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Optimal boundary detection method and window settings for coronary atherosclerotic plaque volume analysis in coronary computed tomography angiography: comparison with intravascular ultrasound

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Abstract

Objective To evaluate optimal methodology for quantitative plaque volume analysis by coronary CT angiography (QCT).
Methods Fifty-one coronary artery segments were evaluated and contour measurements based on two different methods [(1) no gap, or (2) fixed 0.3-mm gap between inner and outer boundary] were compared with intravascular ultrasound (IVUS). In addition, three different window width (WW) and level (WL) settings [fixed (740/220) Hounsfield unit (HU), adjusted (155 % and 65 % of mean luminal intensity of the segment, and aorta adjusted (155 % and 65 % of mean luminal intensity of central aorta)] were used for semiautomated plaque volume analysis.

Results For boundary detection, the no gap method led to underestimation compared with IVUS (105.4±82.3 vs. 136.1±72.8 mm^3, $p<0.001$), while fixed 0.3-mm gap showed no difference between IVUS and QCT (136.1±72.8 vs. 139.8 ±93.9 mm^3, $p=0.50$). Comparison of the three different window settings demonstrated that the aorta adjusted setting underestimated (120.5±74.3 vs. 136.1±72.8 mm^3, $p=$ 0.003), while fixed setting showed the least mean difference compared with IVUS (3.8±39.8 mm^3, $p=0.50$).
Conclusion For plaque volumetric assessment, optimal results were obtained with fixed 0.3-mm gap with fixed HU setting (740/220).
Key Points
• *Quantitative plaque volume analysis by coronary CT angiography has recently emerged.*
• *Different boundary detection methods and window width and level settings were evaluated.*
• *Fixed 0.3-mm gap with fixed HU setting (740/220) afforded optimal results.*

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Abbreviations

AUC	receiver operating area under the curve
CACS	coronary artery calcium score
CAD	coronary artery disease
CCTA	coronary computed tomography angiography
CI	confidence interval
HU	Hounsfield unit
IVUS	intravascular ultrasound
QCT	quantitative computed tomography

WL window level
WW window width

Introduction

Dynamic quantitative or qualitative changes of coronary atherosclerotic plaque have previously been demonstrated by numerous invasive studies [1–3] and have been shown to be closely related to overall prognosis [1]. Quantitative computed tomography (QCT) coronary atherosclerotic plaque analysis software has recently been introduced to provide feasible and accurate three-dimensional plaque assessment such as plaque volume, burden and characterization in a semi- or fully automated manner [4, 5]. Recently, atherosclerotic plaque volume or aggregated plaque volume percentage, a similar concept to aggregated three-dimensional plaque burden, demonstrated a strong correlation with lesion-specific ischaemia (fractional flow reserve, FFR) and demonstrated incremental performance improvement when it was combined with conventional two-dimensional cross-sectional parameters such as minimal luminal diameter (MLD) or minimal luminal area (MLA) [6]. Furthermore, when these features were combined with certain adverse plaque characteristics identified by CT such as positive remodelling (PR), low attenuated plaque (LAP) and spotty calcification (SC), further incremental discriminatory performance was demonstrated [7].

This innovative plaque analysis tool has been applied in a variety of settings including serial quantitative or qualitative follow-up assessment of coronary atherosclerotic plaque [8–10]. However, despite its utilization in variety of clinical settings, optimal and standardized methods for defining outer line plaque boundary and optimal window settings for semiautomated plaque assessment have not been well established. Therefore, we assessed different boundary detection methods and window settings in order to identify optimal semiautomated plaque analysis conditions, using intravascular ultrasound (IVUS) as the reference standard.

Materials and methods

Patient population and data acquisition

We retrospectively analysed 51 coronary segments, including 50 culprit lesions, from 50 consecutive patients with high pretest likelihood of coronary artery disease, who had undergone within a 60-day period both coronary computed tomography angiography (CCTA) and invasive coronary angiography (ICA) with iLAb intravascular ultrasound (IVUS-iLAb) from December 2010 to December 2012. Among 50 patients 62 % were male, mean age was 61.5±12.0 years (age range 42–75 years), 58 % had type 2 diabetes mellitus, 78 % had

hypertension, 80 % had dyslipidaemia and 66 % were current smokers, and we excluded patients with prior coronary artery bypass graft surgery, prior percutaneous coronary intervention, elevated serum creatinine level (≥1.5 mg/dL), allergy to iodinated contrast medium, pregnant state or haemodynamic instability.

CCTA images were acquired using a 64-slice multidetector-row computed tomography scanner (Somatom Sensation 64, Siemens Medical Solutions, Forchheim, Germany) utilizing prospective or retrospective electrocardiographic gating. Patients with heart rates of 65 beats per minute or greater received metoprolol 50 mg orally. In addition, 0.3 mg of nitroglycerin was given sublingually to all patients prior to scanning unless contraindicated [11]. Then, 70 mL of contrast medium (iopamidol 370 mg/mL, Iopamiro 370, Bracco, Milan, Italy) at a flow rate of 5 mL/s followed by 50 mL of saline at a flow rate of 5 mL/s were administered into an antecubital vein via an 18-gauge catheter; the bolus tracking method was used by placing the region of interest (ROI) in the ascending aorta and image acquisition was started 5 s after reaching the predefined threshold of 140 Hounsfield units (HU). The scan parameters were as follows: 64×0.6 mm section collimation, 330 ms rotation time, 100 kVp or 120 kVp tube voltage (depending on body habitus), and 350–600 mAs tube current (depending on body habitus), and the images were reconstructed using a slice thickness of 0.75 mm, an increment interval of 0.5 mm and a medium-smooth convolution kernel of B36f. The estimated radiation dose for CTs ranged between 3 and 11 mSv. IVUS data were acquired by a commercially available IVUS system (iLab, Boston Scientific Scimed, Maple Grove, Minnesota). A motorized transducer pullback method was used throughout the length of the segment of interest after intracoronary administration of 200 μg of nitroglycerin, which permitted cross-sectional area (CSA) measurements at 0.5 mm/s and 30 frames per second.

IVUS and CCTA data analysis and co-registration

The IVUS images of lesion-containing target segments were independently analysed by an experienced IVUS reader in a blinded fashion using offline software (QCU-CMS v4.69, LKEB, Leiden University, the Netherlands; this is the research version of QIvus, Medis Medical Imaging Systems BV, Leiden, the Netherlands). CCTA images were analysed using QAngio CT Research Edition (v2.1.9.1, Medis Medical Imaging Systems BV, Leiden, the Netherlands) in a semiautomated manner; (1) starting with an automatic centreline extraction, (2) on the basis of these centrelines, straightened multi-planar reformatted (MPR) volumes were reconstructed for the segmentation and quantification, (3) longitudinal inner lumen and outer vessel wall contours were detected by automatic algorithm, (4) manual editing of both

inner lumen and outer vessel wall delineations by transversal and longitudinal manner were performed.

The difference between lumen and vessel volume, which were respectively calculated by measuring the contour of the inner and outer boundary of the coronary artery, was defined as plaque volume. Subsequently, we measured plaque volume by CCTA utilizing different boundary detection methods (no gap vs. fixed 0.3-mm gap) and window settings (fixed vs. adjusted vs. aorta adjusted) to find the optimal setting for semiautomated plaque volume analysis. Each of these methods was then compared with IVUS-derived plaque volumes as the reference standard.

Initially, we compared the no gap method versus fixed 0.3-mm gap method utilizing the widely used fixed window setting 740/220 HU. The no gap method, which has been used most frequently in prior published studies for plaque analysis utilizing CCTA [6, 12] (Fig. 1), assumes that there is no gap between vessel wall and lumen. However, on the basis of histopathology studies, it is known that a space exists between the intima and media, which is where atherosclerotic changes occur [13, 14]. On the basis of these histopathology studies, we performed another analysis allowing a 0.3-mm gap between vessel wall and lumen in accordance with previous reports [15–17] (Fig. 1), which would then avoid the innate underestimation of plaque volume using CCTA.

Second, we assessed the three most widely used window width and level HU settings for CCTA in clinical practice, since semiautomated quantitative analysis is greatly dependent on them. These setting included fixed HU with window width (WW) and level (WL) of 740/220 [12], adjusted HU with 155 % and 65 % of mean luminal intensity of the disease-free proximal reference level for WW/WL [6, 18] and aorta adjusted HU with 155 % and 65 % of mean luminal intensity of the aortic root level for WW/WL [19].

The CCTA images were subsequently co-registered and compared with IVUS images as follows. During the IVUS analyses, the slices corresponding to bifurcation proximal and distal to each lesion were recorded. Next, using the extracted MPR stack from the CCTA data, the slice location of the corresponding bifurcations were also recorded. Next, using the slice numbers from IVUS and CCTA, the correspondence between lesion lengths was determined and length differences between the two modalities were corrected. Plaque volume defined as vessel volume minus lumen volume was evaluated (Fig. 1) [4, 5].

We also evaluated the overestimation effect of the calcium blooming artefact using the calcium score from the analysed lesion-containing segment. The difference of plaque volume between IVUS and CT was assessed, especially in mixed plaques.

Inter-observer variability between two expert readers was analysed in a blinded fashion for all segments using the four different combinations of boundary detection methods and window settings respectively. In addition, intra-observer variability for all segments was analysed regarding four different methods in a blinded fashion by one expert reader more than 30 days apart.

Statistical analysis

Mean±standard deviation when normally distributed or median [interquartile range (IQR)] if non-normally distributed were used for continuous variables. Absolute numbers or percentages were used for categorical variables. The paired t test and Pearson correlation coefficient using two-sided p values were used for comparing between IVUS and QCT, and Fisher's Z transformation statistic was used for comparing two correlations. A p value of less than 0.05 was considered statistically significant. Bland–Altman plots with 95 % confidence intervals for correlation were calculated. The area under the receiver operating characteristic curve (AUC) models was employed to evaluate the discrimination of more than 50 % difference between IVUS and CT plaque volume with segment coronary artery calcium (CAC) score. Inter- or intra-observer variability was assessed by intraclass correlation coefficients (ICC) for absolute agreement of single measures between consistent raters. All statistical analysis was performed using commercially available statistics software (MedCalc, version 12.7.5, MedCalc software Inc., Mariakerke, Belgium).

Results

All 51 lesion-containing segments were assessed with CCTA and IVUS (Table 1). The lesion-containing segments evaluated were primarily located in the left anterior descending (n= 45, 88.2 %), followed by right coronary artery (n=4, 7.8 %), left circumflex artery (n=1, 2 %) and the first diagonal branch (n=1, 2 %). The plaque composition profile of the lesions assessed were as follows: non-calcified plaques, 15 (29 %); calcified plaques, 6 (12 %); most of the lesions were composed of mixed plaque 30 (59 %) and 20 (39.2 %) plaques were located in the proximal segments of coronary arteries. The mean reference plaque volume derived from IVUS was 136.1±72.8 mm³ and the mean segment length was 24.2± 7.2 mm.

Boundary gap setting

For boundary detection, the no gap/fixed window method led to significant underestimation compared with IVUS (105.4± 82.3 vs. 136.1±72.8 mm³, $p<0.001$), while the 0.3-mm gap/ fixed window showed no significant difference between IVUS and QCT (136.1±72.8 vs. 139.8±93.9 mm³, $p=0.50$) (Table 1; Figs. 2 and 3). Correlation between IVUS and QCT was slightly higher in the 0.3-mm gap/fixed window compared

Fig. 1 Sample representative images
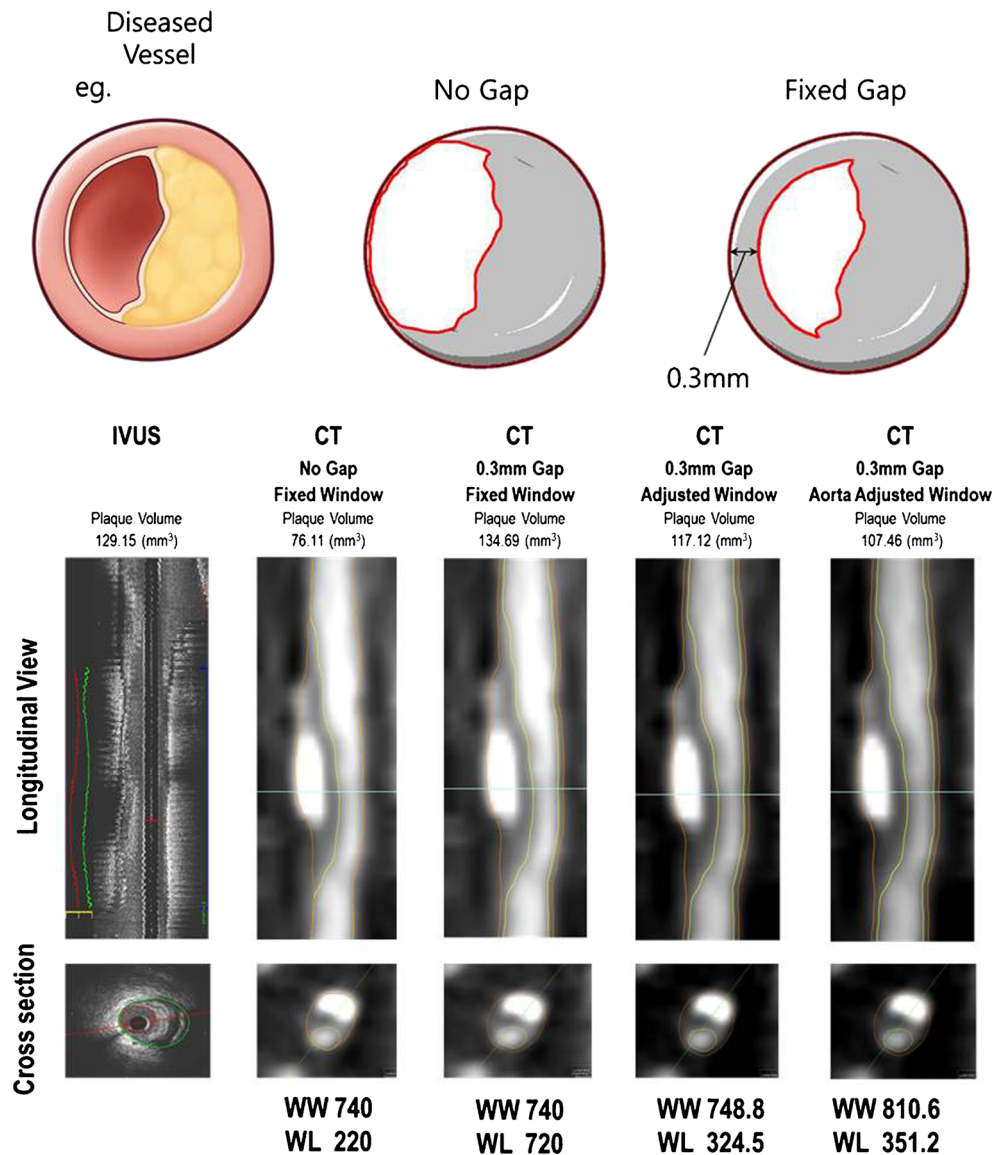
with no gap/fixed window, although these differences were not statistically significant (0.91 vs. 0.86, p=0.15) (Table 1, Fig. 2). When compared with IVUS, the 0.3-mm gap/fixed window QCT measurements showed a smaller mean bias of −1.4 % with 95 % limits of agreement ranging from −61.8 to 59.1 %, while the no gap/fixed window QCT measurements showed a higher mean bias of 26.5 % with 95 % limits of agreement extending from −31.1 to 84.3 mm³ (Fig. 3).

Table 1 Quantitative plaque assessment using each setting of CCTA as well as its differences and correlation with IVUS-derived plaque volume

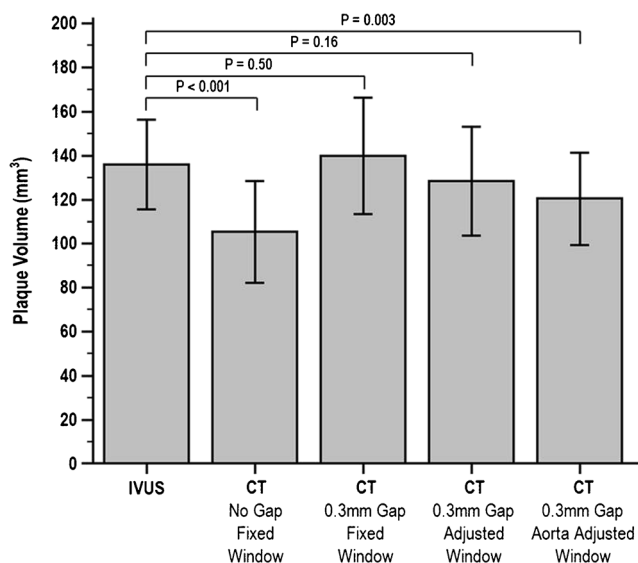| Boundary detection/ window setting	Plaque volume (mm³)	Mean difference (mm³)	P	Correlation coefficient r (95 % CI)	P
IVUS	136.1±72.8	–	–	–	–
CT					
No gap/fixed	105.4±82.3	−30.6±41.7	<0.001	0.86 (0.77–0.92)	<0.001
0.3-mm gap/fixed	139.8±93.9	3.8±39.8	0.50	0.92 (0.86–0.95)	<0.001
0.3-mm gap/adjusted	128.4±88.1	−7.6±38.6	0.16	0.90 (0.83–0.94)	<0.001
0.3-mm gap/aorta adjusted	120.5±74.3	−15.6±34.9	0.003	0.89 (0.81– 0.93)	<0.001

Mean±SD was used

Fig. 2 Comparison of mean plaque volume between no gap and fixed 0.3-mm gap lumen contouring methods under three different window settings (fixed, adjusted and aorta adjusted). *CT* computed tomography, *IVUS* intravascular ultrasound

Window setting

When comparing the three different window settings, the 0.3-mm gap/aorta adjusted window setting led to significant underestimation compared with IVUS (120.5 ± 74.3 vs. 136.1 ± 72.8 mm^3, $p=0.003$). The 0.3-mm gap/fixed window showed the least mean difference compared with IVUS with slight overestimation (mean difference 3.8 ± 39.8 mm^3, $p=0.50$), while the 0.3-mm gap/adjusted window led to slight underestimation (mean difference -7.6 ± 38.6 mm^3, $p=0.16$), although both these differences were not statistically significant when compared with IVUS (Table 1). The Bland–Altman analysis demonstrated that the 0.3-mm gap/fixed window (-1.4 %) setting had the least mean bias as compared to the 0.3-mm gap/adjusted window (6.2 %) or the 0.3-mm gap/aorta adjusted window (10.6 %) settings (Fig. 3).

CAC score and plaque volume analysis in mixed plaque

Among the 30 mixed plaques analysed, a linear correlation ($r=0.75$; 95 % CI 0.54–0.88; $p<0.001$) was found between CAC (Agatston) score in the lesion-containing segment and the difference in plaque volume between IVUS and CT when utilizing the 0.3-mm gap/fixed window setting (Fig. 4). The receiver operating area under the curve (AUC) was 0.84 (95 % CI 0.66–0.95, $p<0.001$) for detection of more than 50 % plaque volume difference between IVUS and CT, with the cut-off value of CAC (Agatston) score being 78 (Fig. 4).

Inter and intra-observer variability

Both inter- and intra-observer variability was excellent as shown in Table 2.

Discussion

In this study, we aimed to evaluate the optimal setting of CCTA for plaque assessment. The fixed 0.3-mm gap method appeared to more accurately assess plaque volume than the no gap method when compared to the IVUS-derived measurements. Among the three different window settings, the aorta adjusted window setting significantly underestimated the plaque volume when compared to the fixed or adjusted setting; and the fixed window setting showed the least mean bias using the fixed 0.3-mm gap method. Furthermore, we found that the CAC score showed a linear association with incremental error in plaque volume measurement and that a CAC score of 78 or higher would result in more than 50 % difference in plaque volume measurement between QCT and IVUS.

Prior studies have noted that CCTA underestimates plaque volume as compared with IVUS [20, 21], especially in non-calcified [18, 21] and mixed plaque [18]. However, we found that if the intima and media thickness is taken into consideration using the fixed 0.3-mm gap method, there are significantly less plaque volume measurements as compared to the conventional no gap method; hence a more sensitive and accurate assessment of atherosclerotic plaque burden might be achieved with this method.

Multiple window width and level settings have previously been used for plaque assessment including fixed settings, such as 500/150 [22], 500/200 [23, 24], 700/200 [20, 25, 26], 740/220 [12] and 800/250 [27], and adjusted window settings including 155 % and 65 % of the mean luminal intensity or using the mean HU of the central aorta [19]; these variable window settings thus affect plaque quantification and characterization. A prior study by Achenbach et al. [20] assessed plaque volume in 83 segments using a fixed window setting of 700/200 HU and demonstrated underestimation of the plaque volume. Another study demonstrated similar findings while assessing non-calcified and mixed plaque using the window setting of 155 % (WW) and 65 % (WL) of the mean intensity of the lesion [18]. However, they demonstrated significant overestimation of plaque volume when assessing calcified plaques [18]. Another study by Moselewski et al. [22] using the fixed window setting of 500/150 HU showed different results; in their study the overall plaque volume was overestimated with moderate correlation with IVUS measurements ($r=0.55$, $p<0.001$), with the correlation being slightly better after excluding lesions with severe calcification ($r=0.60$, $p=0.09$). Marwan et al. [28] analysed the influence of various window settings on vessel wall and lumen area

Fig. 3 Comparison of window settings on plaque volume quantification with IVUS: 0.3-mm gap method with **a** fixed window setting (740/220), **b** adjusted window setting, **c** aorta adjusted window setting. *IVUS* intravascular ultrasound, *PV* plaque volume, *SD* standard deviation
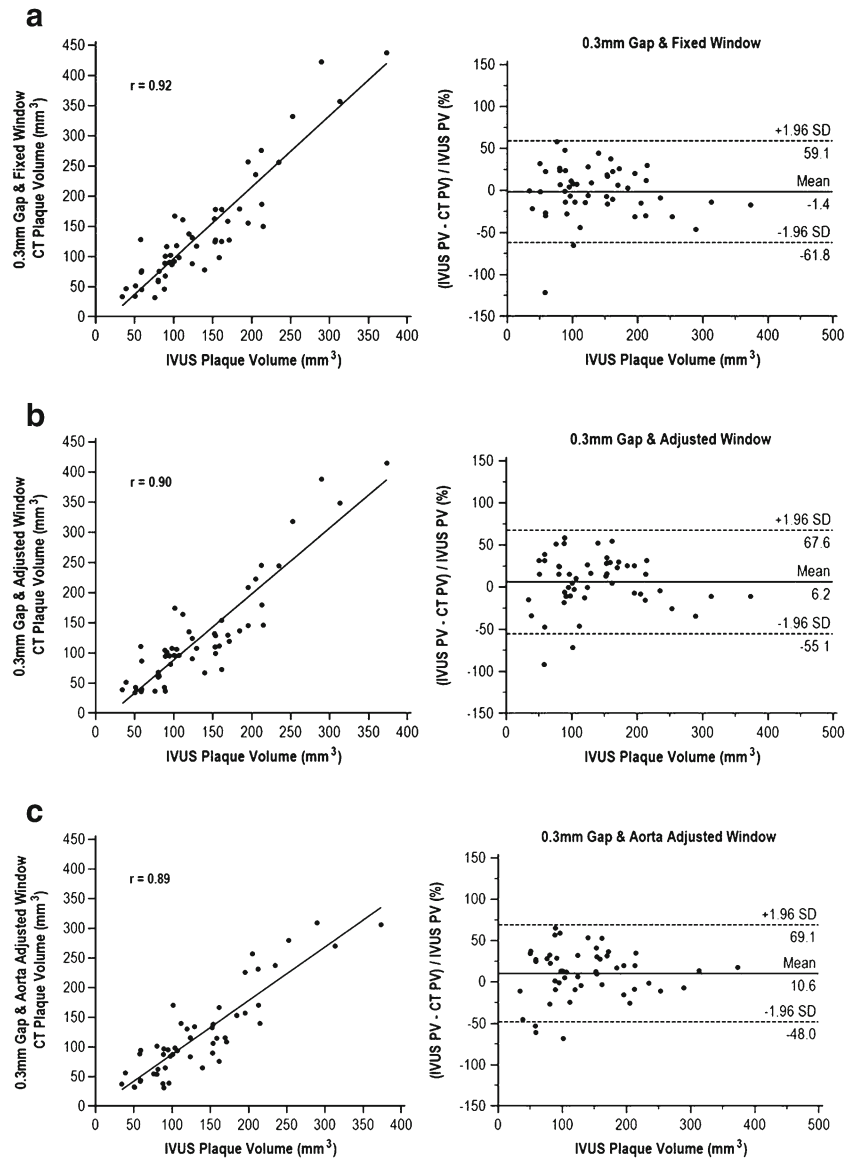
compared to IVUS and noted that all the window settings overestimated the vessel area, although the overall correlation was good. However, they noted that the 155 % (WW) and 65 % (WL) of mean luminal intensity showed the least

overestimation. As for lumen area, all settings showed close correlation but slight underestimation when compared to IVUS-derived measurements, with the least underestimation seen when using the fixed setting of 700/200 HU, which is

Fig. 4 Correlation between CAC score and plaque volume difference measured by CT and IVUS. Fixed 0.3-mm gap and fixed 740/220 window setting was used
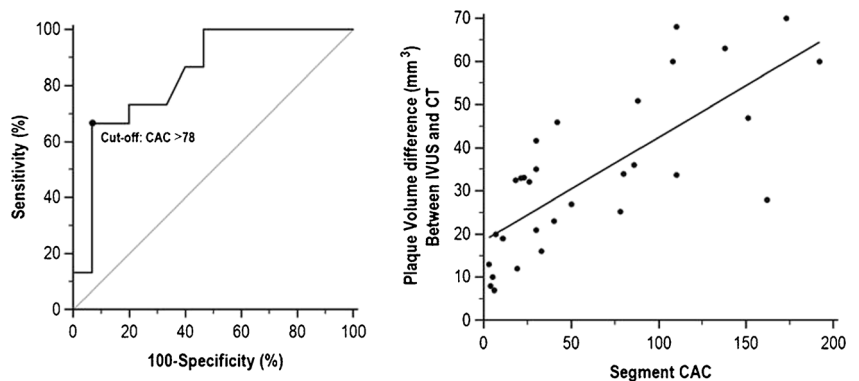
Table 2 Inter- and intra-observer variability of four different methods

	No gap/fixed window ICC (95 % CI)	P	0.3-mm gap/fixed window ICC (95 % CI)	P	0.3-mm gap/adjusted window ICC (95 % CI)	P	0.3-mm gap/aorta adjusted window ICC (95 % CI)	P
Inter-observer variability	0.95 (0.91–0.97)	<0.001	0.94 (0.90–0.97)	<0.001	0.94 (0.89–0.96)	<0.001	0.94 (0.91–0.96)	<0.001
Intra-observer variability	0.97 (0.93–0.99)	<0.001	0.97 (0.95–0.98)	<0.001	0.95 (0.92–0.97)	<0.001	0.97 (0.96–0.99)	<0.001

ICC intraclass correlation, *CI* confidence interval

similar to our results. However, unlike our study most lesions in their study were non-calcified plaques and the proper window setting according to plaque composition was not considered. To our knowledge, our study is the first to evaluate the combination of the intima and media thickness (no gap vs. fixed 0.3-mm gap) and various window settings.

In this study, we evaluated the effect of the calcified portion of the plaque on the overall plaque volume assessment, and we demonstrated a linear increase in plaque volume difference as compared with reference standard IVUS, as the overall calcium increased. Furthermore, we also proposed a CAC (Agatston) score 78 as a cut-off value for more than 50 % plaque volume difference between CT and IVUS. In the near future, we expect that the problems associated with calcium blooming artefact during plaque analysis will become less problematic, as the spatial and temporal resolution of CT scanners continue to improve, as well as the advent of new technology such as dual energy CT. These advances combined with techniques which further reduce the radiation dose during acquisition of cardiac CT [29] would allow QCT to be applied more frequently clinically. However, it should be noted that these advances would not only result in QCT being more universally used in clinical practice for CAD screening and prevention but also in the research field for the evaluation of certain drugs and their treatment response by directly measuring dynamic atherosclerotic plaque changes in a non-invasive, quantitative, timely and cost-effective manner [30]. Recent studies indicated its future possibilities, showing that statin use was strongly associated with a mortality benefit even in patients with non-obstructive CAD by CCTA [31], and another study proved that statin treatment slowed down the progression of coronary atherosclerosis by using CT plaque volume quantification [32].

Our study had limitations. We evaluated the lesion-containing segment based on difficulties with co-registration with IVUS. Therefore, the results may be variable depending on disease severity of each segment and may not be able to be extrapolated to per lesion analysis. However, IVUS is currently the gold standard method for plaque volume assessment; therefore, per segment analysis using IVUS as the reference standard would be the

best possible option at the current time. Also, there are known limitations of CCTA plaque analysis such as the influence of calcium density (CAC score) on the overestimation of plaque volume, the attenuation of contrast-enhanced lumen, which contributes to the increasing overlap between mean density values [24, 33, 34], and lower spatial resolution compared to IVUS. However, despite these inherent limitations, we were able to identify optimal and standardized quantitative plaque analysis methods by comparing various pre-existing boundary detection and window settings, using currently validated software for automatic or semiautomatic measurements of plaque density and volume [5]. Lastly, all CCTA images were acquired with the limited contrast injection protocol and convolution kernel setting which may affect plaque imaging analysis [35, 36], and therefore our results may not be generalized to other scan settings. However, we have tried to use the most widely adopted scan protocol in clinical practice.

In conclusion, the fixed 0.3-mm gap method, which takes both media and intima into consideration, showed better agreement compared to the reference standard than the no gap method. In regards to the different window settings, all three settings showed good correlation with the reference method; however, the fixed window setting (740/220) demonstrated the smallest mean bias among the three. We therefore recommend the fixed 0.3-mm gap boundary detection method with fixed 740/220 window setting as the optimal methodology for semiautomated plaque volume assessment.

Compliance with ethical standards

Disclosure All authors disclose no conflict of interest.

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