Computed tomography coronary angiography : from quantification of coronary atherosclerosis to risk stratification of patients

Graaf, M.A. de

Chapter 4

Automatic quantification and characterization of coronary atherosclerosis with computed tomography coronary angiography: cross-correlation with intravascular ultrasound virtual histology

de Graaf MA, Broersen A, Kitslaar PH, Roos CJ, Dijkstra J, Lelieveldt BP, Jukema JW, Schalij MJ, Delgado V, Bax JJ, Reiber JH, Scholte AJ.

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Abstract

Purpose: Plaque constitution on CTA is associated with prognosis. At present only visual assessment of plaque constitution is possible. An accurate automatic, quantitative approach for CTA plaque constitution assessment would improve reproducibility and allows higher accuracy. The present study assessed the feasibility of a fully automatic and quantitative analysis of atherosclerosis on CTA. Clinically derived CTA and IVUS VH datasets were used to investigate the correlation between quantitatively automatically derived CTA parameters and IVUS VH.

Methods: A total of 57 patients underwent CTA prior to IVUS VH. First, quantitative CTA (QCT) was performed. Per lesion stenosis parameters and plaque volumes were assessed. Using predefined HU thresholds, CTA plaque volume was differentiated in 4 different plaque types necrotic core (NC), dense calcium (DC), fibrotic (FI) and fibro-fatty tissue (FF). At the identical level of the coronary, the same parameters were derived from IVUS VH. Bland-Altman analyses were performed to assess the agreement between QCT and IVUS VH.

Results: Assessment of plaque volume using QCT in 108 lesions showed excellent correlation with IVUS VH ($r = 0.928$, $P < 0.001$) (Figure 1). The correlation of both FF and FI volume on IVUS VH and QCT was good($r = 0.714$, $P < 0.001$ and $r = 0.695$, $P < 0.001$ respectively) with corresponding bias and 95% limits of agreement of 24 mm^3 (-42 ; 90) and 7.7mm^3 (-54 ; 70). Furthermore, NC and DC were well-correlated in both modalities($r = 0.523$, $P < 0.001$) and ($r = 0.736$, $P < 0.001$).

Conclusion: Automatic, quantitative CTA tissue characterization is feasible using a dedicated software tool.

Introduction

Computed tomography coronary angiography (CTA) is a well established non-invasive method for the assessment of coronary atherosclerosis. At present, there is a rich amount of data confirming the correlation between stenosis degree on CTA and invasive coronary angiography.[1, 2] Moreover, several studies have demonstrated the prognostic value of stenosis degree as assessed by CTA in the occurrence of adverse cardiovascular events.[3, 4] In addition to the assessment of stenosis degree, CTA allows in vivo characterization of coronary atherosclerotic plaque to differentiate non-calcified, calcified and mixed plaque. These CTA plaque types have been associated with prognosis.[5] Besides, several additional plaque characteristics on CTA have been associated with plaque vulnerability (e.g. positive remodeling, spotty calcification, low attenuation plaque).[6]

Ultimately, CTA stenosis degree and plaque constitution can be derived by a fully automatic, quantitative approach, allowing high accuracy and good reproducibility. Previously, semi-automated methods to characterize plaque on CTA have been described. [7, 8] However, a dedicated fully automatic quantitative CTA plaque characterization tool to assess plaque constitution is currently unavailable.

The present study assessed the feasibility of an automatic and quantitative analysis of CTA data. In this study, clinically derived CTA and intravascular ultrasound virtual histology (IVUS VH) datasets were used to investigate the correlation between quantitatively, automatically derived CTA parameters and IVUS VH. For this assessment, IVUS VH was defined as the golden standard since it is an approved method for the in-vivo assessment of coronary plaque characteristics and has been well validated against histopathology.[9] IVUS VH allows for the assessment of plaque vulnerability and is associated with outcome.[10] The correlation between CTA plaque characteristics and intravascular ultrasound virtual histology (IVUS VH) has previously been described.[11-13].

In this investigation automatic, quantitative assessed stenosis degree and plaque constitution on CTA were compared to IVUS VH. For this purpose, a dedicated 3-dimensional registration algorithm was used, allowing a slice-by-slice comparison of both modalities. In short, the aim of the present study was 1) to perform an automatic quantitative CTA analysis of stenosis degree and plaque constitution and 2) to validate this against IVUS VH.

Methods

Patient population

The patient population consisted of 57 patients who presented with chest pain at the outpatient clinic (Leiden, the Netherlands) and underwent CTA, followed by clinically referred invasive coronary angiography (ICA). In addition, IVUS VH was performed to further evaluate the severity and extent of coronary artery disease.

CTA images were acquired using either a 64-slice CT scanner (Aquilion 64, Toshiba Medical System, Otawara, Japan) or a 320-row volumetric scanner (Aquilion ONE, Toshiba Medical System, Otawara, Japan). Non-ionic contrast material (Iomeron 400, Bracco, Milan Italy or Ultravist 370, Bayer Schering Pharma AG Berlin, Germany) was administered with an amount of 80-110 ml followed by a saline flush with a flow rate of 5 ml/s. Contra-indications for CTA were: 1) renal insufficiency (glomerular filtration rate < 30 ml/min); 2) known allergy to iodine contrast material; and 3) pregnancy. Only scans with adequate image quality were included for the current analysis. The effective dose was calculated using a conversion factor of 0.014 mSv/(mGy x cm)

IVUS VH examinations were acquired during conventional ICA using a dedicated IVUS console (S5^{tm} Imaging system Volcano Corporation, rancho, Cordova, CA, USA) in combination with a 20MHz, 2,9 F phased-array IVUS Catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, CA, USA). Motorized pullback was performed at a constant speed of 0.5 mm/s until the IVUS catheter reached the guiding catheter. Exclusion criteria for IVUS VH were severe stenosis, (subtotal) vessel occlusion or vessel tortuosity.

Clinical data were prospectively entered into the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center) and retrospectively analyzed. In each patient, the presence of CAD risk factors was recorded.

The feasibility of quantitative CTA analysis software to assess stenosis severity has been reported previously.[14] For the current analysis, the most recent update of this program was used, which allows fully automatic, quantitative assessment of both stenosis severity and plaque constitution (QAngioCT Research Edition version 1.3.6, Medis Medical Imaging Systems, Leiden, the Netherlands). In all patients quantitative computed tomography (QCT) was performed to determine lumen and vessel wall borders. Subsequently, using a dedicated 3-dimensional registration algorithm, CTA images were registered with the corresponding IVUS VH run as shown in Figure 1. Thereafter, automatic lesion quantification was performed in both modalities to assess stenosis parameters and plaque constitution. Finally, the correlations for all parameters (Table 1) between the both modalities were assessed.

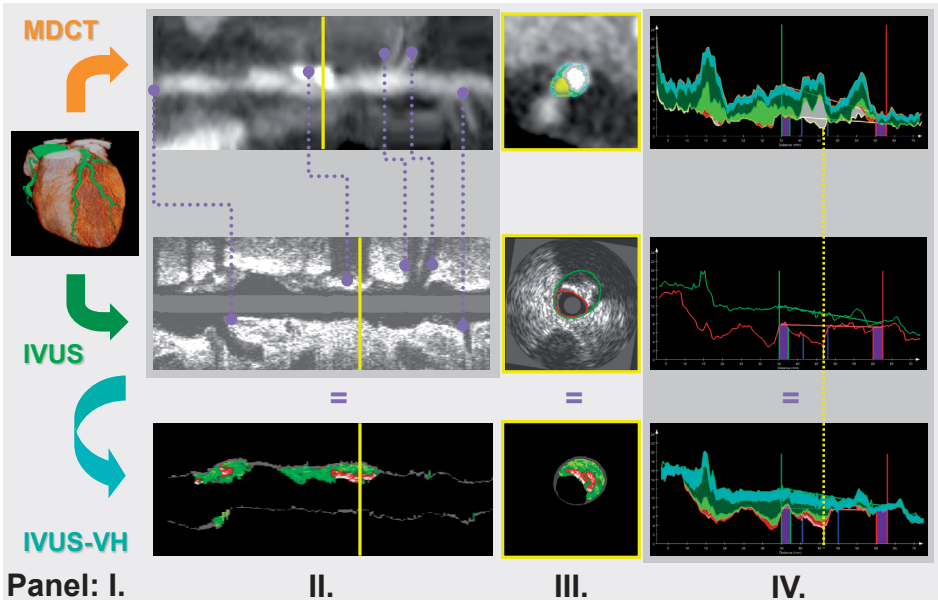

Figure 1. Schematic illustration of the characterization of coronary plaque on CTA: cross-correlation with IVUS VH.

First, the 3-dimensional centerline was generated from the CTA data set using an automatic tree extraction algorithm (Panel I). Using a unique registration a complete pullback series of IVUS images was mapped on the CTA volume using true anatomical markers (Panel II). Fully automatic lumen and vessel wall contour detection was performed for both imaging modalities (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), stenosis parameters, could be calculated for both imaging techniques. Additionally, plaque volumes and plaque types were derived for the whole coronary artery lesion, ranging from the proximal to distal lesion marker (blue markers). Fibrotic tissue was labeled in dark green, Fibro-fatty tissue in light green, dense calcium in white and necrotic core was labeled in red.

Quantitative CTA analysis

Lumen and vessel wall detection.

First, an automatic tree extraction algorithm was used to obtain all the 3-dimensional centerlines of the coronary tree.[15] Based on these centerlines, straightened multiplanar reformatted (MPR) volumes were created of those vessels of which an IVUS VH examination was available. Next, the lumen border contours and vessel wall borders were assessed according to the previously reported method.[14] This method uses spatial first- and second-derivative gradient filters in longitudinal cross sections in combination with knowledge of the expected CTA intensity values in the arteries. Thereafter lumen and vessel contour are detected in the individual transversal

Table 1. QCT derived parameters and their corresponding definitions.

QCT parameter	Definition
Lesion length (mm)	The distance between the proximal and distal ends of the coronary lesion
Lumen volume (mm^3)	Total volume of the lumen between the proximal and distal ends of the coronary lesion
Vessel wall volume(mm^3)	Total volume of the vessel wall between the proximal and distal ends of the coronary lesion
Plaque volume(mm^3)	Total volume of plaque wall between the proximal and distal ends of the coronary lesion. Defined as vessel wall volume – lumen volume
Minimal Lumen Area (MLA) (mm^2)	The minimal lumen area at the point of maximal obstruction.
Percentage lumen area stenosis at the level of the MLA (%)	1 - (MLA/corresponding reference lumen area) x 100%

cross-sections perpendicular to the centerlines, whereby the locations from the longitudinal analyses are taken into account. This method is insensitive to differences in attenuation values between data sets and independent of window and level settings.

Plaque constitution.

Two approaches for tissue (plaque) classification were implemented. The first used predefined fixed intensity cut-off values on the Hounsfield Units (HU) to assess plaque constitution. Currently, different cut-off values are available in the literature, which are obtained by comparing CTA with IVUS VH or histological examination.[6, 16] For the current analysis, the fixed HU cut-off values used for classifying were: -30 – 75, for necrotic core, 76 – 130 for fibro-fatty, 131 – 350 for fibrotic, and 351+ for dense calcium. These values were initially based on the paper by Brodoefel *et al.* and empirically optimized using three representative training sets. [16]

The second approach used an adaptive threshold based on the principle that plaque attenuation values are influenced by luminal contrast densities.[17, 18] Therefore, in this approach, the HU thresholds are adapted according to lumen attenuation values. This method is based on two principles.

The first principle is the decrease in lumen intensity from the proximal to the distal part of the coronary artery. The intensity cut-off values are adapted by the same linear, decreasing trend along the vessel.

The second principle is that the lumen intensities are lower in the parts of a severe stenosis and higher in the parts with severe calcified lesions due to blooming artifacts. Therefore, intensity cut-off values are locally compensated by subtracting a percentage of the difference to correct for the cut-off values in these locations. These dynamic thresholds were automatically derived and are user independent. The

inter- and intra observer variability for the lumen and vessel segmentation have been previously described.[19, 20] The assessment of plaque constitution was performed fully automatically.

Cross-correlation with IVUS VH

To validate the results of the QCT analysis, CTA images were compared to IVUS VH images of the corresponding artery. IVUS VH lumen and vessel wall contours were generated using QCU (QCU- CMS 4.59, Medis, Leiden, The Netherlands). A dedicated software tool was used to fuse the CTA and IVUS VH images as previously described.[14] First using anatomical landmarks (side-branches, ostia, calcified plaques) the IVUS VH images were mapped on the longitudinal CTA centerline. Secondly, the IVUS VH cross-sectional images were translated and rotated to fit onto the corresponding CTA cross-section. This 3-dimensional registration method allows correction of deviations in IVUS VH caused by inconstant motorized pullback speed and enables a slice-by slice comparison of the coronary artery.

In both modalities, CTA and IVUS VH, lesions are manually defined by placing reference locations at non-diseased, non-bifurcated proximal and distal parts of the segment of interest. A slope is automatically defined between these reference locations which represent an estimate of the normal proximal-to-distal tapering of the segment of interest. Consecutively, using the reference slope, the minimal lumen area (MLA) as well as the proximal and distal ends of a lesion were automatically assessed as shown in Figure 1. Subsequently, a number of parameters were derived from QCT and IVUS VH in each analyzed coronary lesion as described in Table 1.

In addition to coronary arteries with atherosclerotic lesions, a vessel-based analysis of non-diseased coronary arteries was performed in the mid part of the coronary artery. In these non-diseased vessels, lumen and plaque volumes were assessed in both modalities. Since no plaque was present in these vessels, no comparison of plaque characteristics was performed.

Statistical analysis

Continuous data are presented as mean ± SD if normally distributed or as median (interquartile range (IQR)) if non-normally distributed. Categorical data are presented as absolute numbers and percentages. A comparison was made between QCT and IVUS VH parameters on a lesion basis. Bland-Altman analyses were performed to assess the bias and the limits of agreement for the comparison between QCT and IVUS VH (GraphPad Prism software, version 5.01, GraphPad software Inc, San Diego, California, MA, USA). Bland-Altman analyses represent the difference of each pair plotted against the average value of each pair. Additionally, to correct for intra-patient correlation linear mixed models were used. The differences for each parameter be-

tween QCT and IVUS VH was calculated and entered as a dependent value. For this analysis, the 95% confidence intervals (95% CI) were calculated. Furthermore, the feasibility of QCT to assess luminal parameters in non-diseased segments was assessed in all plaque free segments.

Results

For this study, 61 patients with diagnostic quality of the CTA were selected. In 4 of these 61 patients (7%) image quality was still insufficient to perform tissue characterization. The remaining 57 patients were included in this study. These 57 patients underwent CTA using either a 320-row volumetric (n = 41) or a 64-row helical scanner (n = 16). Median time between CTA and IVUS VH was 2 (IQR 0 – 64) days. The effective dose of the CTA acquired on 320-row CTA was 6.5 ± 4.0 mSv, The mean radiation dose for 64-slice CT performed in our centre has been previously described (18.1 ± 5.9 mSv) [21] . Baseline characteristics are described in Table 2; the mean age was 57.8 ± 11.5 years and 68% of patients were male. In these 57 patients an IVUS VH run was available of 138 vessels; 29 of these vessels were unsuitable for further analysis because of the presence of a stent (n = 11) or insufficient quality of either the IVUS VH run (n = 6), the CTA extraction (n = 7) or other technical limitations (n = 5). For the final analysis, 109 vessels were used of which 69 revealed atherosclerosis, whereas 40 vessels did not. In these 69 diseased vessels, 108 lesions were identified. These 108 lesions were used for the lesion based comparison.

Coronary plaque volume

The results of the comparison of coronary plaque volumes (per lesion) are depicted in Figure 2. There was an excellent correlation between vessel volume on QCT and vessel volume on IVUS VH (r = 0.957, P <0.001). Based on linear mixed models, vessel volume was significantly overestimated on QCT as compared to IVUS VH, median vessel volume (242 mm^3 (IQR 152 – 371) vs. 238 mm^3 (IQR 141 – 331), respectively, 95% CI of the mean difference ranging from 5.3 to 24.8 mm^3, P = 0.003). Bland-Altman analysis demonstrated a bias of 15 mm^3 with 95% limits of agreement ranging from -84.9 to 115 mm^3. The correlation between lumen volume on QCT and IVUS was excellent (r = 0.917, P <0.001). QCT significantly underestimated the lumen volume: the median volume was 92 mm^3 (IQR 60 – 136) on QCT compared to 111 mm^3 (IQR 64 – 163) on IVUS VH (95 CI of the mean difference ranging from -28.3 to -14.6 mm^3, P <0.001). The bias of the Bland-Altman analysis of lumen volume was -21.5 mm^3 with 95% limits of agreement from -92.3 to 39.4 mm^3. Accordingly, the correlation between plaque volume measured with both modalities was similar

Table 2. Baseline characteristics of study population (n=57).

Men	39 (68)
Age (years)	57.8 ± 11.5
Calcium score	69 (0 – 287) (range 0 – 3247)
Known CAD	11 (19)
Risk Factors	
Diabetes	14 (25)
Hypertension †	38 (67)
Hypercholesterolemia ‡	27 (47)
Smoking	20 (35)
Obesity (BMI ≥ 30 kg/m^2)	14 (25)
Positive family history*	25 (44)
Medication	
Beta-blockade	29 (51)
ACE inhibitor / AT II blockade	30 (53)
Diuretics	19 (33)
Nitrate	11 (19)
Calcium antagonist	10 (18)

Data are represented as mean ± SD, median (interquartile range) or as number and percentages of patients.
†Defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or the use of antihypertensive medication. ‡Serum total cholesterol ≥230 mg/dL or serum triglycerides ≥200 mg/dL or treatment with lipid lowering drugs.
*Defined as the presence of coronary artery disease in first-degree family members at <55 years in men and <65 years in women.
Abbreviations: CAD, coronary artery disease; BMI, body mass index; ACE, angiotensin converting enzyme; AT II, angiotensin II

(r = 0.928, P <0.001). QCT overestimated plaque volume with a bias of 36.5 mm^3 (P <0.001) with limits of agreement of -48.8 to 121.9 mm^3.

Coronary stenosis parameters

Good correlations were observed for the assessment of minimal lumen area (MLA) and lumen area stenosis, r = 0.836 and r = 0.701, respectively. However MLA was underestimated on CTA, as demonstrated by a bias of -1.62 mm^2 with 95% limits of agreement ranging from -5.54 to 2.30 mm^2. Median MLA on QCT was 4.3 mm^2 (IQR 3.12 - 5.83) compared to 5.20 mm^2 (IQR 3.75 – 7.90) on IVUS VH (95% CI of mean difference ranging form -2 to -1.2 mm^2, P <0.001). In contrast, area stenosis was

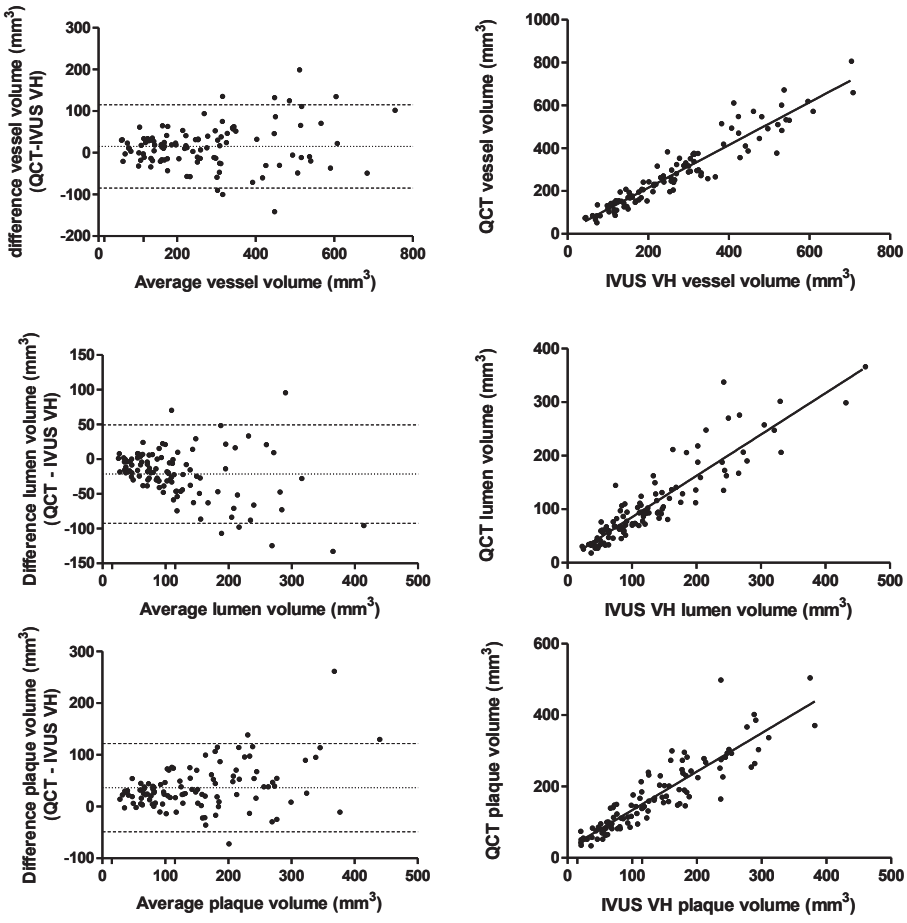

Figure 2. Bland-Altman analyses of vessel volume, lumen volume and plaque volume,.

significantly overestimated on QCT (median 42.8% (IQR 32.22 – 55.12)) compared to IVUS VH (median 40.06% (IQR 28.66 – 50.49) (95% CI of mean difference ranging from 0.7 to 5.6 %, P = 0.01). Bland-Altman analysis demonstrated a bias of 3.17 % with limits of agreement ranging from -21.61 to 27.96 %

Coronary plaque constitution

The results of both fixed and dynamic threshold CTA tissue classifier are demonstrated in Table 3. Bland-Altman analyses of the two different CTA tissue classifier methods are depicted in Figures 3 and 4 respectively.

Table 3. Results of QCT plaque constitution assessment : cross-correlation with IVUS VH (n=108).

	IVUS VH Median (IQR) (mm^3)	**QCT** Median (IQR) (mm^3)	**95 % CI of mean difference**	**P-value**	**Correlation coefficient**	**Bias** (mm^3)	**Lower 95% LOA** (mm^3)	**Upper 95% LOA** (mm^3)
Fixed threshold								
Fibrotic	39.7(19.9-67.3)	43.2 (23.1-76.1)	1.6 ; 13.8	0.013	0.695, <0.001	7.7	-54.8	70.2
Fibro-fatty	9.3(4.9–19.4)	25.9 (16.0-41.6)	13.3 ; 19.0	<0.001	0.714, <0.001	24.4	-41.8	90.7
Necrotic core	11.8(6.0–22.3)	22.8 (14.7-38.9)	10.4 ; 19.1	<0.001	0.523, <0.001	14.8	-29.7	59.2
Dense calcium	5.4(1.7–11.6)	7.6 (2.1-24.9)	6.6 ; 15.9	<0.001	0.736, <0.001	11.3	-36.4	59.0
Dynamic threshold								
Fibrotic	As above	55.7(36.1-94.9)	15.0 ; 25.9	<0.001	0.787, <0.001	20.4	-35.7	76.6
Fibro-fatty	"	28.3(16.2-45.9)	16.7 ; 23.6	<0.001	0.704, <0.001	20.2	-15.2	55.6
Necrotic core	"	11.0(5.6-24.7)	-1.6 ; 3.6	0.458	0.479, <0.001	1.0	-25.9	27.9
Dense calcium	"	6.95(0.9-18.9)	4,5 ; 12.5	<0.001	0.733, <0.001	8.5	-32.5	49.5

IVUS VH, Intravascular Ultrasound Virtual Histology, QCT, quantitative computed tomography, LOA, Limits of agreement, IQR interquartile range

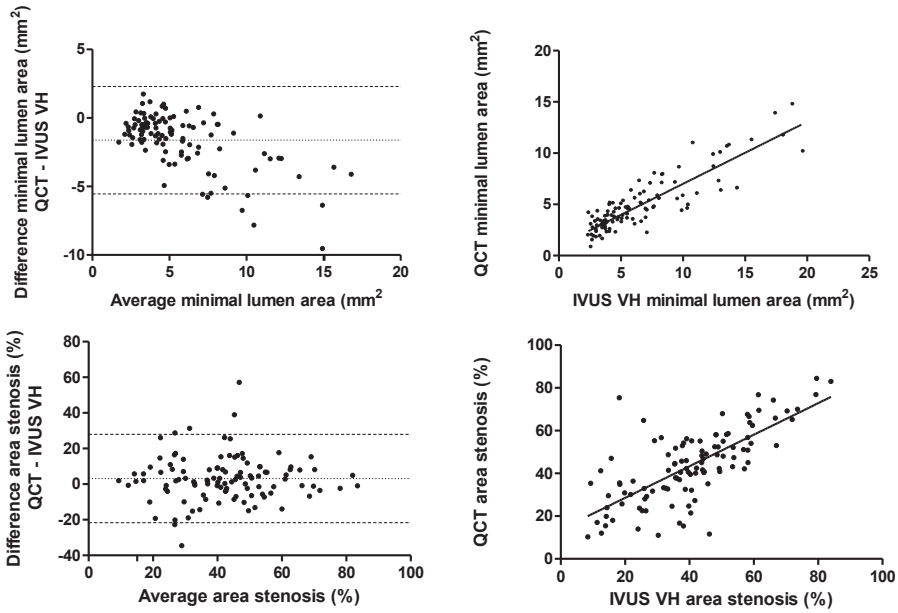

Figure 3. Bland-Altman analyses of minimal lumen area (MLA) and percentage area stenosis.

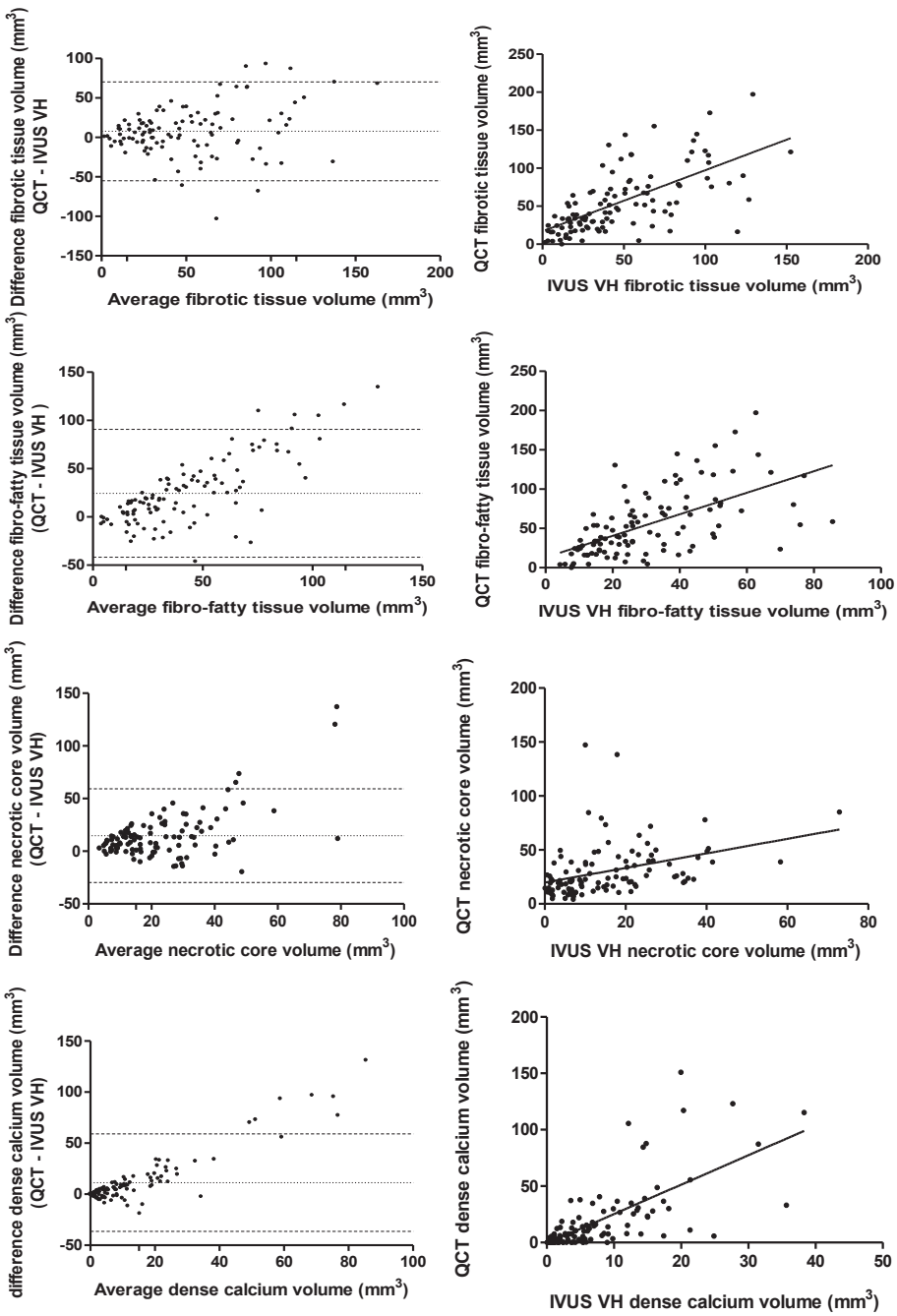

Figure 4. Bland-Altman analyses of plaque constitution as assessed using fixed thresholds.
Comparison between QCT and IVUS VH for fibrotic tissue, fibro-fatty tissue, necrotic core and dense calcium volumes.

Method 1: fixed thresholds.

On a lesion basis, good correlations were observed for volumes of fibrotic tissue ($r = 0.695$, $p < 0.001$), fibro-fatty tissue ($r = 0.714$, $p < 0.001$), necrotic core ($r = 0.523$, $p < 0.001$) and dense calcium ($r = 0.736$, $p < 0.001$). Bland-Altman analysis, as depicted in Figure 3 and described in Table 3, demonstrated a significant overestimation of the volumes of all four plaque types by QCT. For necrotic core, bias was 11.3 mm^3 with limits of agreement ranging from -29.7 to 59.2 mm^3. The smallest bias was observed for fibrotic tissue (7.7 mm^3) with limits of agreement ranging from -54.8 to 70.2. mm^3.

Method 2: dynamic thresholds.

The results of the dynamic CTA tissue classifier are described in Table 3. The volumes of dense calcium, fibrotic and fibro-fatty volumes were all significantly overestimated by QCT ($P < 0.001$.) No significant differences were observed in necrotic core volumes between both modalities ($P = 0.481$). In Figure 5, the Bland-Altman analysis of the dynamic tissue classifier is depicted. The narrowest limits of agreement were observed for necrotic core volume ranging from -25.9 to 27.9 mm^3 with a bias of 1.0 mm^3. However, the correlation coefficient for necrotic core ($r = 0.479$, $P < 0.001$) was smaller compared to the other three plaque types. In Figure 6 an example is demonstrated of CTA plaque constitution assessment of a coronary lesion using the two different methods.

Non-diseased coronary arteries

In non-diseased coronary arteries ($n = 40$), vessel, lumen and plaque volume on QCT were significantly correlated with IVUS VH ($r = 0.947$, $r = 0.920$ and $r = 0.738$, respectively ($p < 0.001$). However median vessel volume was significantly overestimated on QCT as compared to IVUS VH (410 mm^3 (IQR 250 - 616) versus 408 mm^3 (IQR 236 – 550)) (95% CI of the mean difference ranging from 25.5 to 85.5 mm^3, $p = 0.001$)). Lumen volumes were significantly smaller on QCT as compared to IVUS VH (median 190 mm^3 (IQR 92 – 303) versus median 283 mm^3 (IQR 147 - 422) (95% CI of the mean difference ranging from -90.3 to -40.5 mm^3, $p < 0.001$)). Accordingly, plaque volume on QCT was significantly higher (median 236 mm^3 (IQR 157 – 324)) as compared to IVUS VH (median 112 mm^3 (IQR 66 – 153)).

Discussion

The present study has demonstrated the feasibility of a fully automatic, quantitative analysis of CTA images for the assessment of coronary artery stenosis severity and

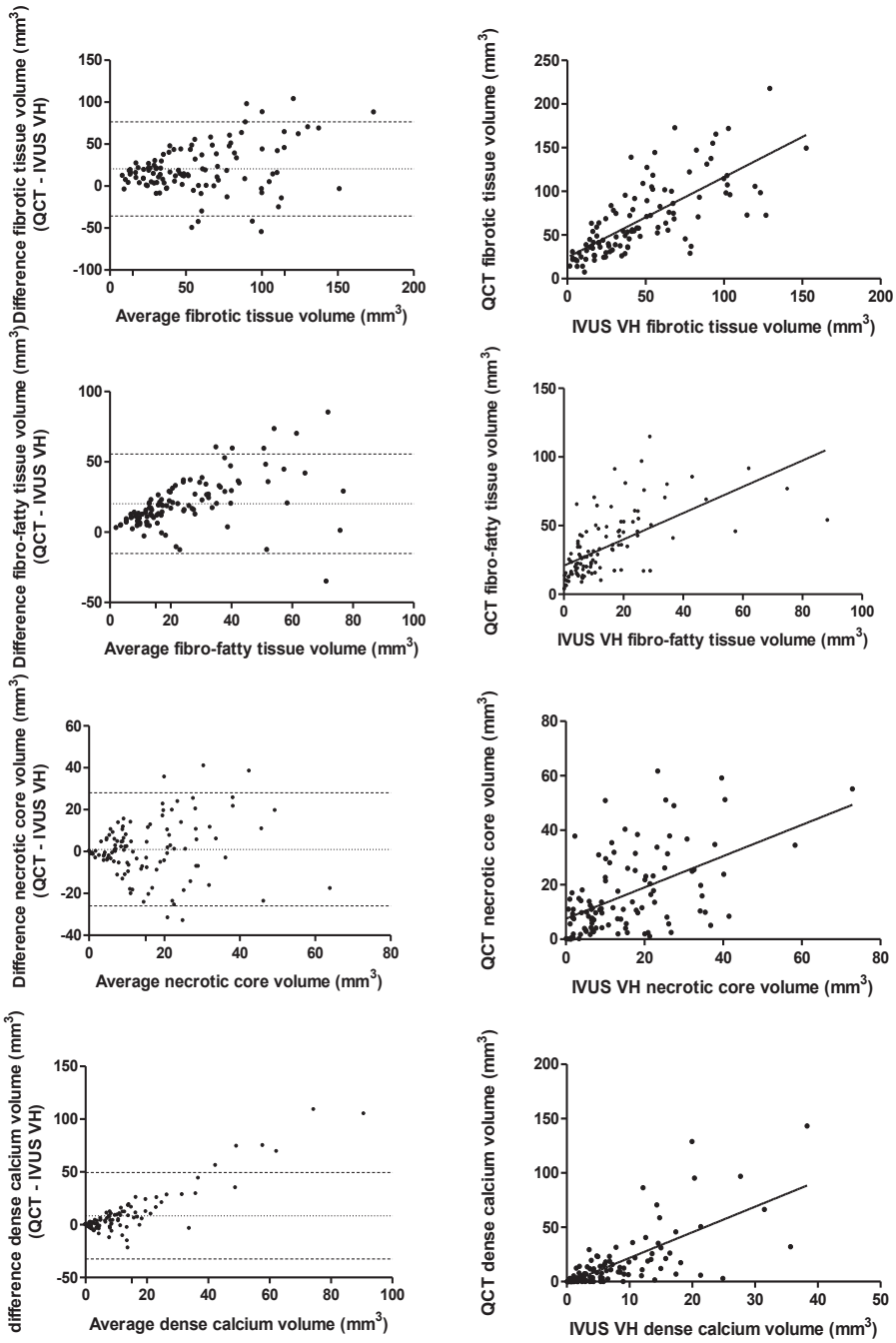

Figure 5. Bland-Altman analyses of plaque constitution as assessed using dynamic thresholds.
Comparison between QCT and IVUS VH for fibrotic tissue, fibro-fatty tissue, necrotic core and dense calcium volumes.

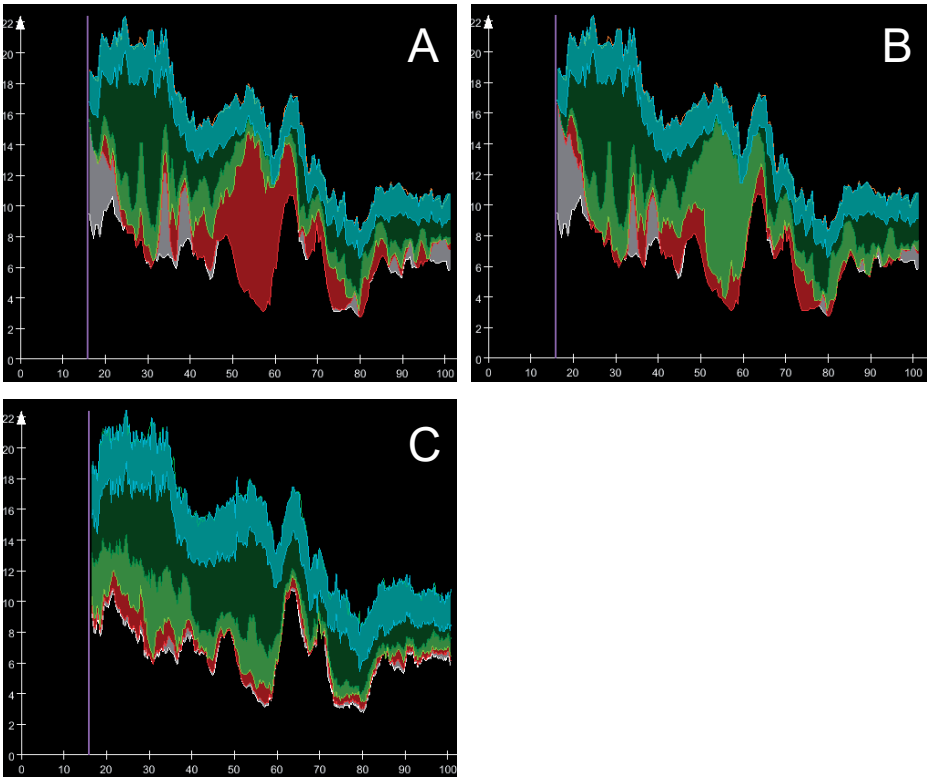

Figure 6. An example of a coronary lesion, plaque constitution is assessed using two methods of tissue characterization.

The x-axis represents the distance from the coronary ostium in mm. The y-axis represents the area of either the lumen (lower part of graph) or the vessel wall (upper part of graph) in mm2. The part between the two graphs shows the plaque constitution using a color code with fibrotic tissue labeled in dark green, fibro-fatty tissue in light green, dense calcium in white and necrotic core labeled in red. Plaque constitution is assessed using either method 1 (Panel A) or method 2 (Panel B). In Panel C the corresponding IVUS VH data is shown. The use of method 2 correlated better with IVUS VH compared to method 1.

plaque constitution. Using a dedicated 3-dimensional registration algorithm a slice-by-slice comparison was made between QCT and IVUS VH. Very good correlations were observed for lumen, vessel and plaque volume between QCT and IVUS VH. Still, lumen volume was slightly underestimated and vessel volume slightly overestimated on QCT. The assessment of MLA and lumen area stenosis using QCT correlated well with IVUS VH(r = 0.836 and r = 0.701, respectively).

In addition, the performance of two different approaches for tissue characterization was evaluated. The differentiation of coronary plaque volume in fibrous, fibro-fatty, necrotic core and dense calcium on QCT correlated well with IVUS VH. The dynamic

threshold approach performed better compared to the fixed threshold approach, as demonstrated by more narrow limits of agreement on the Bland-Altman analyses.

Coronary stenosis assessment

CTA is a suitable method for the non-invasive evaluation of coronary atherosclerosis. Beyond the assessment of luminal narrowing it allows for the visualization of coronary plaque. The prognostic value of CTA has been extensively reported and CTA is commonly used in clinical practice to rule out atherosclerosis in patients with low-to-intermediate pre-test likelihood of CAD.[22] Currently, CTA datasets are mainly visually analyzed to assess luminal narrowing. This visual approach requires an experienced observer, is subjected to interobserver variability and has lesser reproducibility. In the literature a quantitative analysis of CTA datasets on luminal narrowing and plaque constitution has been proposed as an objective and accurate method for analyzing CTA images. Several previous studies have reported different quantitative assessments of CTA images [7, 8, 12, 23]. These studies have shown wide variety in results, mainly caused by differences in CTA contour detection algorithms. In the present study, good correlations were observed for the assessment of plaque volume (r = 0928), lumen volume (r = 0.917) and vessel volume (r = 0.957). Vessel volume was slightly overestimated, whereas lumen volume was underestimated resulting in overestimation of plaque volume. In line with the present findings, Bruining *et al.*[24] have demonstrated an overestimation of coronary plaque volume. In 48 patients, the investigators compared a quantitative CTA analysis with limited manual interference to IVUS. In contrast to the present investigation, the authors report an underestimation of coronary vessel wall volume. This discrepancy is potentially caused by differences in the vessel wall detection algorithm. In the future, the assessment of coronary plaque volume on CTA could be applied as a non-invasive method for the investigation of plaque regression or progression in patients or to assess the effect of medical therapy. In addition to coronary volume parameters, the ability of QCT to assess stenosis severity was investigated. Despite an overestimation on QCT for lumen area stenosis, good correlations were observed compared to IVUS VH. The method applied in the present study is best comparable to the ATLANTA study. [12] In this prospective study 50 patients were enrolled. In 50 lesions, a quantitative analysis of CTA datasets was performed and compared with IVUS VH. Similar to the present findings an overestimation of MLA and an overestimation of plaque volume was observed.

Coronary plaque constitution

Beyond establishing luminal narrowing, CTA allows for the assessment of coronary plaque constitution. Previous studies have indicated the correlation between CTA plaque characteristics and plaque vulnerability.[6] Also, the prognostic value of CTA

plaque constitution has been reported.[25] Potentially, an accurate, quantitative assessment of coronary plaque constitution could provide more detail on the relation between plaque vulnerability and plaque constitution on CTA. However, at present an automatic, quantitative assessment of plaque constitution is unavailable. Previous studies have assessed mean HU of coronary plaques on CTA in different plaque types as assessed with IVUS (e.g. hypo or hyperechogenic).[26] In contrast, the present study has used predefined HU thresholds to compare the four different plaque volumes with both modalities. In previous investigations the feasibility of manual or semi-automatic quantitative CTA plaque constitution analyses has been assessed using IVUS VH as a reference. [7, 12] However, data is lacking evaluating a direct a slice-by-slice comparison between automatically, quantitatively assessed plaque constitution and IVUS VH.

Two different methods were applied for the quantitative analysis of plaque constitution.

Method 1: fixed thresholds.

The first method used fixed, predefined HU thresholds to differentiate coronary plaque volume in four different plaque types. This method has been applied in previous investigations.[7, 12] In the present study, significant correlations were observed for all four plaque components. Still, an overestimation of plaque volume was noted for all different components on QCT. However, corresponding bias on Bland-Altman analysis were small for all components. These results are in line with previous reports. Indeed, using an automated vessel segmentation algorithm in 50 patients, Voros *et al.*[12] demonstrated small difference, but wide limits of agreement for the assessment of plaque constitution on CTA compared to IVUS VH. In contrast, in a study by Brodoefel *et al.*[7] in 14 patients, a comparison was made between plaque constitution on CTA and IVUS VH. The authors reported a good correlation for overall plaque volume; however, no significant correlation could be demonstrated for different plaque types.

Method 2: dynamic thresholds.

Recently, Dalager[17] *et al.* have demonstrated that differences in luminal intensities have an effect on the attenuation values inside the plaque. A decrease in luminal intensity was associated with lower coronary plaque HU. Besides, Choi at al.[27] have shown that coronary stenosis severity has an effect on luminal intensities. A significant decrease in luminal HU was observed at the location of a severe obstruction. It can therefore be expected that at the location of a severe stenosis different thresholds apply for the assessment of plaque constitution. These two previously described mechanisms formed the basis of the second approach on tissue characterization. A dynamic threshold algorithm was applied which automatically adapt HU thresholds

based on the luminal intensity values at the level of the plaque. This was previously proposed in a review by Akram *et al.* [18] suggesting that it is quite important for the implementation of plaque segmentation algorithms to take local attenuation values into consideration. For this reason a dynamic tissue characterization algorithm was implemented. As demonstrated, the performance of the dynamic threshold approach was superior to a fixed threshold approach. For all four plaque types, limits of agreement of Bland-Altman analyses were smaller for the dynamic threshold approach. This indicated that there is indeed an effect of luminal intensities on coronary plaque HU. An accurate characterization of coronary plaque requires a method which accounts for these differences. Possibly, more sophisticated algorithms to account for local difference in plaque attenuation values could be established. This would require further studies into local differences in attenuation values.

Recently, the influence of 100kV scanning on plaque constitution assessment became a topic of interest. In the present study none of the patients were scanned using 100kV In a recent publication by Horiguchi *et al.* [28] using in vitro models the authors demonstrated equal performance of 100 kV in 120 Kv in soft plaque densitometry. In contrast, the intracoronary CT values were approximately 50 HU higher in 100 kV scans compared to 120kV scans. Potentially, applying the dynamic threshold algorithm used in the present study could correct for these intracoronary density differences and would allow for more accurate tissue characterization.

Clinical implications

At present the clinical value of quantitative CTA plaque constitution assessment has yet to be established. Although a reasonable correlation was observed for the assessment of coronary plaque constitution between QCT and IVUS VH, there still is a large variability in different plaque volumes between both modalities. It is unlikely that full agreement of coronary plaque constitution between QCT and IVUS VH will be achieved. To appreciate the prognostic value of quantitatively assessed plaque constitution on CTA, future studies are needed.

Limitations

Although the present study demonstrated that automatic quantification of coronary plaque is feasible, some limitations need to be considered. For the present study only scans with sufficient quality were included. Therefore, the value of QCT in scans with severe noise or motion artifacts is unknown. The present analysis was a single-center, single-vendor study. An analysis of CTA datasets acquired by different CT-scanners could provide additional valuable insight. IVUS VH was used as the gold standard. However, two limitations of this technique need to be considered. First, the radial resolution of IVUS VH is limited to 100μm, allowing less accurate assessment of

coronary plaque. Secondly, coronary calcium creates an acoustic shadow on IVUS VH caused by the inability of the echo signal to penetrate calcium. Although, plaque located behind calcifications is labeled on IVUS VH, the accuracy of characterizing tissue surrounding dense calcium is unknown. Potentially this leads to an underestimation of calcium volume on IVUS VH. In addition, a direct comparison between QCT plaque characterization and histopathology could provide further insights into the pathophysiology of CTA plaque constitution.

Conclusions

The present study has demonstrated the feasibility of automatic, quantitative analysis of CTA images. QCT demonstrated excellent correlations for the assessment of plaque volume and stenosis parameters as compared to IVUS VH. Furthermore, plaque constitution was well-correlated between both modalities. In a direct comparison between a fixed threshold approach and a dynamic threshold approach for the quantification of plaque type volume, the dynamic threshold performed better as shown by better correlations with IVUS VH.

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