Head-to-Head Comparison of Coronary Plaque Evaluation Between Multislice Computed Tomography and Intravascular Ultrasound Radiofrequency Data Analysis

Gabija Pundziute, MD,*‡ Joanne D. Schuijf, PhD,* J. Wouter Jukema, MD, PhD,* Isabel Decramer, MSc,§ Giovanna Sarno, MD,§ Piet K. Vanhoenacker, MD,§ Johannes H. C. Reiber, PhD,† Martin J. Schalij, MD, PhD,* William Wijns, MD, PhD,§ Jeroen J. Bax, MD, PhD*

Leiden, the Netherlands; Kaunas, Lithuania; and Aalst, Belgium

Objectives The purpose of this study was to perform a head-to-head comparison of plaque observations with multislice computed tomography (MSCT) to virtual histology intravascular ultrasound (VH IVUS).

Background The VH IVUS allows in vivo coronary plaque characterization with high spatial resolution. Noninvasively, plaques may be evaluated with MSCT, but limited data are available.

Methods A total of 50 patients underwent 64-slice MSCT followed by VH IVUS. The Agatston score was evaluated on MSCT in coronary segments where IVUS was performed. Plaques were classified on MSCT as noncalcified, mixed, and calcified. Four plaque components (fibrotic, fibro-fatty, and necrotic core tissues and dense calcium) were identified on VH IVUS, and the presence of thin-cap fibroatheroma was evaluated.

Results A moderate correlation was observed between the Agatston score and calcium volume on VH IVUS ($r = 0.69$, $p < 0.0001$). In total, 168 coronary plaques were evaluated (48 [29%] noncalcified, 71 [42%] mixed, 49 [29%] calcified). As compared with calcified plaques, noncalcified plaques contained more fibrotic ($60.90 \pm 9.21\%$ vs. $54.60 \pm 8.33\%$, $p = 0.001$) and fibro-fatty tissues ($28.11 \pm 13.03\%$ vs. $21.37 \pm 9.75\%$, $p = 0.006$) on VH IVUS. Mixed and calcified plaques contained more dense calcium ($7.61 \pm 8.94\%$ vs. $2.68 \pm 3.01\%$, $p = 0.001$; $10.18 \pm 6.71\%$ vs. $2.68 \pm 3.01\%$, $p < 0.0001$, respectively). Thin-cap fibroatheromas were most frequently observed in mixed plaques as compared with noncalcified and calcified plaques (32%, 13%, 8%, $p = 0.002$, respectively).

Conclusions A good correlation was observed between calcium quantification on MSCT and VH IVUS. In addition, plaque classification on MSCT paralleled relative plaque composition on VH IVUS, although VH IVUS provided more precise plaque characterization. Mixed plaques on MSCT were associated with high-risk features on VH IVUS. (J Am Coll Cardiol Intv 2008;1:176–82) © 2008 by the American College of Cardiology Foundation
During the last decade, multislice computed tomography (MSCT) coronary angiography has rapidly matured into a technique that could be used as an alternative imaging modality to detect coronary stenoses in patients with suspected coronary artery disease (CAD). Moreover, the technique allows direct visualization of coronary plaques, in contrast to conventional coronary angiography. Accordingly, MSCT may also have the potential to provide information on plaque composition in addition to the degree of stenosis (1–4). Indeed, Schroeder et al. (4) showed that in comparison with grayscale intravascular ultrasound (IVUS), differentiation between noncalcified, intermediate, and calcified plaques is possible on MSCT based on the differences in the average plaque signal intensity. Moreover, MSCT observations may be different among various clinical presentations. For example, a lower prevalence of completely calcified plaques on MSCT was demonstrated in previous studies in patients presenting with acute coronary syndromes (5–7).

Potentially, more detailed information on plaque composition could be derived from virtual histology IVUS (VH IVUS). This technique has recently been introduced as a novel IVUS modality. This invasive imaging technique allows accurate in vivo evaluation of coronary plaque components, namely fibrotic, fibro-fatty, and necrotic core tissues and dense calcium (8). Indeed, as compared with histopathology, VH IVUS allowed detection of the necrotic core with a predictive accuracy of 88.3%, whereas the accuracy to detect regions of dense calcium was as high as 96.5% (8). In addition, differences in plaque composition have been demonstrated in different clinical settings using this technique. In patients presenting with acute coronary syndromes, the amount of necrotic core tissue and the density of thin-cap fibroatheromas (TCFA) (features that are associated with high risk of plaque rupture) were shown to be significantly higher as compared with patients with stable CAD (8–10).

As a consequence, VH IVUS could provide more insight into plaque composition on MSCT. In addition, it is unclear which coronary plaques on MSCT may represent lesions with high-risk features. However, no systematic comparisons between MSCT and VH IVUS are currently available. Accordingly, the purpose of the study was to perform a head-to-head comparison of coronary plaque composition as determined by MSCT to VH IVUS. With regard to plaque classification, we expected to demonstrate a fair relation between plaque type (noncalcified, mixed, or calcified) as determined by MSCT versus relative composition as determined by VH IVUS. However due to the higher spatial resolution of VH IVUS, we expected to observe more details on VH IVUS. Finally, noncalcified and mixed lesions on MSCT appear to occur more frequently in unstable conditions, and therefore, we expected noncalcified and mixed plaques to be related to high-risk features on VH IVUS.

**Methods**

**Patient population and study protocol.** In total, 50 patients scheduled for conventional coronary angiography based on clinical presentation were prospectively included in the study. All patients underwent 64-slice MSCT coronary angiography, followed by invasive coronary angiography in combination with VH IVUS. Noninvasive and invasive examinations of coronary plaques were performed within 1 month. The clinical history of the patients was evaluated prior to conventional coronary angiography to ensure that no acute coronary events or worsening of angina occurred between examinations.

Only patients without contraindications to MSCT and IVUS were included in the study. Exclusion criteria for MSCT were (supra)ventricular arrhythmias, renal insufficiency (serum creatinine >120 μmol/l), and known allergy to iodine contrast media. Exclusion criteria for IVUS were severe vessel tortuosity or occlusion.

The study protocol was approved by the local ethics committee and informed consent was obtained from all patients.

**MSCT**

**Data acquisition.** The 64-slice MSCT coronary angiography was performed using a Toshiba Aquilion (Toshiba Medical Systems, Tokyo, Japan) scanner. First, a coronary calcium scan without contrast was obtained, followed by 64-slice MSCT coronary angiography performed during electrocardiographic gating and the administration of nonionic contrast at 5 ml/s according to the protocol as described previously (11). If the heart rate was ≥65 beats/min, additional oral beta-blockers (metoprolol, 50 or 100 mg, single dose, 1 h prior to the examination) were provided if tolerated. After acquisition, the data were reconstructed and transferred to a remote workstation for post-processing. When extensive coronary calcifications were present, sharp reconstruction algorithms were used to reduce partial volume effects of coronary calcium.

**Data analysis.** Data were evaluated using a remote workstation with dedicated software (Vitrea 2, Vital Images, Minnetonka, Minnesota, or Advantage, GE Healthcare, Milwaukee, Wisconsin). The MSCT angiograms and calcium scans were evaluated by 2 experienced observers who were unaware of the clinical characteristics and the IVUS findings. Disagreements were immediately resolved in consensus. First,
coronary artery calcium score was assessed in each coronary segment. For this purpose, side branches and coronary ostia were used as landmarks, and the contrast-enhanced images were viewed for verification of the segmentation. In addition, the intra- and interobserver agreement of calcium scoring on a segmental basis was evaluated. For the intraobserver agreement analysis, the same observer remeasured segmental coronary calcium scores after 2 months. The difference between the measured calcium scores was calculated for each segment. The mean difference for all measurements was calculated to express the intraobserver agreement. For the interobserver agreement analysis, a second observer remeasured the segmental coronary calcium scores. For each segment, the difference between these measurements by the 2 observers was calculated. The mean difference was used to express interobserver agreement.

Subsequently, the presence of coronary plaques was visually evaluated on the contrast-enhanced coronary angiograms using axial images and curved multiplanar reconstructions. Coronary plaques were defined as structures >1 mm² within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding tissue, as previously described (2). Side branches and coronary ostia were used as landmarks to define the location of plaques in the arteries. After localization of a coronary plaque, the start and the end positions were visually identified and verified according to the criteria mentioned above. In cases when atheroma was diffusely present over the entire course of the artery, plaques were evaluated per coronary segment. Accordingly, landmarks defining the coronary segments were used to indicate the start and the end positions in these cases. Plaques were visually classified as follows: 1) noncalcified = plaque having lower density compared with the contrast-enhanced vessel lumen present without any calcification discernible; 2) calcified plaque = plaque with predominantly high density present; and 3) mixed plaque = plaque with noncalcified and calcified elements present.

**Conventional coronary angiography.** Conventional invasive coronary angiography was performed according to standard protocols. Coronary angiograms were evaluated by an experienced observer blinded to all study results; the presence of an obstructive lesion was defined as ≥50% luminal narrowing in 2 orthogonal views.

**VH IVUS**

**Data acquisition.** For each IVUS examination, a 20-MHz, 2.9-F, phased-array IVUS catheter (Eagle Eye, Volcano Corp., Rancho Cordova, California) was used. After administration of intracoronary nitrates, the IVUS catheter was introduced to the distal coronary artery. Using an automated pullback device, the transducer was withdrawn at a continuous speed of 0.5 mm/s up to the coronary ostium. Cine runs before and during contrast injection were performed to define the starting position of the IVUS catheter. The electrocardiographically triggered IVUS radiofrequency signals were acquired and stored for off-line analysis.

**Data analysis.** Off-line VH IVUS analyses were performed using dedicated software (pcVH 2.1, Volcano Corp.) by an experienced observer blinded to baseline patient characteristics. After automated detection, external elastic membrane and lumen borders were manually edited. The contours of the external elastic membrane and the lumen-intima interface enclosed an area defined as coronary plaque plus media area. Atherosclerotic coronary plaques were characterized based on spectral analysis of IVUS backscattered signals, as described and validated previously (8,12). Four tissues were differentiated, including fibrotic tissue being labeled in dark green, fibro-fatty in light green, necrotic core in red, and dense calcium in white (Fig. 1). The region of interest corresponding to plaques observed on MSCT was defined using side branches and coronary ostia as landmarks. For each region of interest, the mean value of the 4 relative compositional quantitative plaque parameters was obtained. In addition, the volume of dense calcium in coronary segments where IVUS examination was performed was measured in all patients. Finally, the presence of IVUS-derived TCFA was evaluated in 3 consecutive frames within 10 mm of the minimum lumen area slice of each plaque. The TCFAs were defined as lesions fulfilling the following criteria: 1) plaque burden >40%; 2) the presence of confluent necrotic core of >10%; and 3) no evidence of an overlying fibrous cap (Fig. 2B) (10,13).

**Comparison of MSCT and VH IVUS.** To ensure that identical plaques were assessed by MSCT and VH IVUS, coronary ostia and side branches were used as landmarks and distances from the landmarks to the target lesions were measured. The distances were measured on multiplanar reconstructions of the coronary arteries on MSCT. On IVUS, the corresponding plaque was identified using longitudinally reconstructed IVUS images and validated previously (8,12). Four tissues were differentiated, including fibrotic tissue being labeled in dark green, fibro-fatty in light green, necrotic core in red, and dense calcium in white (Fig. 1). The region of interest corresponding to plaques observed on MSCT was defined using side branches and coronary ostia as landmarks. For each region of interest, the mean value of the 4 relative compositional quantitative plaque parameters was obtained. In addition, the volume of dense calcium in coronary segments where IVUS examination was performed was measured in all patients. Finally, the presence of IVUS-derived TCFA was evaluated in 3 consecutive frames within 10 mm of the minimum lumen area slice of each plaque. The TCFAs were defined as lesions fulfilling the following criteria: 1) plaque burden >40%; 2) the presence of confluent necrotic core of >10%; and 3) no evidence of an overlying fibrous cap (Fig. 2B) (10,13).
datasets (3). The transversal IVUS sections were further inspected and the start and the finish frames of the lesions were depicted on electrocardiographically triggered IVUS datasets of VH IVUS analyses.

**Statistical analysis.** Categorical variables are expressed as numbers (percentages) and compared between groups with 2-sided chi-square test or Fisher exact test. Continuous variables are expressed as mean (standard deviation) and compared with 1-way analysis of variance test. In case of significant differences, the differences between the samples were further evaluated using post hoc Bonferroni test. Correlation between the Agatston calcium score and the volume of dense calcium on VH IVUS were assessed with Pearson correlation analysis. The p values <0.05 are considered as statistically significant. Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc., Chicago, Illinois).

**Results**

**Patient characteristics.** The MSCT coronary angiography and VH IVUS imaging were performed in 50 patients. All MSCT scans and IVUS images were of diagnostic quality, and no patient was excluded from analysis. The baseline patient characteristics are provided in Table 1. Briefly, 31 patients (62%) were males, and the average age was 60 ± 11 years.

**Agatston calcium score on MSCT versus calcium content on VH IVUS.** The correlation between the Agatston calcium score on MSCT and the volume of dense calcium on VH IVUS in segments in which IVUS examination was performed is presented in Figure 3. A significant correlation was observed between the Agatston calcium score and the volume of dense calcium on VH IVUS (r = 0.69, p < 0.0001). In addition, intraobserver and interobserver agreement was evaluated. A good intraobserver agreement was observed for the quantification of calcium score per coronary segment on MSCT (mean difference in segmental calcium scores 3.2 ± 5.4). Similarly, a good interobserver agreement was observed and the mean difference in segmental calcium scores was 3.4 ± 6.5 between both observers.

**Plaque type on MSCT versus composition on VH IVUS.** An example of the different plaque types as identified on MSCT images is presented in Figure 2. On VH IVUS, plaque containing predominantly fibrous and fibro-fatty tissues is demonstrated.}

**Table 1. Baseline Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 50</th>
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<tbody>
<tr>
<td>Male gender</td>
<td>31 (62%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>60 ± 11</td>
</tr>
<tr>
<td>Obesity</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>30 (60%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (56%)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>21 (42%)</td>
</tr>
<tr>
<td>Typical angina</td>
<td>26 (52%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>8 (16%)</td>
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CAD = coronary artery disease; PCI = percutaneous coronary intervention.
MSCT and their corresponding VH IVUS images are provided in Figure 2. In total, 168 coronary plaques fulfilled the predefined criteria and were included in the analysis. Of these lesions, 40 (24%) plaques were obstructive, whereas the remaining 128 (76%) lesions were nonobstructive (as determined on conventional invasive coronary angiography). Based on the MSCT scans, 48 (29%) plaques were classified as noncalcified, 71 (42%) as mixed, and 49 (29%) as calcified. Thirteen (27%) noncalcified plaques, 17 (24%) mixed plaques, and 10 (20%) calcified plaques were classified as obstructive stenoses on conventional invasive coronary angiography (p = 0.7).

Results from VH IVUS are specified per plaque type in Table 2 and Figure 4. No differences were observed in lesion length. Noncalcified plaques contained significantly more fibrotic and fibro-fatty tissues as compared with calcified plaques (60.90 ± 9.21% vs. 54.60 ± 8.33%, p = 0.001, and 28.11 ± 13.03% vs. 21.37 ± 9.75%, p = 0.006, respectively). Mixed and calcified plaques showed more dense calcium on VH IVUS as compared with noncalcified plaques (7.61 ± 8.94% vs. 2.68 ± 3.01%, p = 0.001, and 10.18 ± 6.71% vs. 2.68 ± 3.01%, p < 0.0001, respectively). More necrotic core tissue was observed in mixed and calcified plaques as compared with noncalcified plaques (11.22 ± 5.65% vs. 8.31 ± 5.50%, p = 0.02, and 13.85 ± 6.32% vs. 8.31 ± 5.50%, p < 0.0001, respectively). Prevalence of TCFA in 3 types of plaques on MSCT. Regarding the VH IVUS qualitative assessment, TCFAs were most frequently observed in mixed plaques as compared with noncalcified and calcified plaques (Table 2, Fig. 5). Twenty-three (32%) of mixed plaques fulfilled the TCFA criteria on VH IVUS as compared with only 6 (13%) in noncalcified and 4 (8%) in calcified plaques (p = 0.002).

**Discussion**

The findings of the present study demonstrated a good correlation between plaque composition on MSCT and VH IVUS. Coronary calcium score with MSCT showed a significant correlation with dense calcium volume measurements on VH IVUS. Similarly, only a very limited amount of dense calcium was observed in noncalcified plaques on MSCT, whereas increasingly more dense calcium on VH IVUS was demonstrated in mixed and calcified plaques. At the same time, significantly more fibrotic and fibro-fatty tissues were demonstrated in noncalcified plaques as compared with calcified plaques (A, B). Mixed and calcified plaques contained significantly more necrotic core tissue and dense calcium on VH IVUS as compared with noncalcified plaques (C, D). Abbreviations as in Figures 1 and 2.
time, calcified and mixed plaques contained increasingly less fibrotic and fibro-fatty tissues as compared with noncalcified plaques. However, VH IVUS with superior spatial resolution allowed a more precise evaluation of plaque composition as compared with MSCT. Calcified plaques on MSCT were shown to contain a considerable amount of noncalcified tissue on VH IVUS. Plaques deemed to be completely noncalcified on MSCT, on the other hand, still contained some small amount of calcium, albeit only very limited. Also, distinction between fibrous and fibro-fatty tissue may not be feasible using MSCT. Finally, of particular interest was the observation that plaques were more prevalent in mixed plaques, suggesting a higher degree of vulnerability of these mixed plaques on MSCT.

**Correlation of plaque composition between 2 techniques.** In the present study, the Agatston calcium score on MSCT significantly correlated with the volume of dense calcium on VH IVUS. This observation is in line with previous studies comparing the Agatston calcium score obtained by electron beam computed tomography with histopathology. Indeed, Mautner et al. (14) have previously demonstrated an excellent correlation between calcium score and calcium area on histologic sections of the coronary arteries ($r = 0.96$, $p < 0.0001$). Similarly, accurate detection of calcified plaques was demonstrated on coronary artery scanning without contrast enhancement as compared with grayscale IVUS. In a study by Baumgart et al. (15), calcium on electron beam computed tomography was detected with a sensitivity of 97% and a specificity of 80%. Moreover, our findings indicate significantly more dense calcium in mixed and calcified plaques on noninvasive coronary angiography with MSCT as compared with lesions deemed to be noncalcified on MSCT. In line with these observations, previous comparative studies with grayscale IVUS demonstrated accurate detection of plaques containing calcium on MSCT, with mixed plaques showing a sensitivity of 94%, whereas the same sensitivity was demonstrated to detect calcified plaques (94% to 95%) (1,3). Similarly, MSCT plaque density values were higher in plaques containing calcium as detected by grayscale IVUS and histopathology (4,16). Conversely, noncalcified plaques on MSCT in our study contained significantly more fibrotic and fibro-fatty tissues as compared with calcified plaques.

However, in contrast to grayscale IVUS, VH IVUS may allow more detailed analysis of plaque composition, including the in vivo quantification of specific histologic components of noncalcified plaque tissue. Noncalcified plaques in this study contained fibrotic, fibro-fatty, and necrotic core tissues, whereas the superior spatial resolution of the technique (100 to 200 µm) as compared with MSCT (0.4 mm) also allowed the detection of minimal amounts of calcium. In addition, plaques located in coronary segments without detectable calcium on coronary calcium scoring contained small volumes of dense calcium on VH IVUS (Fig. 3), highlighting the fact that minor calcifications may be missed by MSCT. Interestingly, calcified plaques on MSCT still contained a high amount of noncalcified components on VH IVUS. This could be explained by the partial volume effect of coronary calcium that occurs during MSCT imaging. Indeed, it has been well established that the presence of high-attenuation objects, such as dense calcifications, leads to overestimation of the lesion. As a result, adjacent tissues with lower attenuation values cannot be adequately depicted in the presence of dense calcium, and remain unrecognized (17).

**Prevalence of TCFA in different plaque types.** Previous histological studies have demonstrated that lesions containing a considerable amount of necrotic core tissue without evidence of an overlying fibrous cap (TCFA lesions) may be considered as a precursor of coronary plaque rupture (18). In vivo, TCFA may be detected by VH IVUS and have indeed been more frequently observed in patients with acute coronary syndromes as compared with those with stable CAD. In a study by Rodriguez-Granillo et al. (10), nonculprit, nonobstructive lesions were examined by VH IVUS in 23 patients presenting with acute coronary syndromes and in 32 patients with stable CAD, demonstrating significantly higher incidence of TCFA in patients with acute coronary syndromes. An important finding of the present study is that TCFA were most frequently located in mixed plaques on MSCT. Accordingly, one could argue that mixed plaques might resemble high-risk lesions, because these lesions were also associated with other features of vulnerability on VH IVUS, such as an elevated amount of necrotic core tissue and less extensive calcification (18). Moreover, in studies comparing plaque type on MSCT between patients presenting with acute coronary syndromes and stable CAD, completely calcified plaques were less prevalent in patients presenting with acute coronary syndromes (5–7). Finally, a recent study exploring potential prognostic predictors of cardiovascular events on MSCT showed that mixed lesions were associated with adverse events on follow-up (19).
Ideally, features of TCFA would be determined on MSCT directly. Indeed, previous studies have attempted to characterize features of TCFA on MSCT (3). In comparison to grayscale IVUS, lipid core was identified on MSCT with an accuracy of 70% (3). Nevertheless, it is important to realize that the insufficient spatial resolution of MSCT precludes exact location of lipid accumulation in the plaque as well as visualization of the thin fibrous cap. Accordingly, direct identification of TCFA on MSCT is at present not feasible.

Study limitations. Several limitations of the study should be acknowledged. First, noninvasive and invasive examinations were performed within 1 month. Accordingly, minor changes in plaque burden and composition may have occurred. Second, no validation of lesion length or distance measurements on MSCT and IVUS was performed and differences between modalities may have affected the accuracy of our results to a minor extent. Third, VH IVUS is a relatively new technique. Therefore, more extensive validation in larger patient populations and with the different VH IVUS systems that are available remains to be seen, while also more standardized representation of VH IVUS data is needed. Fourth, no plaque density measurements were performed on MSCT as it remains uncertain whether these measurements are reproducible. Indeed, operator dependency as well as potential variations in contrast attenuation changes in plaque burden and composition may have occurred. Finally, MSCT is still associated with a substantial radiation dose, and administration of contrast material is required.

Conclusions

This study demonstrated a good correlation between quantification of calcium on MSCT and VH IVUS. In addition, plaque classification on MSCT paralleled relative plaque composition on VH IVUS, although VH IVUS provided more precise plaque characterization. Mixed plaques on MSCT were associated with high-risk features on VH IVUS, which suggests that MSCT observations might be useful for risk stratification. Further studies are needed to confirm the results.

Reprint requests and correspondence: Dr. Jeroen J. Bax, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, P.O. Box 9600, 2333 ZA Leiden, the Netherlands. E-mail: j.j.bax@lumc.nl.

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