

Automated Three-dimensional Quantification of Noncalcified Coronary Plaque from Coronary CT Angiography: Comparison with Intravascular US¹

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Purpose:

To determine the accuracy of a previously developed automated algorithm (AUTOPLAQ [APQ]) for rapid volumetric quantification of noncalcified and calcified plaque from coronary computed tomographic (CT) angiography in comparison with intravascular ultrasonography (US).

Materials and Methods:

This study was approved by the institutional review board and was HIPAA compliant; all patients provided written informed consent. APQ combines derived scan-specific attenuation threshold levels for lumen, plaque, and knowledge-based segmentation of coronary arteries for quantification of plaque components. APQ was validated with retrospective analysis of 22 coronary atherosclerotic plaques in 20 patients imaged with coronary CT angiography and intravascular US within 2 days of each other. Coronary CT angiographic data were acquired by using dual-source CT. For each patient, well-defined plaques without calcifications were selected, and plaque volume was measured with APQ and manual tracing at CT and with intravascular US. Measurements were compared with paired *t* test, correlation, and Bland-Altman analysis.

Results:

There was excellent correlation between noncalcified plaque volumes quantified with APQ and intravascular US ($r = 0.94$, $P < .001$), with no significant differences ($P = .08$). Mean plaque volume with intravascular US was $105.9 \text{ mm}^3 \pm 83.5$ (standard deviation) and with APQ was $116.6 \text{ mm}^3 \pm 80.1$. Mean plaque volume with manual tracing from CT was $100.8 \text{ mm}^3 \pm 81.7$ and with APQ was $116.6 \text{ mm}^3 \pm 80.1$, with excellent correlation ($r = 0.92$, $P < .001$) and no significant differences ($P = .23$).

Conclusion:

Automated scan-specific threshold level-based quantification of plaque components from coronary CT angiography allows rapid, accurate measurement of noncalcified plaque volumes, compared with intravascular US, and requires a fraction of the time needed for manual analysis.

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Direct noninvasive quantification of coronary atherosclerotic plaque morphology and burden may be important for improving cardiovascular risk stratification and for monitoring the course of coronary artery disease. The total amount of coronary artery calcium, measured with nonenhanced computed tomography (CT), is well established as a strong predictor of cardiovascular events (1–3). Although calcified plaque quantification with nonenhanced CT is standardized (4,5), to our knowledge, no validated approach for noninvasive quantification of noncalcified plaque is currently available (6). Coronary CT angiography performed by using multidetector CT scanners has become an increasingly effective clinical tool for noninvasive assessment of the coronary arteries (7–9), with substantial potential for noninvasive plaque component characterization (10–14). The current standard for coronary CT angiography plaque quantification requires manual tracing of contours, separating epicardial fat from the vessel wall and enclosing noncalcified and calcified plaque components, which is time-consuming and may be prone to intraobserver variability (15,16). We recently developed automated computer software, AUTOPLAQ (APQ), at the Cedars-Sinai Medical Center, Los Angeles, Calif (D.D., P.J.S., D.S.B.), for three-dimensional plaque segmentation and quantification of noncalcified and calcified plaque and showed its excellent agreement with manual plaque quantification performed by experts in an initial feasibility study (17). The purpose of this study was to determine the accuracy of APQ for quantification of

noncalcified plaque in comparison with quantification with intravascular ultrasonography (US).

Materials and Methods

Patients and Plaque Selection

Our study was a retrospective analysis of patients from a research protocol that enrolled 70 consecutive patients, who were suspected of having coronary artery disease or progression of known coronary artery disease and were scheduled to undergo invasive coronary angiography, including intravascular US, at the University of Erlangen (Erlangen, Germany) between October 2007 and July 2009 (18). Exclusion criteria were contraindications to iodinated contrast agents, renal insufficiency (serum creatinine level, >1.5 mg/dL [133 μmol/L]), clinical instability, absence of a sinus rhythm, and inability to perform a 10-second breath hold. These are our standard exclusion criteria for coronary CT angiography, and none of the 70 patients needed to be excluded. Coronary CT angiographic acquisition was performed with dual-source CT within 2 days (48 hours) before the invasive coronary angiographic procedure. An experienced, independent study coordinator (S.A.), who was not involved in the later comparative analysis, evaluated dual-source CT data sets with good or excellent image quality and the corresponding intravascular US data side by side to identify focal, noncalcified plaques in the proximal or middle section of a major coronary artery, with clearly defined proximal and distal boundaries at both CT and intravascular US. Noncalcified plaques were identified at CT as structures greater than 1 mm² within and/or adjacent to the vessel lumen and

surrounding epicardial tissue, with no visually identified calcifications, as previously described (10). Twenty subjects with 22 focal noncalcified plaque lesions, identified with both intravascular US and CT, in the proximal to middle segments of the coronary arteries and with a clearly defined proximal and distal border were thus retrospectively chosen for analysis. The patient demographics are given in Table 1. The mean age was 55 years ± 12 (standard deviation) for men and 58 years ± 10 for women; this difference in age did not reach significance ($P = .17$, Student *t* test). The distribution of noncalcified plaque lesions in the coronary tree was as follows: left main coronary artery ($n = 6$), proximal left anterior descending artery ($n = 9$), middle left anterior descending artery ($n = 4$), proximal right coronary artery ($n = 2$), and proximal left circumflex coronary artery ($n = 1$). Following patient and plaque selection, noncalcified plaque quantification was performed with intravascular US and coronary CT angiography independently by experienced readers (M.M., with 4 years of CT experience and 2 years of intravascular US experience; T.S., with 4 years of CT experience), who were blinded to coronary CT angiographic and intravascular US results, respectively, as described below. This study was approved by the institutional review boards (University of Erlangen and Cedars-Sinai Medical Center), all patients provided written informed consent, and the study was Health Insurance Portability and Accountability Act compliant.

Advances in Knowledge

- Automated scan-specific threshold level-based quantification of plaque components from coronary CT angiography allows rapid, accurate measurement of noncalcified plaque, compared with US.
- The automated method requires a fraction of the time needed for equivalent manual analysis.

Implication for Patient Care

- Following further validation, the automated tool in this study could potentially be applied routinely to provide rapid noninvasive quantitative assessment of coronary plaques with coronary CT angiography.

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Author contributions:

Guarantors of integrity of entire study, D.D., M.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, D.D., P.J.S.; clinical studies, T.S., P.J.S., S.A.; statistical analysis, D.D., S.A.; and manuscript editing, D.D., T.S., M.M., P.J.S., D.S.B., S.A.

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Table 1

Patient Characteristics	
Characteristic	Data
No. of patients	20
Sex	
No. of women	5
No. of men	15
Age (y)*	56 ± 11
Body mass index (kg/m ²)*	27 ± 4
Current smoker [†]	4/20 (20)
Hypertension [†]	12/20 (60)
Diabetes mellitus [†]	4/20 (20)
Hypercholesterolemia [†]	13/20 (65)
2 or more risk factors [†]	12/20 (60)
No. of patients with symptoms [‡]	18 (90)

* Data are the means ± standard deviations.
[†] Data are the numbers of patients, and numbers in parentheses are percentages.
[‡] Symptoms included chest pain and/or shortness of breath. Datum is the number of patients, and number in parentheses is the percentage.

Intravascular US

Intravascular US was performed by one author (S.A., with 8 years of intravascular US experience) as part of the diagnostic procedure for the evaluation of one coronary artery without angiographic evidence of greater than 50% stenosis after the administration of 100–200 µg of nitroglycerin. A 40-MHz 2.5-F, 135-cm intravascular US catheter (Atlantis SR Pro; Boston Scientific, Boston, Mass), with motorized automatic pullback at 0.5 mm/sec, was inserted into the most distal position of the selected vessel that could be safely reached, and the catheter location was documented with cine angiography. Intravascular US data with a running audio commentary describing the location of the ongoing intravascular US interrogation were stored on a CD-ROM for off-line analysis.

Plaque Volume Measurement with Intravascular US

Intravascular US images were analyzed by an experienced independent, blinded observer (M.M.), according to established and validated standards (19). According to the American College of Cardiology recommendations, atherosclerotic plaques were defined as structures located between the media and the intima with a thickness of at least 0.5 mm

(19). Starting from the last frame toward the start frame of the target plaque, cross sections spaced 0.5 mm apart were selected for analysis. Because the intravascular US frame rate was 30 frames/sec and the pullback was 0.5 mm/sec, every 30th intravascular US image yielded cross sections that were 0.5 mm apart. For each cross-sectional image, the external elastic membrane (defined by the interface at the border between the media and the adventitia [19]) and the lumen-intima interface were manually traced as illustrated in Figure 1a. Atheroma (intima plus media) area for each cross section was calculated by subtracting the luminal area from the external elastic membrane cross-sectional area, as suggested by the American College of Cardiology recommendations (19). Plaque volume per lesion was calculated from atheroma cross-sectional areas, according to the Simpson rule (18).

Coronary CT Angiography Imaging Protocol

All patients were imaged by using a dual-source CT scanner (Somatom Definition; Siemens Healthcare, Forchheim, Germany). Oral beta-blockers (atenolol, 50–100 mg) were administered in patients with a heart rate greater than 60 beats per minute at 1 hour before the scan (18). If the heart rate remained greater than 65 beats per minute at the time of the scan, up to four doses of 5 mg of metoprolol each were given intravenously. An intravenous bolus (60–90 mL) of contrast agent (iomeprol), with 350 mg of iodine per milliliter, was injected at a flow rate of 6 mL/sec to determine the contrast agent transit time (18). Image acquisition was initiated at 2 seconds after the contrast agent transit time, with 0.6-mm collimation, z-flying focal spot, gantry rotation time of 330 msec, reference tube current of 400 mAs per rotation, and tube voltage of 120 kVp. All scans were obtained by using electrocardiographically gated tube-current modulation. Maximal tube current was limited to an interval of 30%–80% of the cardiac cycle for patients with heart rates greater than 60 beats per minute and 60%–80% of the cardiac cycle for patients with heart rates of 60 beats per

minute or less. Transaxial images were reconstructed with 0.75-mm section thickness, 0.4-mm increment, and a medium-soft convolution kernel (B26f). The position of the reconstruction window in the cardiac cycle was individually selected to minimize artifacts. Motion-free data sets, typically in mid diastole, were collected for analysis. Beta-blockers to reduce the heart rate were given in 90% of patients, resulting in a mean heart rate during CT scanning of 57 beats per minute ± 6 (range, 45–70 beats per minute).

Plaque Volume Measurement with Coronary CT Angiography

Manual method.—Each identified focal noncalcified plaque lesion was quantified manually by an independent experienced reader (T.S.), who was blinded to the intravascular US results, as previously reported (16,18). To ensure that identical plaques that were evaluated with intravascular US were assessed, easily identifiable anatomic landmarks (eg, side branches and bifurcations) were selected to define the proximal and distal fiducial points. To allow for exact separation between blood vessel, surrounding tissue, plaque, and lumen, window level and window width were initially displayed at a predefined CT window-level setting (window width, 700 HU; window level, 200 HU); adjustments of the window-level settings were performed at the discretion of the observer as deemed necessary for best visualization (18), as is commonly done in clinical practice. After the identification of the lesion on axial images, serial multiplanar reformatted images (1.0-mm section thickness, 0.5-mm interval) orthogonal to the longitudinal axis of the coronary artery were rendered to obtain cross-sectional images of the respective vessel segment at a workstation (Multimodality Workplace; Siemens Healthcare) (Fig 1b). Plaque areas were then manually traced in each cross-sectional segment, and the total noncalcified plaque volumes were calculated by multiplying the corresponding total plaque areas by the increment (16,18).

Automated method.—Each plaque lesion was analyzed by using APQ

Figure 1

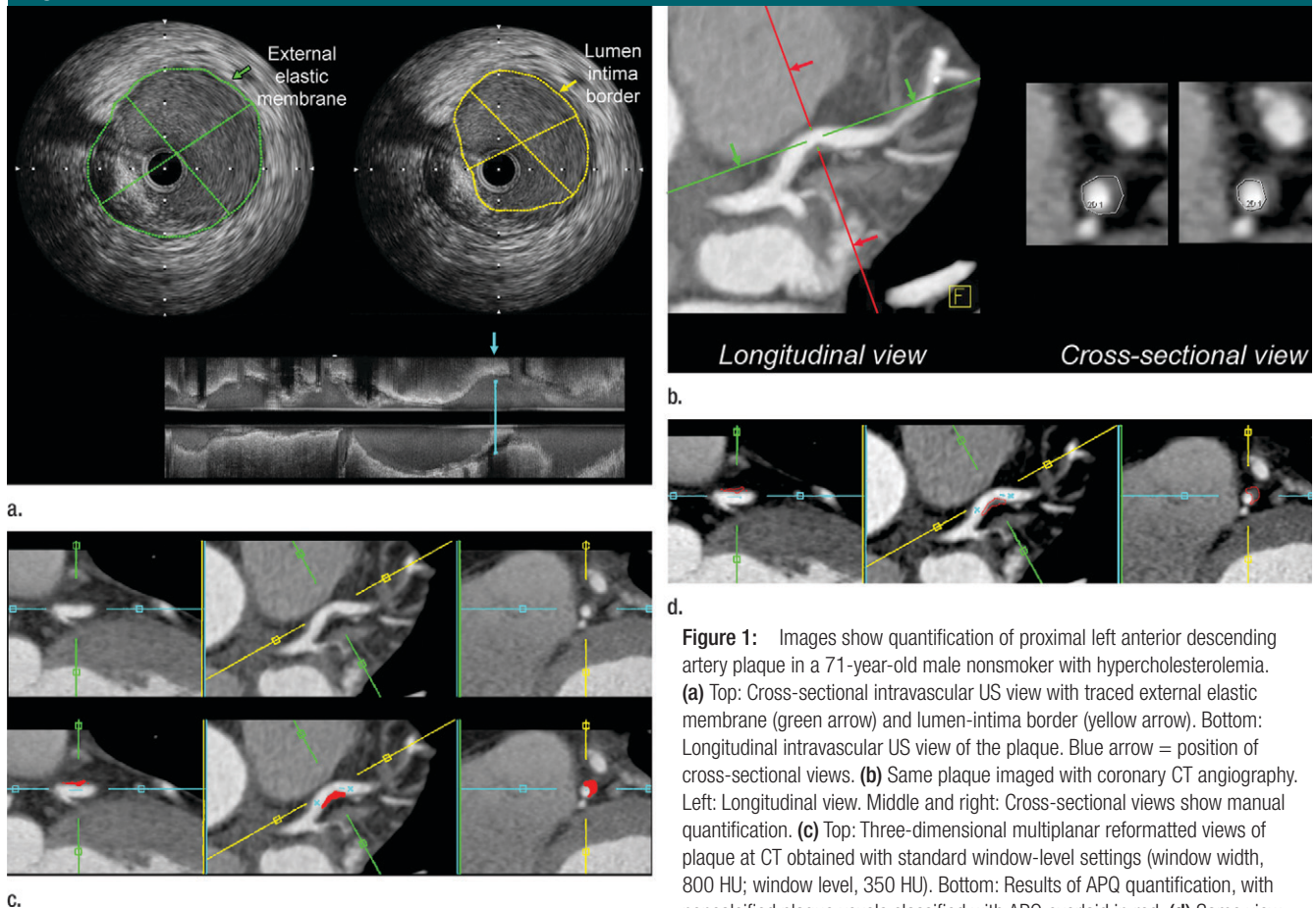


Figure 1: Images show quantification of proximal left anterior descending artery plaque in a 71-year-old male nonsmoker with hypercholesterolemia. **(a)** Top: Cross-sectional intravascular US view with traced external elastic membrane (green arrow) and lumen-intima border (yellow arrow). Bottom: Longitudinal intravascular US view of the plaque. Blue arrow = position of cross-sectional views. **(b)** Same plaque imaged with coronary CT angiography. Left: Longitudinal view. Middle and right: Cross-sectional views show manual quantification. **(c)** Top: Three-dimensional multiplanar reformatted views of plaque at CT obtained with standard window-level settings (window width, 800 HU; window level, 350 HU). Bottom: Results of APQ quantification, with noncalcified plaque voxels classified with APQ overlaid in red. **(d)** Same view of plaque as in **c** obtained with automated scan-specific window-level setting (window width of 155% and window level of 65% of normal contrast enhancement, as previously recommended [11]).

running on a standard 2.5-GHz computer running software (Windows; Microsoft, Redmond, Wash) by an independent observer (T.S.), who was blinded to the intravascular US data. To quantify each lesion, the identical coronary CT angiographic data set that was quantified manually was exported to the workstation in Digital Imaging and Communications in Medicine format. Within the APQ environment, the independent observer generated a view similar to the longitudinal axis of the coronary artery used for manual quantification, by using multiplanar reformatting, and marked the proximal and distal limits of the plaque to be analyzed, by using the fiducial markers as mentioned above. The same observer placed a circular region of interest in the aorta, defining the “normal blood pool,” and placed five to seven control points in the arterial lumen

to define the luminal centerline, as previously described (17). After these interactive steps, subsequent plaque quantification was fully automated. The APQ algorithm computed the total noncalcified plaque volumes within the automatically segmented boundaries of the vessel. The results of plaque quantification were displayed as colored overlays on the three-dimensional coronary CT angiographic data for visual assessment. Further details about the automated method are included in Appendix E1 (online).

Statistical Analysis

The results of plaque quantification were analyzed with software (Analyse-it, version 2.12; Analyse-it Software, Leeds, England; www.analyse-it.com). All con-

tinuous variables were expressed as the mean \pm standard deviation. To compare agreement between quantification methods, the Pearson correlation coefficient was calculated and Bland-Altman plots were created. The paired *t* test was used to compare differences between intravascular US and CT plaque quantification methods. A difference with $P < .05$ was considered significant.

Results

Processing times ranged from 15 to 35 minutes for intravascular US plaque quantification. Processing times ranged from 5 to 15 minutes for CT manual plaque quantification; the number of cross-sectional segments that needed

to be traced ranged from 8 to 28 per plaque. Following identification of the start and end of the atherosclerotic lesion, the time for automated plaque segmentation and quantification was less than 20 seconds.

Figure 1 shows an example of a noncalcified plaque imaged with intravascular US and coronary CT angiography. In our patient cohort, mean noncalcified plaque volume quantified with intravascular US was $105.9 \text{ mm}^3 \pm 83.5$ and mean noncalcified plaque volume quantified with APQ was $116.6 \text{ mm}^3 \pm 80.1$, and the difference was not significant ($P = .08$). In addition, mean noncalcified plaque volume quantified with CT assessed by the expert reader and with APQ were not significantly different ($100.8 \text{ mm}^3 \pm 81.7$ versus $116.6 \text{ mm}^3 \pm 80.1$, $P = .12$). Compared with intravascular US, the mean absolute difference in noncalcified plaque volume was $21.2 \text{ mm}^3 \pm 20.0$ for APQ and $30.5 \text{ mm}^3 \pm 30.8$ for manual quantification from CT, and the difference was not significant ($P = .23$).

Figure 2 shows the correlation and Bland-Altman comparison of APQ and intravascular US results. There was excellent correlation between APQ and intravascular US plaque volumes ($R = 0.94$, $P < .001$), and the relationship could be described by the linear function $y = 1.03x$. For the Bland-Altman comparison, the 95% limits of agreement ranged from -42.9 to 64.4 mm^3 , with a positive bias of 10.8 mm^3 . With APQ, scan-specific threshold levels are automatically derived for epicardial fat, noncalcified plaque, normal lumen, and calcified plaque from the coronary CT angiographic scan. Table 2 shows the APQ attenuation threshold levels in Hounsfield units that were computed for the following: epicardial fat, the upper level for noncalcified plaque, the normal lumen at the midplaque level, and the lower level for calcified plaque in the patients in our study.

Figure 3 shows the correlation and Bland-Altman comparison of plaque volumes quantified with APQ and manual tracing. There was excellent correlation between manually quantified plaque volumes and those quantified with APQ ($R = 0.92$, $P < .001$), and the relationship could be described by the linear function

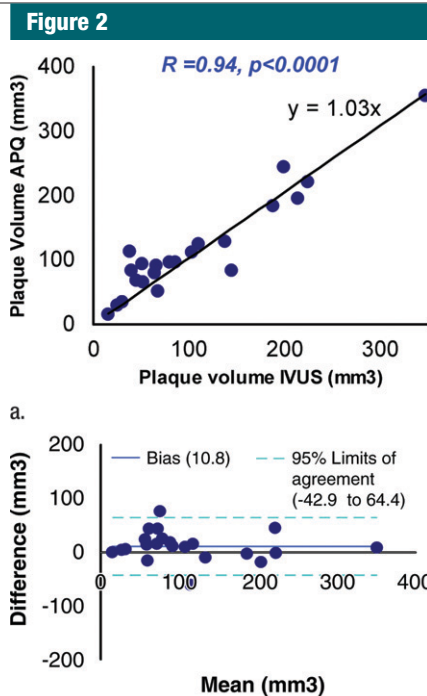


Figure 2: Comparison of APQ quantification of noncalcified plaque volume with intravascular US quantification. (a) Correlation. (b) Bland-Altman plot. Solid line = best-fit line.

$y = 1.06x$. From Bland-Altman comparison, the 95% limits of agreement ranged from -45.9 to 77.6 mm^3 , with a positive bias of 15.8 mm^3 . In Figure 3b, the difference from the mean appears to increase in a roughly linear pattern for plaque volumes of less than 100 mm^3 . This is likely caused by curved configuration of some of these larger plaques, resulting in expected larger volumes quantified with APQ compared with those obtained with manual quantification (17), as well as some overestimation with APQ owing to location of these larger plaques at the left main bifurcation.

In addition, mean noncalcified plaque volumes obtained with intravascular US and with manual quantification with CT did not differ significantly ($100.8 \text{ mm}^3 \pm 81.7$ versus $105.9 \text{ mm}^3 \pm 83.5$, $P = .54$) and showed strong correlation ($r = 0.91$, $P < .001$). The results of Bland-Altman analysis of noncalcified plaque volumes quantified with intravascular US and noncalcified plaque volumes manually quantified with CT showed that there was a slight trend of underestimation of

Table 2

Attenuation Threshold Levels Computed with APQ in 22 Plaques

Threshold Level	Attenuation (HU)*
Epicardial fat, upper level	-21.2 ± 13.5
Noncalcified plaque, upper level	242.6 ± 25.9
Midlesion normal contrast enhancement	443.5 ± 60.9
Calcified plaque, lower level	535.0 ± 67.4

* Data are the means \pm standard deviations.

plaque volume (with a negative bias of -5.0 mm^3), and the 95% limits of agreement ranged from -78.8 to 68.7 mm^3 .

We visually assessed results of APQ quantification, by using both a standard window-level setting (window width, 800 HU; window level, 250 HU), as shown in Figure 1, and by using an automatically set scan-specific window-level setting, as recommended by Leber et al (11), with a window width equal to 155% and a window level equal to 65% of normal contrast enhancement in Hounsfield units, as shown in Figure 1d. Visually, the APQ plaque overlay was found to extend correctly over the entire plaque in all cases, with no missing voxels, with some epicardial fat incorrectly included as noncalcified plaque; this inclusion is reflected in the small positive bias in the Bland-Altman plots (Figs 2b, 3b).

Discussion

In our study, there was excellent correlation, and there were no significant differences in noncalcified plaque volumes quantified with intravascular US and multidetector CT, with both automated and manual methods. Compared with CT manual quantification, quantification with APQ showed a trend toward smaller absolute differences from plaque volume quantified with intravascular US and narrower 95% limits of agreement. However, the 95% limits of agreement for intravascular US quantification of -42.9 to 64.4 mm^3 (range, 107.3 mm^3) for APQ and those for manual CT quantification of -45.9 to 77.6 mm^3 (range, 123.5 mm^3) were wide compared with the mean plaque

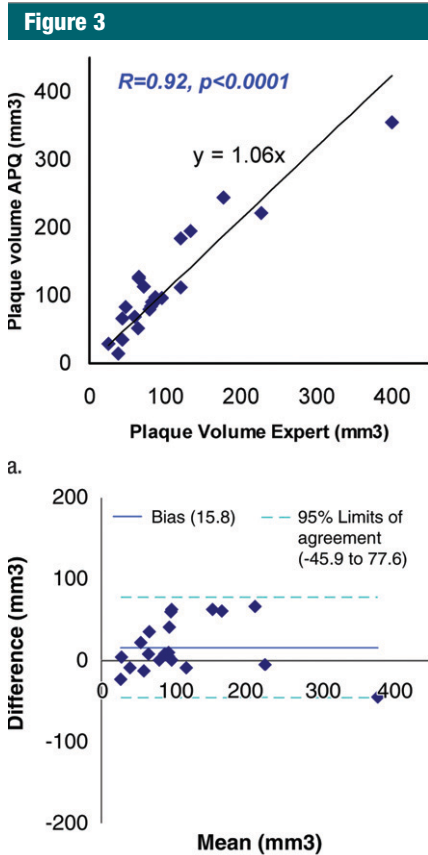


Figure 3: Comparison of APQ quantification of noncalcified plaque volume with expert manual quantification. **(a)** Correlation. **(b)** Bland-Altman plot. Solid line = best-fit line.

volumes. Several factors may account for these differences. First, with the limitations in temporal and spatial resolution of current multidetector CT scanners, accurate delineation of the coronary vessel wall from surrounding epicardial fat is challenging for both the expert reader and automated software. Second, intraluminal plaque and media, excluding the adventitia, are measured with intravascular US, whereas all components of the coronary vessel wall, including the adventitia, are measured with multidetector CT (18). Therefore, the adventitia was included for both manual and automated CT plaque quantification, which is a potential source of intermethod variability. Furthermore, because of these differences, measurement of outer vessel wall thickness with CT cannot be easily validated with

measurement with intravascular US. Third, although landmarks were carefully identified, misregistration of landmarks in the two modalities probably contributed to some discrepancies. Finally, with APQ, segmentation of the coronary arteries and quantification of plaque by using a fully three-dimensional approach were achieved (17), whereas for manual quantification with intravascular US and CT, plaque areas in serial cross sections were summed, which can also be a potential source of intermethod variability.

Several investigators compared plaque volumes that were manually derived with coronary CT angiography with corresponding data derived with intravascular US and reported a strong correlation and concordance, with overall underestimation of noncalcified plaque and overestimation of calcified plaque (10–12,14,20,21). In comparison with intravascular US, a significant overlap of CT attenuation values between lipid-rich and fibrous noncalcified plaque has been reported (14,20); however, attenuation values for noncalcified and calcified plaque have been shown to be significantly different, suggesting that accurate quantification of noncalcified plaque and calcified plaque can be robustly achieved (14). Significant intraobserver variability has been reported for manual plaque quantification from CT (11,14); and it has been suggested that interobserver variability is affected by plaque size, as well as by image quality (22). Recently, Schepis et al (18) reported intraobserver variability of 11% for manual quantification of noncalcified plaque. Clouse et al (23) described a “voxel analysis” technique by using software (Analyze; AnalyzeDirect, Overland Park, Kan; www.analyzedirect.com), the biomedical imaging software suite of the Mayo Clinic (Rochester, Minn). This technique requires manual drawing of multiple profiles through the plaque, and luminal and plaque volumes are calculated by using these manually defined points. Brodoefel et al (24) compared plaque volumes obtained with this technique with those obtained with intravascular virtual-histology US in 12 patients, with a good correlation and concordance between both methods.

In our study, our patient cohort underwent intravascular US for clinical reasons, which may explain larger plaque volumes compared with those reported in recent studies (25). The mean middle-luminal attenuation in our cohort was $443.5 \text{ HU} \pm 60.9$, higher than that reported by Brodoefel et al (24) and Clouse et al (23), who also used contrast agents with the same iodine concentration but with injection rates of 5 and 4 mL/sec, respectively, and higher also than other similar comparisons (12,14). This is most likely owing to the higher luminal iodine concentration, which also affects noncalcified plaque, possibly because of volume averaging of attenuation of adjacent voxels (26,27).

Although the mean luminal attenuation differs with acquisition protocols, it also differed between patients scanned with the same protocol both in our current study and in our previous study (17). Along with accurate outer vessel wall segmentation, correct scan-specific attenuation threshold levels are, therefore, important for accurate plaque quantification.

Our study had limitations. Our comparative analysis was retrospective, and our sample size, although larger than in other validation studies (24), was small. Our comparison was restricted to primarily noncalcified plaques. However, the primary reason behind this selection was to minimize errors in measurement of plaque volume with intravascular US owing to the acoustic shadowing effect. Additional future validation with atherosclerotic lesions containing both calcified and noncalcified plaque may be necessary. Although not validated with intravascular US, we previously assessed APQ performance with atherosclerotic plaques from a consecutive cohort and found that measurements of noncalcified and calcified plaque components agree closely with measurements with manual quantification by two experts (17). We restricted our sample to coronary plaques with well-defined proximal and distal limits, primarily to ensure that the same plaques were quantified at CT and at intravascular US. Only dual-source CT data sets with good or excellent image quality were considered for analysis, and no conclusions as to

accuracy in data sets of lesser quality could be drawn. Our automated algorithm required manual steps, including marking the start and the end of the plaque lesions. Finally, we did not analyze intra- and interobserver variability or reproducibility of plaque quantification; however, these factors have previously been analyzed (17,18,28), and this was not the focus of our study.

Automated scan-specific threshold level-based quantification of plaque components with coronary CT angiography allows rapid, accurate measurement of noncalcified plaque, compared with intravascular US quantification, and requires a fraction of the time needed for equivalent manual analysis.

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