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Impact of Coronary Artery Calcium Characteristics on Accuracy of CT Angiography

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OBJECTIVES This study sought to evaluate which specific calcium characteristics impact diagnostic accuracy of coronary computed tomography angiography (CTA).

BACKGROUND Coronary calcifications comprise one of the most significant factors interfering with diagnostic accuracy of coronary CTA. Despite this fact, there is paucity of data regarding this phenomenon.

METHODS A total of 525 coronary lesions (252 calcified and 273 reference [noncalcified] lesions) within 97 arteries of 60 patients (19 women, age 63 ± 10 years) underwent assessment with both 2 × 64-slice computed tomography and intravascular ultrasound (IVUS). Nineteen calcium characteristics were determined. The main outcome was coronary CTA inaccuracy defined as the deviation of minimum lumen area within the calcification measured with coronary CTA from that measured with IVUS, in both absolute (mm^2) and relative (%) terms.

RESULTS Presence of calcification was found to be independently correlated to coronary CTA inaccuracy in both absolute and relative terms ($p < 0.001$ for both). The relative (%) inaccuracy of coronary CTA was independently correlated to total calcium length ($p = 0.004$), total calcium volume ($p = 0.008$), cross section calcium thickness ($p = 0.023$), cross section calcium area ($p = 0.023$), and cross section lumen area ($p = 0.001$). The absolute inaccuracy of CTA was correlated to calcium length ($p = 0.010$), calcium volume ($p = 0.017$), and cross section calcium area ($p < 0.001$). The presence of both total calcium arc ≥47° and mean lumen diameter of ≤2.8 mm provided the best predictive accuracy for detection of excessive lumen underestimation by CTA. The best accuracy for prediction of excessive lumen overestimation provided combination of 2 of 3 features: maximum calcium density <869 HU, OR whole calcium length <2.4 mm, OR total calcium volume <6.4 mm^3.

CONCLUSIONS Our results indicate which specific calcium characteristics impact accuracy of coronary CTA in lumen assessment within calcified lesions. This may provide practical assistance in predicting coronary lumen underestimation or overestimation by coronary CTA, therefore mitigating risk of diagnostic errors in clinical practice. (J Am Coll Cardiol Img 2014;7:49–58) © 2014 by the American College of Cardiology Foundation

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Coronary computed tomography angiography (CTA) is applied clinically for exclusion of significant coronary stenoses in patients with intermediate probability of coronary artery disease (1). Recent developments, such as virtual fractional flow reserve (FFR) measurement, may expand the potential value of coronary CTA (2); however, this requires very precise delineation of the narrowed coronary lumen in the presence of atherosclerosis, which in most cases contains calcifications (3). One of the main current limitations of coronary CTA is its inaccuracy in evaluating calcified lesions (3–7). More extensive calcifications often lead to overestimation or paradoxically underestimation of coronary stenosis severity (3,5–7). Improvement of coronary CTA diagnostic precision requires detailed understanding of the relationship between specific calcium characteristics and the degree of coronary lumen distortion. Despite its clinical relevance, there is a paucity of data regarding this phenomenon.

Therefore, we assessed a range of quantitative parameters characterizing coronary calcium as seen on coronary CTA and evaluated their relationship to the deviation of coronary lumen area measured with coronary CTA from the reference of intravascular ultrasound (IVUS). The primary focus of our analysis was to identify accurate predictors of coronary lumen overestimation and underestimation by coronary CTA.

ABBREVIATIONS AND ACRONYMS

CI = confidence intervals
CT = computed tomography
CTA = computed tomography angiography
FFR = fractional flow reserve
IVUS = intravascular ultrasound
MLA = minimum lumen area
NPV = negative predictive value
PPV = positive predictive value

METHODS

This was a cross-sectional study with prospectively acquired data. From June 2009 to January 2011, we enrolled 60 consecutive patients who underwent routine coronary CTA due to suspected coronary artery disease. On the basis of the results of coronary CTA (suspected significant coronary stenosis on coronary CTA) the patients were further scheduled for invasive coronary angiography (ICA). Additional inclusion criterion was the presence of at least 1 nondiagnostic or ambiguous coronary stenosis, due to associated coronary calcium deposit. Patients with uncorrectable motion artifacts on coronary CTA study, body mass index >40 kg/m^2, atrial fibrillation, previous bypass surgery, or unstable coronary disease were excluded from the study. The CTA scan preceded coronary angiography and IVUS by 43 ± 37 days. Baseline clinical data were obtained from medical records.

The study protocol was approved by the ethics committee of Institute of Cardiology. All participating patients gave their informed consent for the study.

Coronary CTA and IVUS. Coronary CTA was performed with a dual source 2 × 64-slice computed tomography scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany) with 330 ms rotation time. In all patients sublingual nitrates (0.8 mg) were administered prior to the scan. In case of heart rate ≥70 beats/min, an intravenous metoprolol (sequence of 5 mg, up to 20 mg) was given. A 60 to 80 ml bolus of iomeprol (Iomeron 400, Bracco, Italy) was injected intravenously at 6.0 ml/s. A retrospective, electrocardiogram-gated acquisition protocol was used in all patients, with 0.6-mm collimation, and 100 to 120 kV tube voltage adjusted manually depending on body mass index. Coronary datasets were reconstructed in mid-diastole (60% to 70% of R-R interval) and systole (40% to 50% of R-R interval) with 0.6 mm slice thickness and 0.3 mm increment.

Image noise was derived from the standard deviation of the density values (in Hounsfield units) within a large region of interest in the left ventricle. The contrast-to-noise ratio was defined as the difference between the mean density of the contrast-filled left ventricular chamber and the mean density of the left ventricular wall, which was divided by image noise. The signal-to-noise ratios were assessed in the proximal segments of the left and right coronary artery as the mean density values of the contrasted coronary lumen divided by the standard deviation of these density values.

IVUS was performed with 20 MHz IVUS catheter (Eagle Eye Gold, Volcano Therapeutics, Rancho Cordova, California) on a 5s console, after administration of 200 μg of intracoronary nitroglycerin. The imaging probe was advanced distally to the coronary segment containing the index calcification, and retrograde imaging was performed with an automatic pullback of 0.5 mm/s. All calcifications imaged with IVUS during pullback were included in the analysis.

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Table 1. Correlation of the Calcium Characteristics With Absolute and Relative Difference Between Coronary CTA and Intravascular Ultrasound Derived Lumen Area Measurements

		Absolute Difference (mm^2)		Relative Difference (%)	
	n = 252	Kendall's Tau	p Value	Kendall's Tau	p Value
Cross section level					
Calcium overlapping lumen (yes/no)*	159/93	0.069	0.182	0.124	0.016
Number of separate calcium deposits*	1 ± 1	0.160	0.002	0.205	<0.001
Location (superficial/mid/deep)	191/41/20	0.017	0.735	0.022	0.657
Maximum calcium arch, degrees	42.5 (30.0–68.0)	0.167	<0.001	0.208	<0.001
Total calcium arch, degrees*†	50 (31.0–78.0)	0.192	<0.001	0.240	<0.001
Distance between lumen and calcium edge, mm	0.0 (0.0–0.3)	0.012	0.798	0.013	0.784
Distance between opposite lumen wall and the calcium edge, mm*	2.3 (1.8–29)	−0.119	0.006	−0.212	<0.001
Distance between calcium maximum density point and the lumen center, mm	1.8 (1.5–2.1)	0.054	0.218	−0.016	0.711
Calcium maximum thickness, mm	0.8 (0.6–1.2)	0.162	<0.001	0.172	<0.001
Calcium area, mm^2†	1.6 (0.9–2.8)	0.214	<0.001	0.238	<0.001
Mean calcium density, HU†	707 (579–852)	0.098	0.022	0.102	0.016
Mean calcium density SD, HU†	143 (104–193)	0.161	<0.001	0.160	<0.001
Maximum calcium density, HU†	932 (723–1150)	0.152	<0.001	0.171	<0.001
Lumen area, mm^2*	5.8 (4.0–8.1)	−0.142	0.001	−0.247	<0.001
Mean lumen diameter, mm*	2.7 ± 0.7	−0.144	<0.001	−0.248	<0.001
Whole calcium level					
Whole calcium length, mm†	3.1 (2.0–5.4)	0.133	0.002	0.164	<0.001
Maximum calcium thickness, mm	1.5 (1.0–2.1)	0.089	0.039	0.112	0.009
Total calcium volume, mm^3*†	10.5 (3.4–21.9)	0.189	<0.001	0.211	<0.001
Number of separate calcium deposits	1 (1–2)	−0.005	0.922	0.017	0.730

Values are n for proportions, mean ± SD for normally distributed data, or median (25th, 75th percentile) for non-normally distributed data. Positive correlation (R > 0) means that coronary computed tomography angiography (CTA) underestimates coronary lumen proportionally to increasing values of the parameter. *Independent correlates of excessive lumen underestimation by coronary CTA. †Independent correlates of excessive lumen overestimation by coronary CTA.
HU = Hounsfield units.

Calcium analysis. Our focus was to provide the least subjective assessment, optimally derived from automated analysis of the coronary arteries. Therefore, we chose SurePlaque (version 3.9, Toshiba Medical Systems, Tokyo, Japan), which is one of the most extensively validated software for automatic coronary lumen and plaque analysis on coronary CTA (8,9). The program automatically traces the 3 major coronary vessels. The lumen border is detected adaptively by the program on the basis of the contrast in the vessel and the outer vessel border. In current analysis lumen areas within the calcified and the reference (noncalcified) sites were automatically delineated by the SurePlaque software and manually corrected if necessary.

A single coronary calcification comprised at least 1 calcium deposit, defined according to previous authors as a structure with a density of above 130 Hounsfield units (HU), brighter than the surrounding vessel wall, visible separately from the contrast-enhanced coronary lumen (either "embedded" within noncalcified plaque or discernible from the contrast-enhanced lumen) in at least 2 independent planes (8,10,11). A series of calcium deposits overlapping in the longitudinal vessel axis comprised a single coronary calcification. Separate calcifications required boundary cross section without visible calcium. For each calcification at the levels of minimum lumen area (MLA) cross section and the whole calcified segment a series of lumen and calcium measurements was performed (Table 1). The references were noncalcified (verified by IVUS) cross sections closest to the MLA site (12). None of the primarily selected calcified lesions were excluded from the analysis. According to previous authors, quantitative analysis of calcium at the threshold of 130 HU is inappropriate for contrast studies. Therefore, for automated calcium measurements we chose a previously validated threshold of 350 HU (12,13).

IVUS measurements were performed precisely at the same cross sections as the MLA and the reference sites selected for CTA analysis. The identification of the same cross sections was based on anatomic landmarks including side branches or calcium characteristics. Off-line IVUS analysis of MLA was performed on a Volcano s5 imaging system software by a single experienced observer (M.K.) blinded to patient coronary CTA measurements.

The co-primary endpoints of this study were: 1) the relative deviation of lumen area measured on CTA versus IVUS (%) ([MLA_{CTA} − MLA_{IVUS}]· 100% / MLA_{IVUS}); and 2) the absolute difference in MLA (mm^2) (MLA_{CTA} − MLA_{IVUS}).

Statistics. Continuous data with normal distribution are presented as mean (SD) and non-normally distributed variables are presented as median (25th, 75th quartiles). Categorical data are reported as frequencies. Independent samples *t* test, paired *t* test, Mann-Whitney test, or Wilcoxon test was used to assess differences between continuous variables as appropriate. Categorical variables were compared using chi-square or Fisher exact test where appropriate. Correlations were established with use of Kendall's tau. Univariable and multivariable regression analyses were performed after correction for within-patient clustering with generalized estimating equations. Non-normally distributed data were analyzed after logarithmic transformation. Receiver-operating characteristic curves were analyzed to assess the best cutoff values of selected calcium parameters to predict excessive lumen overestimation or underestimation by coronary CTA. Intraclass correlation coefficient (a method of agreement for continuous variables) was used to assess intraobserver variability in IVUS and coronary CTA measurements. Bland-Altman plots were used for visualization of the difference between measurements by CTA and IVUS. All tests were 2-sided and $p < 0.05$ was considered statistically significant. All analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, Illinois) or MedCalc 12.3.0.0 (MedCalc Software, Mariakerke, Belgium).

The study size was estimated based on a guideline that more than 10 observations must be present for each analyzed calcium parameter (14). Therefore, we required at least 200 observations (calcified lesions), which we assumed would be provided by data derived from 60 patients. Under these assumptions we would show the difference of coronary CTA accuracy between the calcified versus reference lesions of 0.282 times the standard deviation, with probability of 80% at a 2-sided 0.05 significance level.

RESULTS

Of 60 study patients (mean age 63 ± 10 years), 19 (32%) were women, 55 (92%) had hyperlipidemia, 16 (27%) diabetes, 52 (87%) had hypertension, 16 (27%) had family history of coronary disease, and 15 (25%) were smoking. Mean serum creatinine was 87 ± 19 μmol/l, weight 80 ± 14 kg, height 172 ± 9 cm, and body mass index 27 ± 4 kg/m^2. Mean calcium score was 433 ± 353, contrast density in the proximal segment of coronary artery was 490 ± 110 HU, standard deviation was 43 ± 14 HU, signal to noise was 13 ± 5, and contrast to noise was 3.4 ± 1.4.

Overall 525 coronary lesions were assessed within 97 arteries. These included 252 calcified lesions and 273 reference noncalcified lesions.

Average measures of interobserver variability evaluated with intraclass correlation coefficients for CTA parameters was 0.96 (95% confidence interval [CI]: 0.92 to 0.98) for lumen area, 0.77 (95% CI: 0.51 to 0.89) for calcium arch, 0.81 (95% CI: 0.61 to 0.91) for calcium area, and 0.90 (95% CI: 0.77 to 0.96) for calcium volume (the same cross sections assessed more than 6 weeks apart within 30 lesions).

Diagnostic accuracy of coronary CTA in calcified versus noncalcified coronary cross sections. Lumen areas measured with IVUS did not differ between calcified versus reference cross sections (6.0 [4.4 to 8.7] mm^2 vs. 6.7 [4.8 to 9.5] mm^2, $p = 0.164$). Lumen area measurements with coronary CTA and IVUS were highly correlated within the noncalcified (reference) lesions (Kendall's tau = 0.812; 95% CI: 0.789 to 837), as well as within the calcified cross sections (Kendall's tau = 0.604; 95% CI: 0.540 to 0.658) (Fig. 1).

Diagnostic performance of coronary CTA within calcified versus noncalcified (reference) cross sections is presented in Figure 1. Within the noncalcified (reference) sections, coronary CTA overestimated lumen area as compared to IVUS by 2.9% (7.0 [5.0 to 9.9] mm^2 vs. 6.7 [4.8 to 9.5] mm^2, respectively, $p = 0.028$) (Fig. 1A); but there was no significant difference for the median diameters (3.0 [2.6 to 3.6] mm vs. 3.0 [2.5 to 3.5] mm, $p = 0.151$, for coronary CTA and IVUS, respectively). Within calcified sections, coronary CTA underestimated lumen area measurement by 5.0% as compared with IVUS (5.8 [4.0 to 8.1] mm^2 vs. 6.0 [4.4 to 8.7] mm^2, respectively, $p = 0.004$) (Fig. 1B); the median diameter difference was also significantly different (2.7 [2.2 to 3.2] mm vs. 2.8 [2.4 to 3.3] mm, $p < 0.001$, for CTA and IVUS, respectively).

The presence of calcification was found to be an independent of heart rate, mA, kV, patient, and

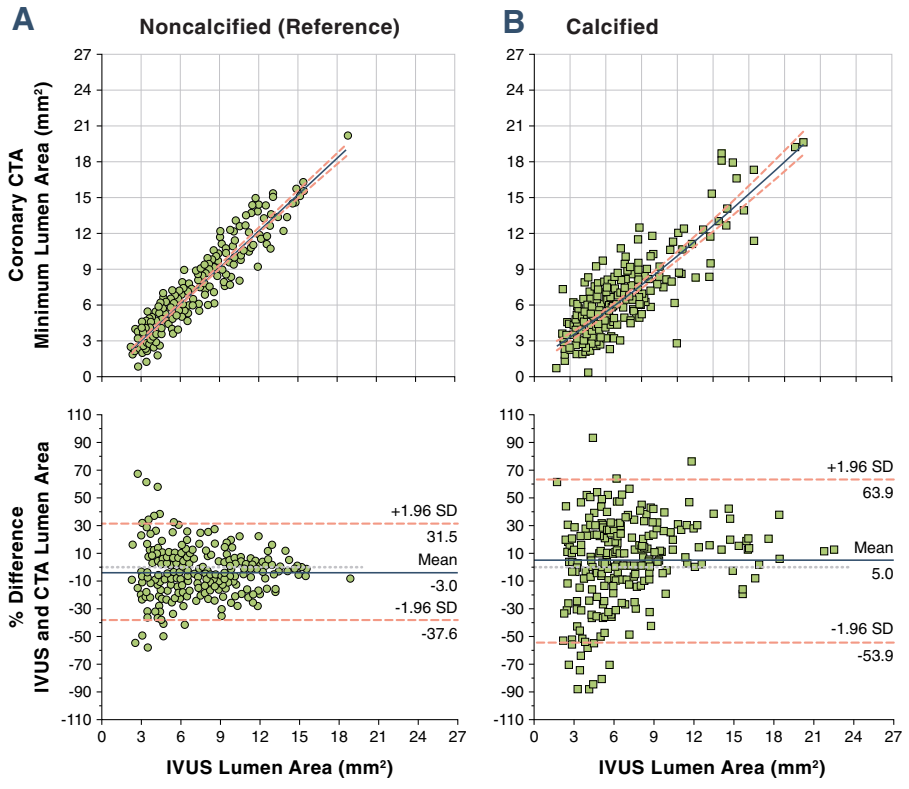

Figure 1. Lumen Area Measurements

Scatterplots of relationship between lumen area measured with coronary computed tomography angiography (CTA) and intravascular ultrasound (IVUS), and Bland-Altman plots of relative (%) difference between lumen area as assessed by IVUS versus dual-source computed tomography within noncalcified (reference) lesions **(A)**, and calcified lesions **(B)**. Within the scatterplots the **blue** lines represent fitted regression lines and the **red** lines represent 95% confidence intervals.

IVUS lumen area correlate of the discrepancy between lumen areas measured by IVUS and CTA, in both absolute (mm^2) and relative (%) terms ($p < 0.001$ for both).

Relationship of calcium characteristics and accuracy of coronary CTA. A wide array of calcium characteristics was correlated with the discrepancy between lumen area measured with coronary CTA and IVUS (Table 1). The relative (%) inaccuracy of coronary CTA was independently correlated to following variables: total calcium length ($p = 0.004$), total calcium volume ($p = 0.008$), cross section calcium thickness ($p = 0.023$), cross section calcium area ($p = 0.023$), and cross section lumen area ($p = 0.001$) (p values after correction for within patient clustering, kV, mA, and heart rate). The absolute difference (mm^2) between the coronary CTA and IVUS lumen areas was independently associated with total calcium length ($p = 0.010$), total calcium volume ($p = 0.017$), and cross section calcium area ($p < 0.001$) (Fig. 2).

Correlates of excessive diagnostic inaccuracy of coronary CTA within calcified lesions. Excessive diagnostic coronary CTA inaccuracy within calcified lesions was defined as the deviation of relative lumen measurement with coronary CTA from IVUS exceeding 1.96 standard deviations established for noncalcified lesions (15,16) (Fig. 1A). Therefore, excessive lumen underestimation was ascertained as the difference of IVUS and coronary CTA lumen measurements above 31.6%, which was present within 41 (16.3%) calcified lesions.

The correlates of excessive lumen underestimation by coronary CTA independent of mA, kV, and heart rate are listed in Table 1. Based on area under the receiver-operating characteristic curve, the following best cutoff points for these variables were established: ≥47° for total calcium arc, ≤3.5 mm^2 for lumen area, ≥9.2 mm^3 for calcium volume, ≤2.0 mm for distance between opposite lumen wall and the calcium edge, ≤2.8 mm for mean diameter, above 1 calcium deposit seen on a cross section, and

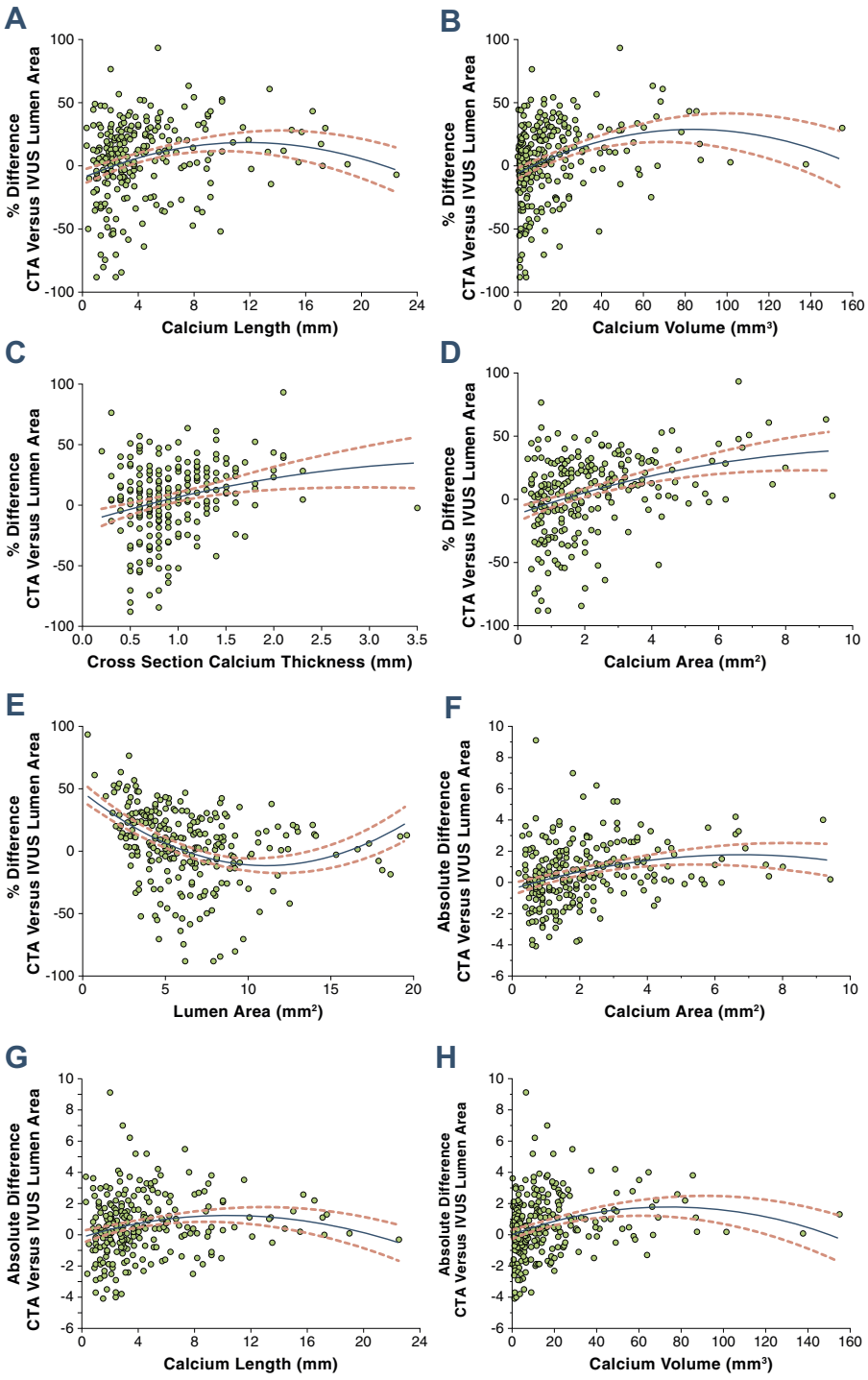

Figure 2. Relationship Between Individual Calcium and Lumen Characteristics and Inaccuracy of Coronary CTA

(A to E) Correlates of the relative difference between coronary CTA and IVUS; **(F to H)** correlates of the absolute difference between coronary CTA and IVUS. **Solid lines** represent regression and **dashed lines** represent 95% confidence intervals. Abbreviations as in Figure 1.

calcium overlapping lumen. The presence of both total calcium arc ≥47° and mean diameter of ≤2.8 mm provided the best predictive accuracy for detection of excessive lumen underestimation by coronary CTA (sensitivity = 70.7, specificity = 71.1, accuracy = 71.0, positive predictive value [PPV] = 32.2, negative predictive value [NPV] = 92.6). Inclusion of additional parameters did not improve the accuracy of the model. We also tested the accuracy of 45° and 90° of calcium arch thresholds, which in clinical practice can be visually estimated without additional tools. Application of 45° and 90° thresholds provided sensitivities of 80.5 and 36.6 at specificities of 52.6, and 84.8, respectively.

Respectively, the difference between measurements below −37.3% were present in 21 (8.3%) cases and indicated excessive lumen overestimation by coronary CTA. The correlates of excessive lumen overestimation by coronary CTA independent of mA, kV, and heart rate are listed in Table 1. The best cutoff points for these correlates predictive of lumen overestimation by coronary CTA were: ≤61° for total calcium arc, ≤2.6 mm^2 for calcium area, ≤621 HU for mean calcium density, ≤149 HU for mean calcium density standard deviation, ≤869 HU for maximum calcium density, ≤2.4 mm for whole calcium length, and ≤6.4 mm^3 for total calcium volume. The best accuracy for prediction of lumen overestimation by coronary CTA provided combination of 2 of 3 features (maximum calcium density OR whole calcium length OR total calcium volume) (sensitivity = 81.0, specificity = 63.6, accuracy = 65.1, PPV = 16.8, NPV = 97.4). However, the second best accuracy provided just the presence of total calcium volume ≤6.4 mm^3 (sensitivity = 76.2, specificity = 63.2, accuracy = 64.3, PPV = 15.8, NPV = 96.7).

DISCUSSION

The unique findings of our study were the identification of quantitative parameters associated with impaired accuracy of coronary CTA within calcified lesions and the indication of the specific calcium characteristics assessed on coronary CTA that most accurately predicted lumen underestimation or overestimation. The results underlined the significance of lumen size and relative calcium parameters for the problem of lumen area underestimation by coronary CTA, challenging the paradigm of the role of massive calcifications for inaccuracy of coronary CTA. Moreover, our data indicated that coronary lumen area overestimation by coronary CTA was related to smaller and less dense calcifications.

Lumen area underestimation by coronary CTA. According to our study, coronary CTA significantly underestimated coronary lumen area within calcified lesions by a mean of 5%. These findings remained in accordance with earlier studies. Hoffmann et al. (5) identified calcification as the major cause underlying overestimation of luminal narrowing by coronary CTA (94% of false-positive findings) as compared with ICA. Subsequently, Brodoefel et al. (6) found calcifications as the single factor impacting diagnostic accuracy of coronary CTA relative to ICA. More recent reports evaluated selected calcium characteristics and not just the presence of calcium. Within stenoses containing large calcifications (defined arbitrarily), coronary CTA correctly predicted the presence of obstructive disease in two-thirds of the cases as opposed to over 90% lesions with small or moderate calcifications (3). In a substudy of the CORE-64 (The Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) trial, calcium arc above 90° was related to stenosis overestimation by coronary CTA in 14% of analyzed segments (7). In our study the excessive lumen underestimation by coronary CTA was observed in 16.3% of calcified lesions and was independently correlated not only to absolute massive calcium characteristics, but as importantly, to a smaller lumen. Our analysis indicated the coexistence of calcium arc exceeding 47° and mean lumen diameter of <2.9 mm as the most accurate marker of excessive lumen underestimation by coronary CTA, with a high negative predictive value of 92% (in absence of these features there is low probability of lumen underestimation). These findings were strikingly parallel to the well-validated concept of inaccuracy of coronary CTA for assessment of coronary stents with diameter below 3.0 mm (1). The relevance of this comparison was supported by the shared mechanism of partial volume artifact contributing to both phenomena.

Therefore, in the presence of coronary calcium, the primary diagnostic problem seemed to be related to smaller or stenosed arteries (MLA ≤3.5 mm^2, distance between opposite lumen wall and the calcium edge ≤2.0 mm), and not just massive calcifications. In these sites, already on the verge of significance, artifacts caused even by moderate calcium deposits may turn into critical diagnostic errors.

Lumen area overestimation by coronary CTA. The problem of lumen overestimation by coronary CTA was less common (8.3% of calcified lesions);

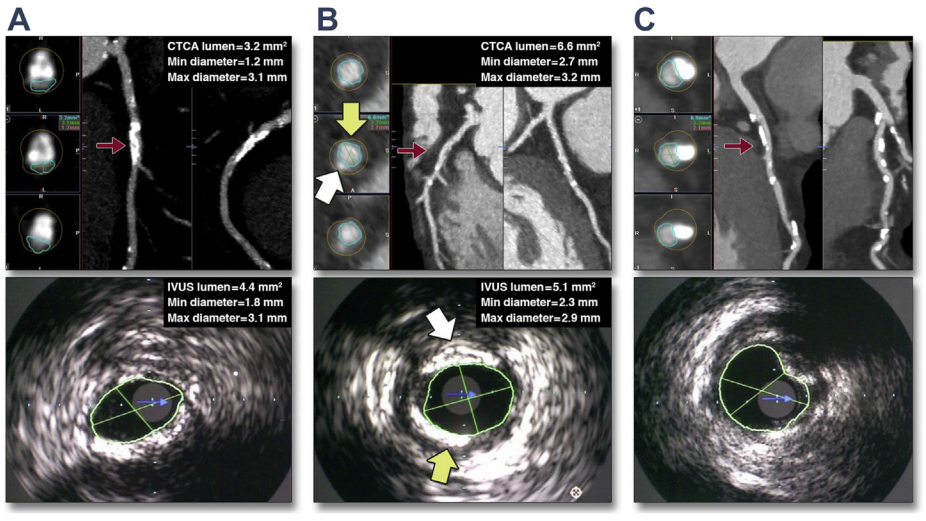

Figure 3. Examples of Lumen Overestimation and Underestimation by CTA as Compared With IVUS

In **A**, on coronary CTA, calcium arch exceeds 47° and the mean lumen diameter is below 2.8 mm. In **B**, the **white arrow** points at the small, low-density coronary calcium seen on coronary CTA, and the **yellow arrow** points at the calcium not identified on coronary CTA, but visible on IVUS. **(C)** Illustrates coronary lumen indentation made by coronary calcium. **Red arrows** indicate the level of cross section on the curved multiplanar reformatted images. Upper images generated by SurePlaque, lower images derived from IVUS. Abbreviations as in Figure 1.

however, its effect—decreasing sensitivity of coronary CTA—affects the core value of this diagnostic method. According to the previously cited study by Hoffmann et al. (5), calcifications were associated with 14% of false negative findings. Similar to our study, the prevalence of lumen overestimation by coronary CTA within calcified lesions of 6% for mildly and 8% for more severe calcifications was provided by another report (7). Our data indicated, however, that lumen overestimation by coronary CTA was best predicted by the presence of smaller or less dense calcifications. Our findings were supported by data of van der Giessen et al. (12), who showed that around one-half of the calcium deposits seen on IVUS images could not be detected on contrast enhanced 64-slice computed tomography angiography because of their small size. Therefore, it may be hypothesized that some small and hypodense calcifications may be associated with further small calcium deposits indiscernible from the lumen (Fig. 3B).

Methodological issues. Despite the importance of the issue, there are relatively few previous studies assessing the impact of coronary calcifications or their characteristics on accuracy of coronary CTA (3–7). Our study is unique and differs from all of the previous studies with regard to 2 major issues: 1) the in-depth analysis of calcified lesions depicted by multiple (19), comprehensive, (semi-) automatically quantified calcium parameters, as opposed to just 1 arbitrarily selected and manually delineated parameter; and 2) use of IVUS as the reference method, as opposed to invasive coronary angiography. Although coronary angiography is regarded as a gold standard for imaging of coronary arteries, its use as the reference method for coronary CTA studies and, in particular, for analysis of calcified lesions may be questioned in the light of contemporary research (17,18). First of all, calcified lesions may present with a filling defect on angiography, which makes assessment of actual coronary stenosis impossible (19,20). Furthermore, due to limited number of 2-dimensional projections, angiography does not provide optimal lesion assessment especially within ostia, bifurcations (frequent site of coronary calcifications), or in cases of overlapping arteries. It has been shown that in cases of equivocal angiographic appearance, coronary CTA results were correlated to IVUS, but not to angiography (21–23). Moreover, an applied threshold of 50% or 70% stenosis has also been questioned as a valid indicator of coronary stenosis significance (24). Target lesion cross-sectional lumen assessment with IVUS as the reference imaging method has allowed us to avoid these limitations.

Implications. At the current stage our results may help to recognize patterns related to coronary lumen underestimation or overestimation present on routine coronary CTA studies, sensitizing reading

physicians to possible errors. However, current study has exploratory character, and the exact improvement of CTA diagnostic accuracy with use of the findings has not been established. Furthermore, the information regarding the calcium or lumen characteristics that impact coronary CTA accuracy within calcified lesions indicates which technology developments are likely to improve its clinical utility. In terms of disappointing results of the recent DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic AngiOgraphy) study, it may be speculated that the virtual FFR method, irrespective of the accuracy of the blood flow models, remains subject to imperfect lumen delineation within diseased (i.e., usually calcified) lesions. Virtual FFR misses 10% of significant stenoses while overestimating 46% of stenoses (2). The mean calcium score of patients enrolled in the DeFACTO study (at 381) was similar to our cohort (at 433). Because coronary resistance is related exponentially to the stenosis lumen area, even its small misalignment might have translated into critical diagnostic errors.

Our data suggest that improvement of diagnostic accuracy of coronary CTA within calcified lesions may be attained in the future through increasing spatial resolution of coronary CTA. We did not find a significant relationship between high calcium density (important determinant of blooming artifact) and inaccuracy of coronary CTA. On the contrary, less dense calcifications may be overlooked and fused with the lumen, posing the greatest challenge for extended coronary CTA clinical utility.

Study limitations. Assessment of coronary calcifications with coronary CTA is a challenge because it confronts all of the major limitations of CT technology including its borderline or suboptimal spatial resolution, presence of partial volume artifact, lack of objective, universally applicable, and histology validated thresholds for calcium and lumen delineation. Given these limitations, we strove for least error prone endpoints (lumen are matched with IVUS), least arbitrary calcium characterization (multiple and if possible continuous parameters), automation of the process for structures delineation (use of SurePlaque software), and use of the best validated thresholds for calcium delineation within contrast filled arteries (11–13). Despite the high reproducibility, however, our results depended on imperfect methods as is indicated by a systematic bias and a scatter in estimation of coronary lumen even within noncalcified arteries. However, the systematic bias at 2.9% of the lumen area is low and equates to ~1.5% of the lumen diameter. Analogously, the ~30% scatter of the noncalcified lumen area measured with IVUS and coronary CTA approximates 16% of the lumen diameter that, for 2.5 mm diameter vessels, equals to ± 0.4 mm (i.e., not more than a voxel's size). The choice of inclusion criterion on the basis of the presence of at least 1 stenosis, which is ambiguous/nondiagnostic due to a calcification may introduce a bias in patients and lesions selection as compared to a consecutive series of patients referred for coronary CTA. However, forced inclusion of "the worst" calcifications aimed to ensure applicability of our results to the lesions which are most challenging in clinical practice. Therefore, being strict, our results may be applicable to patients with at least 1 nondiagnostic/ambiguous coronary stenosis due to calcification.

CONCLUSIONS

Our results indicate which specific calcium characteristics impact the inaccuracy of coronary CTA in lumen assessment within calcified lesions. This may provide practical assistance in predicting coronary lumen underestimation or overestimation by coronary CTA, therefore mitigating the risk of diagnostic errors in clinical practice. Using this information may also direct improvements of coronary CTA technology.

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