correlations for automated assessment of MLA, lumen area stenosis, and plaque burden. Finally, even though QCT showed underestimation of MLA and overestimation of lumen area stenosis along with plaque burden, QCT was reproducible for quantification of MLA, lumen area stenosis, mean plaque burden, plaque burden at the MLA, and remodelling index.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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