Accuracy of 64-Slice Computed Tomography to Classify and Quantify Plaque Volumes in the Proximal Coronary System

A Comparative Study Using Intravascular Ultrasound

Alexander W. Leber, MD,*§ Alexander Becker, MD,* Andreas Knez, MD,* Franz von Ziegler, MD,* Marc Sirol, MD,§ Konstantin Nikolaou, MD,† Bernd Ohnesorge, PtID,‡ Zahi A. Fayad, PtID,§ Christoph R. Becker, MD,† Maximilian Reiser, MD,† Gerhard Steinbeck, MD,* Peter Boekstegers, MD*
Munich and Forchheim, Germany; and New York, New York

OBJECTIVES
We evaluated the accuracy of a new 64-slice computed tomography (CT) scanner, compared with intravascular ultrasound, to visualize atherosclerosis in the proximal coronary system.

BACKGROUND
Noninvasive determination of plaque composition and plaque burden may be important to improve risk stratification.

METHODS
In 20 patients, a 64-slice CT scan (Sensation 64, Siemens Medical Solutions, Forchheim, Germany) and an intravascular ultrasound investigation of vessels without stenosis >50% was performed. Diagnostic image quality with 64-slice CT was obtained in 36 vessels in 19 patients.

RESULTS
In these vessels, which were divided in 3-mm sections, 64-slice CT enabled a correct detection of plaque in 54 of 65 (83%) sections containing noncalcified plaques, 50 of 53 (94%) sections containing mixed plaques, and 41 of 43 (95%) sections containing calcified plaques. In 192 of 204 (94%) sections, atherosclerotic lesions were excluded correctly. In addition, 64-slice CT enabled the visualization of 7 of 10 (70%) sections revealing a lipid pool and could identify a spotty calcification pattern in 27 of 30 (90%) sections. The correlation coefficient to determine plaque volumes per vessel was $r^2 = 0.69$ ($p < 0.001$) with an underestimation of mixed and noncalcified plaque volumes ($p < 0.03$) and a trend to overestimate calcified plaque volumes by 64-slice CT. The interobserver variability to determine plaque volumes was 37%. Interobserver agreement to identify atherosclerotic sections was good (Cohen's kappa coefficient $= 0.75$).

CONCLUSIONS
We conclude that 64-slice CT reveals encouraging results to noninvasively detect different types of coronary plaques located in the proximal coronary system. The ability to determine plaque burden currently is hampered by mainly an insufficient reproducibility. (J Am Coll Cardiol 2006;47:672–7) © 2006 by the American College of Cardiology Foundation

Direct noninvasive determination of coronary atherosclerotic plaque morphology and plaque burden may have important value to improve risk stratification and to monitor the course of the disease. It has been established that evidence of coronary calcium, identified using computed tomography (CT), is an indicator for coronary artery disease and that the quantity of calcification is a strong predictor for coronary events (1,2). In addition, it has been shown that serial calcium measurements can illustrate the effect of drug therapies (3). However, there is striking heterogeneity among human atherosclerotic lesions, and coronary plaques often consist of noncalcified tissue. Thus, even in coronary vessels without calcified plaques, severe atherosclerosis may be present. Hence, the visualization of both calcified and noncalcified plaques is desirable. Recently, the potential of multi-detector computed tomography (MDCT) (4- and 16-slice) has been demonstrated to allow the detection and classification of coronary plaques and to determine vessel remodeling (4–6). However, thus far, the ability of MDCT to identify important morphological features of atherosclerotic lesions, such as the presence of a lipid core or the calcification pattern (spotty vs. wide), as well as the potential to determine plaque volumes is unknown. Therefore, the aim of the present study was to determine the accuracy of a new 64-slice MDCT scanner with improved spatial and temporal resolution to identify different types of coronary plaques and to determine plaque volumes in comparison to intravascular ultrasound (IVUS).
Abbreviations and Acronyms

CT = computed tomography
IVUS = intravascular ultrasound
MDCT = multi-detector computer tomography

METHODS

Patients. From August 2004 to February 2005, we performed a contrast-enhanced 64-slice MDCT investigation as part of a research protocol in 112 patients who were scheduled for coronary angiography because of suspected coronary artery disease and referral from an independent external cardiologist. In 20 of these patients (18 men, 2 women, 59 ± 9 years) IVUS was performed in one to three vessels as part of the invasive catheterization procedure to evaluate coronary vessels without angiographic evidence of a significant stenosis >50% diameter reduction. In 12 patients, no history of coronary artery disease was known. Eight patients had coronary artery disease with previous stent implantation. The MDCT was performed at least 1 day (range, 1 to 2 days) before coronary catheterization. In patients with heart rates >70 beats/min, 50 to 100 mg of metoprolol was administered orally 60 min before the CT scan. In the presence of contraindications for a beta-blocker or an unsatisfactory lowering of the heart rate, the scan was performed at even greater heart rates. Patients with atrial fibrillation, contraindications for the administration of contrast agent, or an unstable clinical condition were not enrolled. The institutional review board of the Medical University of Munich approved the research protocol, and all patients gave informed consent.

64-slice CT scanning technique. The CT angiography was performed using a Sensation 64-slice CT scanner (Sensation 64, Siemens Medical Solutions, Forchheim, Germany). A bolus of 80 ml of contrast agent (Solutrast 300, 300 mgI/ml, Altana, Konstanz, Germany) was injected intravenously (5 ml/s, 0.6 mm, gantry rotation speed was 330 ms per rotation, and tube voltage was 120 kV at a current of 550 to 750 mAs (depending on patient size) during 55% of the cardiac cycle (diastole) and a reduction of the current by 80% during the remaining time of the R-R interval. Per rotation, each detector is read out twice using a wobbling X-ray beam, resulting in 64 overlapping slices per rotation. This technology (z-sharp, Siemens Medical Solutions, Forchheim, Germany) allows one to generate slices with an overlap of 0.3 mm, resulting in a reconstructed slice thickness of approximately 0.4 mm. A detailed description of the technology is given elsewhere (7).

In heart rates >65 beats/min, a half scan algorithm was applied, and for heart rates >65 beats/min, a two-segment reconstruction-algorithm offering a maximal temporal resolution of 83 ms was used (7,8). Using retrospective ECG-gating, the optimal ECG-phase providing best image quality was chosen. 64-slice CT image analysis. The display setting used for lumen and plaque quantification was empirically determined in a subset of six patients (recruited from the study population). In each patient, four different coronary sites that were easy to identify because of their location next to landmarks were selected. The image display setting at each site was then manipulated so that the MDCT image equaled the IVUS image in size (external elastic membrane area) and pattern and allowed exact separation between vessel, surrounding tissue, plaque, and lumen. The values for window width and window level of the respective section were recorded and were set in relation to the mean intensity within the lumen at the corresponding site. The results of this analysis revealed that the optimal setting to detect plaque and outer vessel boundaries is obtained on average at a width representing 155% (range, 395 to 809 Hounsfield units [HU]) of the mean intensity within the lumen and at a level representing 63% of the mean intensity (range, 165 to 339 HU). By keeping the window level (65% of mean intensity within the corresponding lumen) and reducing width to 1, lumen measurements provided optimal matching with IVUS. An independent investigator who was not involved in the later comparative analysis performed those initial measurements.

To allow comparison to IVUS, the coronary artery was divided in 3-mm sections, each section was classified according to the following criteria: Any structure with a density of 130 HU or more that: 1) could be visualized separately from the contrast-enhanced coronary lumen (either because it was “embedded” within noncalcified plaque or because its density was above the contrast-enhanced lumen); 2) could be assigned to the coronary artery wall; and 3) could be identified in at least two independent planes was defined as calcified atherosclerotic plaque (4). Structures clearly assignable to the vessel wall (in at least two views) with densities less than the lumen contrast were classified as noncalcified plaque components (5,9). Plaques in which >50% of the plaque area was occupied by calcified tissue (in the respective 3-mm section) were classified as calcified, and lesions with <50% calcium as mixed and lesions without any calcium were classified as noncalcified lesions. In addition, we classified the pattern of calcified tissue as spotty (at least two calcium spots <2 mm² embedded in noncalcified plaque tissue) or wide calcification (calcified areas >2 mm²). In the next step, all sections were analyzed for the presence of hypodense spots (lipid pools) that were defined as structures >2 mm² revealing a density of at least 20 HU less than the average value of surrounding noncalcified plaque tissue. The plaque volume for each 3-mm section was determined by multiplying the maximum plaque area within this section by 3. By adding plaque volumes of all respective sections, vessel plaque burden was calculated. Two indepen-
dent investigators, both blinded to the IVUS results, did the analysis.

**IVUS.** We used a Volcano Eagle Eye IVUS-catheter (20-MHz, electronic transducer, Volcano Inc., Rancho Cordova, California) that accords to the technical requirements for IVUS systems recommended by the American College of Cardiology (10). The tip of the IVUS catheter was placed in the coronary vessel unless a diameter <2.5 mm was present. The pullback was performed automatically with 0.5 mm/s (Volcano Track Back II). The complete investigation was stored digitally, and the data sets were assessed offline by a cardiologist blinded to the 64-slice CT results. Because one IVUS pullback contains more than 1,000 frames, our analysis was performed by subsampling intervals of 1 mm acquired at diastole. As with MDCT, 3-mm sections were analyzed. 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 (10). The plaque volume for each 3-mm section was determined by multiplying the maximum plaque area by 3. By adding plaque volumes of all respective sections, vessel plaque burden was calculated.

Calcified plaques were defined as plaque tissue containing any tissue with an echogenicity as bright or brighter than the adventitia causing acoustic shadows with an arc of calcium >180° in the respective 3-mm section. Mixed plaques were defined as having an arc of calcium <180° in the respective 3-mm section. Finally, noncalcified plaques were defined as plaque tissue without acoustic shadowing. Furthermore, we defined plaques containing an echolucent zone (no signal) as lipid core plaques, and we specifically determined the pattern of calcium as either spotty (multiple small calcium spots, arc <90°) or wide (arc >90°) (11,12).

**Comparison of 64-slice CT and IVUS.** To ensure that the same corresponding coronary sections were always compared with IVUS and MDCT, we selected fiduciary points, such as side branches, characteristic calcifications, or stents, for the distal starting reference. The distances between the fiduciary points and the coronary ostium were measured using the longitudinal reconstructed IVUS data sets and multiplanar reconstructions of the 64-slice CT datasets to ensure that distance measurements were the same with both methods. A measurement-discrepancy of 1.5 mm per vessel was tolerated. In the case of larger discrepancies, our comparison was restricted to smaller subsections. Starting from the distal reference point the coronary vessel was analyzed in 3-mm intervals and each section was directly compared with both methods.

**Statistical analysis.** For comparison of plaque volumes obtained by 64-slice CT and IVUS, Bland–Altman analysis was performed. The paired Student *t* test was used to test for potential differences between mean values obtained by both methods. To determine the correlation of volume measurements by both methods, Spearman’s correlation coefficient was calculated. The interobserver variability for 64-slice CT measurements was calculated by the following formula: (volume observer 1 − volume observer 2) / [(0.5 × volume observer 1) + (0.5 × volume observer 2)], by averaging the values obtained for each individual patient the average variability was determined. For the reproducibility to detect atherosclerotic lesions within the respective sections, Cohen’s kappa coefficient was calculated. A p value <0.05 was considered to be significant.

**RESULTS**

We performed IVUS in 38 vessels in 20 patients. Beta-blockers to reduce the heart rate were given in 12 patients. During the 64-slice CT scan, 17 patients revealed heart rates <65 beats/min and 3 patients >65 beats/min. Diagnostic CT image quality was obtained in 19 patients and 36 vessels. A total of 365 sections were available for the comparison with IVUS; in 161 of these (26 vessels), atherosclerotic plaques were present. The use of 64-slice CT enabled a correct detection of plaque in 54 of 65 (83%) sections containing noncalcified plaques, 50 of 53 (94%) sections containing mixed plaques, and 41 of 43 (95%) sections containing calcified plaques, resulting in an accuracy of 90% to detect any plaque (145 of 161). In 192 of 204 (94%) sections, atherosclerotic lesions were correctly excluded. In addition to the ability to classify calcified, mixed, and noncalcified lesions, 64-slice CT enabled the visualization of lipid pools in 7 of 10 (70%) sections and enabled us to identify a spotty calcification pattern in 27 of 30 (90%) sections. In three sections without evidence for echolucency on IVUS, hypodense areas (lipid cores) were identified by 64-slice CT. In 314 of 365 sections (86%), consensus between IVUS and 64-slice CT was achieved regarding the morphologic classification (Table 1). The plaque type was misclassified by 64-slice CT in 23 of 145 atherosclerotic sections (Table 1).

Spearman’s correlation coefficient for plaque volumes determined by 64-slice CT and IVUS was *r*² = 0.69, *p* < 0.001. Bland–Altman analysis showed that noncalcified and mixed plaque volumes were systematically underestimated (59.8 ± 76.6 mm³ vs. 67.7 ± 67.9 mm³ and 47.7 ± 87.5 mm³ vs. 57.5 ± 99.4 mm³, *p* < 0.03). Calcified plaques were systematically overestimated (65.8 ± 110.0 mm³ vs. 53.2 ± 90.3 mm³, *p* = 0.19). The Bland–Altman plot and the correlation-diagram for determination of vessel-plaque volume are given in Figure 1. The interobserver variability for plaque-volume measurements by 64-slice CT was 37%.

| Table 1. Consensus Table of 64-Slice CT and IVUS to Detect and Classify Coronary Plaques |
|---------------------------------------------|-----------------|-----------------|-----------------|
| 64-Slice CT | None | Calcified | Mixed | Noncalcified |
| None | 192 | 2 | 3 | 11 |
| Calcified | 1 | 34 | 8 | 0 |
| Mixed | 1 | 7 | 38 | 4 |
| Noncalcified | 10 | 0 | 4 | 50 |

CT = computed tomography; IVUS = intravascular ultrasound.
Cohen's kappa coefficient for the sole detection of atherosclerotic sections was 0.75, indicating good agreement.

**DISCUSSION**

The newly developed 64-slice CT technology offers the opportunity to accurately identify different types of coronary plaques. Of particular interest is the finding that features that frequently are associated with plaque ruptures, such as lipid cores and spotty calcifications, can be imaged noninvasively (Figs. 2 and 3). The determination of plaque burden by this innovative technology is limited by an only moderate concordance to IVUS measurements and an insufficient reproducibility.

Clinical data concerning the accuracy of MDCT to identify atherosclerotic plaques in vivo are rare. The two existing studies using a 16-slice CT reported from a sensitivity of 91% and 95% to detect calcified and 78% and 58% for noncalcified lesions (5,6). Most probably, the improved spatial resolution of the scanner used in the present study increased the sensitivity to detect noncalcified lesions to 83%. Because of the high CT attenuation of calcified tissue, their differentiation from fibrous and lipid-rich lesions is easy. The subclassification of noncalcified plaques in contrast is more challenging. Previous reports consistently showed a wide overlap of density values measured within hyperechoic and hypoechoic plaques that substantially complicates a prospective discrimination (6,13,14). Taking into account the natural course of atherosclerotic plaque evolution, these overlapping density values are not surprising. Atherosclerotic lesions typically consist of multiple different components ranging from necrotic to calcified tissue (e.g., high-risk plaques with a lipid core and a thin fibrous cap may be either predominantly calcified [Stary IVa], fibrous [Stary IVb], or soft [Stary IVc], but all are assigned to Stary class IV), so that intrinsic CT attenuation of lesions even within the same Stary class may differ (15). Furthermore, do technical restrictions of CT prevent an accurate assessment of plaque densities, in particular because of partial volume effects caused by the high attenuation of contrast agent or calcifications (16)? However, other morphologic features of coronary plaques exist that may serve as potential targets for noninvasive imaging. Invasive studies demonstrated that lipid pools and spotty calcifications embedded in atherosclerotic lesions are associated with plaque vulnerability (11,12,17,18). Thus, the present study aimed to evaluate the potential of 64-slice CT to identify these features instead of classifying plaques on the basis of their density.

It is uniformly reported that plaques revealing large lipid cores constitute the majority of culprit lesions in acute coronary syndromes. So far, there is only one prospective study imaging coronary plaques before an acute coronary event. In this study Yamagishi et al. (19) underscored the critical importance of lipid core plaques. They found that 12 of 16 lesions that revealed a lipid core at baseline IVUS examination counted for 12 of 14 acute coronary events during a 22-month follow-up period.

Although our results are encouraging in the identification of lipid cores by means of 64-slice CT, there are some important limitations: 1) the sensitivity of IVUS to detect lipid pools is limited to 50% to 75%; and 2) all lipid pools detected in our study were located in large proximal segments. Hence, it has to be assumed that the true accuracy of 64-slice CT to detect lipid pools is significantly lower than observed here.

The pattern of calcification within plaques constitutes another potential morphologic target in particular for MSCT. Just recently, Ehara et al. (11) described the frequent presence of spotty calcium depositions in vulnerable plaques. Thus, our results indicate the unique potential of 64-slice CT to detect lipid pools is significantly lower than observed here.

Evidence suggests that coronary plaque burden and changes of plaque volume over the course of time may be important prognostic parameters; thus, one of the aims of the present study was to evaluate the accuracy of 64-slice...
CT to assess plaque burden noninvasively. Although promising, the results of our study clearly demonstrate the current limitations of 64-slice CT: technical restrictions concerning spatial and temporal resolution prevent an exact separation of lumen, plaque, and vessel wall. The major challenge for plaque quantification is the edge definition of the outer vessel boundary. Because coronary plaques and surrounding tissue are very heterogeneous, it is extremely difficult, if not impossible (with the given resolution), to define thresholds that would allow accurate automated or semiautomated edge detection. Therefore edge definition is, at least in part, always dependent on the respective investigator. As a consequence, we observed a high interobserver variability for 64-slice CT measurements and an only moderate concordance to IVUS measurements.

Study limitations. A potential limitation of the present study is the fact that we did not enroll consecutive patients. However, all patients in the present study were recruited from clinical routine without any additional preselection criteria (e.g., obese patients, low heart rates, older patients) that may have affected the 64-slice CT results. An important issue and limitation for all CT studies is the significant radiation exposure to the patient, which is in the range of 9 to 14 mSv with the current 64-slice CT-technology. This exposure is critical, especially if this technique is considered for preventative purposes in asymptomatic patients.

To find the optimal display settings allowing for the most accurate edge definition, we empirically determined image settings in a subset of our patients. Consequently, all results are related to these settings and may vary with the use of other settings. However, it is not likely those other settings will significantly improve the performance of 64-slice CT because only an improvement in resolution will diminish partial voluming and motion artifacts.

Figure 2. Lipid core within a mixed plaque detected by intravascular ultrasound (IVUS) and 64-slice computed tomography (CT). ca = calcium; lc = lipid core.

Figure 3. Noncalcified section with an embedded lipid core indicated by echolucency on intravascular ultrasound (IVUS) and hypodensity on 64-slice computed tomography (CT).
REFERENCES