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Noninvasive Detection and Evaluation of Atherosclerotic Coronary Plaques With Multislice Computed Tomography

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OBJECTIVES The aim of the present study was to evaluate the accuracy in determining coronary lesion configuration by multislice computed tomography (MSCT). The results were compared with the findings of intracoronary ultrasound (ICUS).

BACKGROUND The risk of acute coronary syndromes caused by plaque disruption and thrombosis depends on plaque composition rather than stenosis severity. Thus, the reliable noninvasive assessment of plaque configuration would constitute an important step forward for risk stratification in patients with known or suspected coronary artery disease. Just recently, MSCT scanners became available for general purpose scanning. Due to improved spatial and temporal resolution, this new technology holds promise to allow for differentiation of coronary lesion configuration.

METHODS The ICUS and MSCT scans (Somatom Volume Zoom, Siemens, Forchheim, Germany) were performed in 15 patients. Plaque composition was analyzed according to ICUS (plaque echogenity: soft, intermediate, calcified) and MSCT criteria (plaque density expressed by Hounsfield units [HU]).

RESULTS Thirty-four plaques were analyzed. With ICUS, the plaques were classified as soft (n = 12), intermediate (n = 5) and calcified (n = 17). Using MSCT, soft plaques had a density of 14 ± 26 HU (range −42 to +47 HU), intermediate plaques of 91 ± 21 HU (61 to 112 HU) and calcified plaques of 419 ± 194 HU (126 to 736 HU). Nonparametric Kruskal-Wallis test revealed a significant difference of plaque density among the three groups ($p < 0.0001$).

CONCLUSIONS Our results indicate that coronary lesion configuration might be correctly differentiated by MSCT. Since also rupture-prone soft plaques can be detected by MSCT, this noninvasive method might become an important diagnostic tool for risk stratification in the near future. (J Am Coll Cardiol 2001;37:1430–5) © 2001 by the American College of Cardiology

Coronary plaque disruption and subsequent thrombosis make coronary atherosclerosis a potentially life-threatening disease (1). Evidence suggests that atherosclerotic plaque composition and configuration are important predictors of plaque stability (2). The risk of plaque rupture seems to depend on plaque composition rather than on plaque volume. Most ruptures occur in plaques containing a soft, lipid-rich core that is covered by a thin and inflamed cap of fibrous tissue (3). Small ruptures often remain clinically silent, but more extensive plaque ruptures may cause the onset of unstable angina, myocardial infarction or sudden death (4).

Thus, the reliable noninvasive detection and classification of coronary lesions would constitute an important step forward in risk stratification of patients with known or suspected coronary artery disease (CAD).

In the past, coronary calcification scores, derived from electron beam computed tomography (EBCT) scans, were used as parameters to identify patients at risk for unheralded myocardial infarctions (5). A more precise differentiation of plaque configuration by EBCT fails because of technical limitations (6).

Although soft plaques might be detected by magnetic resonance imaging (MRI), especially when focusing on carotid arteries (7,8), MRI coronary angiography is still in the early stage of clinical research and further technical efforts are required to improve spatial resolution and signal to noise ratio (9–14). Multislice scanning is the first major technological breakthrough in computed tomography (CT) since the introduction of spiral CT in the early 1990s. These scanners allow for the simultaneous acquisition of four slices, 500-ms scanner rotation and up to 125-ms temporal resolution (15,16). These improvements have the advantage of considerably faster coverage of the heart volume, when compared with conventional single-slice scanning. The increased scan speed allows for single breath-hold examinations with thinner collimated slice widths. Thus, improved spatial and contrast resolution can be achieved which is indispensable for high resolution examinations such as CT angiography of the coronary arteries.

Initial results indicate that this technique does not only

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Abbreviations and Acronyms

CAD = coronary artery disease
CT = computed tomography
EBCT = electron beam computed tomography
HU = Hounsfield unit
ICUS = intracoronary ultrasound
LAD = left anterior descending artery
MRI = magnetic resonance imaging
MSCT = multislice computed tomography
PTCA = percutaneous transluminal coronary angioplasty
RCA = right coronary artery

allow for the detection of coronary lesions, but also for the differentiation of lesion configuration. The aim of the present study was to evaluate the accuracy of the determination of coronary plaque configuration by multislice CT (MSCT). The results were compared with findings of intracoronary ultrasound (ICUS) in patients undergoing percutaneous coronary interventions.

METHODS

Patients and study protocol. We report on a series of 15 patients who were included in a prospective trial. The study protocol was approved by the local ethics committee. All patients gave informed consent before inclusion in the study. The study population consisted of patients with chronic stable angina due to at least one high grade stenosis in the left anterior descending coronary artery (LAD) or the right coronary artery (RCA) scheduled for ICUS-guided percutaneous transluminal coronary angioplasty (PTCA). The angiographic criteria for enrollment in the study included a lesion with a stenosis of >70% and the absence of severe vessel angulations (>90°) in the proximal vessel segments. Angiographic exclusion criteria were left main stem disease, total occlusions, vessel diameter <2.0 mm and bypass lesions. Clinical exclusion criteria were renal failure (creatinine >1.5 mg/dl), unstable angina pectoris, acute myocardial infarction, known allergic reactions to contrast media, elevated exposure to radiation in the last 12 months (>15 mSv), pregnancy, hyperthyroidism (basal thyroid-stimulating hormone <0.03 mU/liter in combination with elevated thyroid hormone levels in the peripheral blood), known epilepsy, liver dysfunction (glutamic oxaloacetic and glutamic pyruvic transaminase values >3 × reference value), or advanced heart failure (New York Heart Association III to IV). According to the study protocol, MSCT of the heart was performed within 24 h prior to the intervention. Immediately before the intracoronary intervention, ICUS was performed to analyze the vessel configuration proximal to or at the target lesion. To ensure that the identical plaques were assessed by the different techniques and to allow correlations, landmarks were used, that is, origin of side branches and distance to target lesion.

ICUS and PTCA. The transfemoral Judkins technique was used for all interventions. Before PTCA and ICUS, all patients received a bolus of 10,000 IU of unfractionated heparin intra-arterially. All patients were receiving aspirin 100 mg/d for at least 24 h. Selective angiography was performed in multiple views before and after intervention. After passage of the guidewire across the target lesion, ICUS was performed under fluoroscopic guidance (UltraCross 3.2F, 30-MHz coronary imaging catheter, axial/lateral resolution: 0.07/0.20 mm, SCIMED, Boston Scientific Corporation, San Jose, California) after the intracoronary administration of 0.2 mg nitroglycerin. Continuous ultrasound images were received as the catheter was automatically pulled back (0.5 mm/s) from preferably 10 mm distal to the lesion into the guiding catheter. The images were immediately digitalized by using echoPlaque-Software (Indec Systems Inc, Mountain View, California). After the ultrasound images were obtained, the ultrasound catheter was withdrawn and the intervention was performed according to standard techniques.

Definitions. Intracoronary lesions were identified as atherosclerotic vessel alterations, narrowing the vessel lumen >40%. Only those plaques were analyzed that could be clearly identified and in which plaque burden could be visualized in its total extension. Plaque configuration was classified according to ICUS criteria as recently reported (17–20). Briefly, the classification consists of three groups.

SOFT PLAQUE. More than 80% of the plaque area was composed of tissue with an echogenity lower than the echogenity of the adventitia (arc of lesion calcium <90%).

INTERMEDIATE PLAQUE. More than 80% of the plaque area was composed of tissue producing echoes as bright or brighter than the adventitia but without acoustic shadows (arc of lesion calcium <90%).

CALCIFIED PLAQUE. This plaque involves bright echoes with acoustic shadowing accompanying >90° of the vessel wall circumference.

The ICUS classification was performed by one observer who was blinded to the MSCT results, and was repeated by a second independent observer to account for reproducibility. In case of different classifications, the plaques were reevaluated until consensus of the two observers was achieved.

MSCT. For MSCT, a Somatom Volume Zoom (Siemens, Forchheim, Germany) scanner was used. This technology allows the application of dedicated spiral algorithms that provide up to 125 ms of temporal resolution (spatial resolution up to 10 line pairs/cm, pixel size 0.29 × 0.29 mm) and ECG-triggered heart phase selective image reconstruction. After a low-dose precontrast spiral scan (collimation 2.5 mm, pitch 1.5, 140 kV, 60 mA, rotation time 500 ms) with simultaneously recorded ECG signal, a test bolus of 20 ml of contrast medium and a chaser bolus of 20 ml of saline solution were injected through an 18-gauge

catheter into an antecubital vein to determine the circulation time. For the contrast-enhanced scan (collimation 1.0 mm, pitch 1.5, 140 kV, 300 mA, rotation time 500 ms), 150 ml of contrast agent (400 mg/ml) was injected at 4 ml/s followed by 30 ml of saline solution. These scans were performed after the sublingual application of 400 μg nitroglycerin. The start of the contrast-enhanced scan was adapted to the calculated circulation time. All scans were performed during one breath-hold.

The gantry rotation time is 500 ms; however, partial scan technique is used for multislice data acquisition. This means that only data from 180° of scan rotation are used for image reconstruction. This provides a temporal resolution of approximately half the rotation time, which is 250 ms in the used technology (15). If the heart rate increases to >65 beats/min, current reconstruction software switches from a single-phase algorithm (using data from one heart cycle only) to a bi-phase algorithm by using image data obtained within two consecutive heart cycles. The use of image data from more than one cardiac cycle with these advanced segmented reconstruction algorithms allows us to further improve temporal resolution, which is necessary to achieve sufficient image quality in higher heart rates. If the number of heart cycles is two, a temporal resolution of up to 125 ms can be obtained. Theoretically, sampling of data obtained within more than two heart cycles is feasible and results in a further improvement of temporal resolution. However, spatial resolution decreases. Thus, current standard reconstruction software solely provides the use of single- and bi-phase reconstruction algorithms (16).

The raw data of the scans were reconstructed using algorithms optimized for ECG-gated multislice spiral reconstruction. In our series of patients, image reconstruction was performed in the diastolic phase with a relative retrospective gating of 38% to 50% for the right coronary artery and 50% referred to the RR interval for the left coronary artery (Fig. 1). For plaque detection, contrast media-enhanced axial slices were analyzed. The reconstructed image data of the CT angiography were transferred to a computer workstation for postprocessing (3D Virtuoso, Siemens, Forchheim, Germany).

Definitions. Intracoronary lesions were identified as atherosclerotic vessel alterations, narrowing the vessel lumen >40%. Only those plaques were analyzed that could be clearly identified and in which plaque burden could be visualized in its total extension. To determine plaque configuration by MSCT, density measurements (as expressed by Hounsfield units [HU]) at 16 randomly selected points in at least four (LAD) or more (RCA) different axial slices within the plaque area were performed in each plaque.

Statistics. Continuous variables were described by their means and standard deviations. To evaluate potential within-patient effects, a two-factor analysis of variance with the factors "plaque configuration" and "patient group," controlled for interaction of the two factors, was performed. Nonparametric Kruskal-Wallis test was used to compare the means of the density measurements of the three groups. p values <0.05 were considered to identify significant differences. All analyses were done using Prism 3.0 (GraphPad Software Inc., San Diego, California).

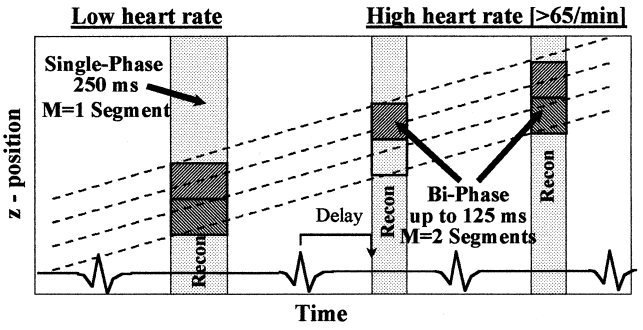

Figure 1. Retrospectively ECG-gated four-slice spiral reconstruction using segmented reconstruction with 500-ms rotation time. **Left:** Single phase reconstruction with a temporal resolution of 250 ms ($T_{rotation}/2 = 250$ ms). Reconstruction with M = 1 sectors is performed for heart rates ≤65 beats/min. **Right:** Bi-phase reconstruction with a temporal resolution of up to 125 ms ($T_{rotation}/4 = 125$ ms) using image data obtained within two consecutive RR intervals. Reconstruction with M = 2 sectors is performed for heart rates >65 beats/min. **Recon:** Image reconstruction at a defined time point within the RR interval. In our series: relative retrospective gating with 38% to 50% referred to the RR interval (in early diastole) for image reconstruction of the right coronary artery, and approximately 50% RR (in mid diastole) for reconstruction of the left coronary artery. **z-position:** patient position.

RESULTS

The ICUS and MSCT scans were performed in 15 patients. All scans showed sufficient image quality for analysis and no patient was excluded. Almost artifact-free images could be reconstructed in our study population with a mean heart rate of 68.5 ± 13.6 (ranging from 56 to 108) beats/min. The patient characteristics are summarized in Table 1.

A total of 40 plaques were detected by both methods. Six plaques were excluded from the analysis because the plaque burden could not be completely visualized by MSCT due to subtotal vessel lesions. This was due to the fact that blood flow was severely impaired in the vessel segments distally to these lesions, prohibiting adequate contrast enhancement in the MSCT images. The 34 remaining plaques (RCA n = 12, LAD n = 22) were further analyzed by both methods with respect to lesion configuration.

Table 1. Patient Characteristics and Cardiovascular Risk Factors

	n (%)
Age (yrs)	58 ± 10 (44–71)
Male gender	13 (86.7%)
Female gender	2 (13.3%)
Smoking	9 (60.0%)
Diabetes mellitus	4 (26.7%)
Hyperlipidemia	11 (73.3%)
Hypertension	10 (66.7%)
Body mass index, (kg/m^2)	27.35 ± 3.05
Family history	7 (46.7%)
Myocardial infarction	7 (46.7%)

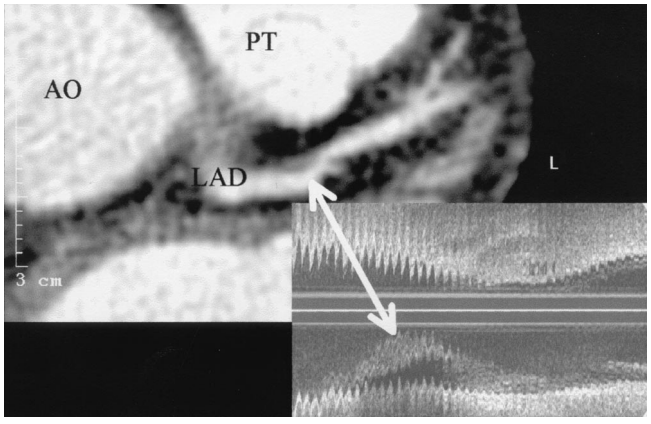

Figure 2. Soft plaque as assessed by MSCT and ICUS. **Left:** MSCT image, axial slice. **Right:** ICUS image, longitudinal slice. Plaque marked by an **arrow.** Ao = aorta; ICUS = intracoronary ultrasound; LAD = left anterior descending artery; MSCT = multislice computed tomography; PT = pulmonary trunk.

On ICUS, 12 plaques were classified as soft (Fig. 2), 5 plaques as intermediate (Fig. 3) and 17 plaques as calcified (Fig. 4). No lesions classified as "soft plaques" actually contained calcifications, whereas 3 of 5 intermediate plaques contained echogenic sprinkles, indicating the presence of calcium. Using MSCT, soft plaques (n = 12) showed a mean density of 14 ± 26 HU (ranging from −42 to +47 HU), intermediate plaques (n = 5) of 91 ± 21 HU (ranging from 61 to 112 HU), and calcified plaques (n = 17) of 419 ± 194 HU (ranging from 126 to 736 HU) (Fig. 5).

Nonparametric Kruskal-Wallis test revealed a statistically significant difference of plaque density as determined by MSCT among the three groups ($p < 0.0001$).

To study the occurrence of within-patient effects on the outcome of the density measurements, the study group was subdivided into subgroups according to the number of plaques detected in each patient on ICUS and MSCT: group 1—plaques of patients with 1 plaque only (n = 4 plaques of 4 patients); group 2—plaques of patients with 2 plaques (n = 10 plaques of 5 patients); group 3—plaques of patients with 3 plaques (n = 15 plaques of 5 patients); and group 4—plaques of patients with 5 plaques (n = 5 plaques of 1 patient).

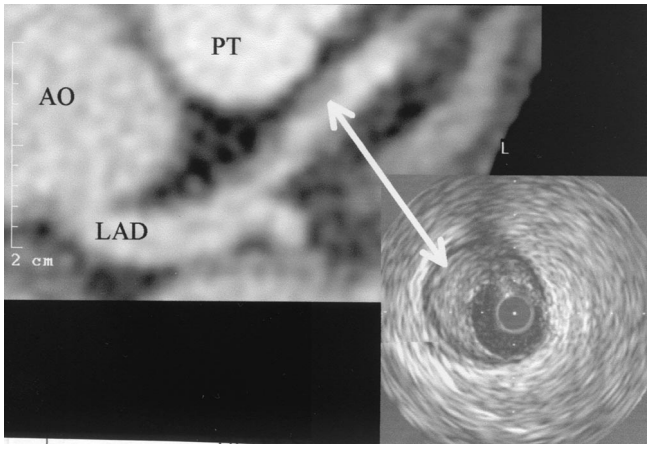

Figure 3. Intermediate plaque as assessed by MSCT and ICUS. **Left:** MSCT image, axial slice. **Right:** ICUS image, sagittal slice. Plaque marked by an **arrow.** Ao = aorta; ICUS = intracoronary ultrasound; LAD = left anterior descending artery; MSCT = multislice computed tomography; PT = pulmonary trunk.

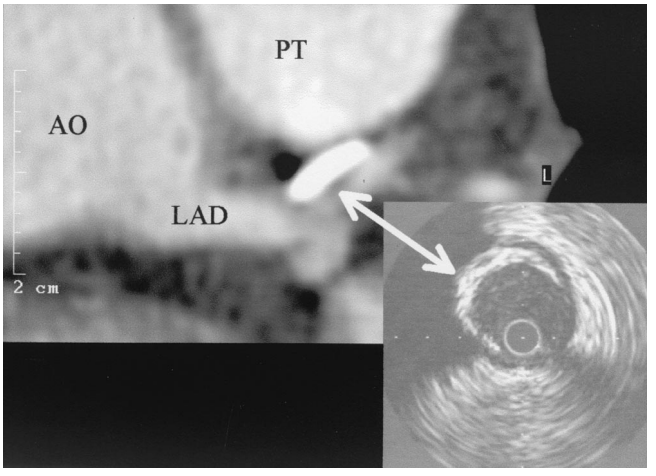

Figure 4. Calcified plaque as assessed by MSCT and ICUS. **Left:** MSCT image, axial slice. **Right:** ICUS image, sagittal slice. Plaque marked by an **arrow.** Ao = aorta; ICUS = intracoronary ultrasound; LAD = left anterior descending artery; MSCT = multislice computed tomography; PT = pulmonary trunk.

A two-factor analysis of variance with the factors "plaque configuration" and "patient group," controlled for interaction of the two factors, was performed. In this analysis, the variable "patient group" was not significant ($p = 0.876$), and there was no interaction between "plaque configuration" and "patient group" ($p = 0.817$). The variable "plaque configuration," however, had a highly significant influence on the density measurements ($p < 0.0001$). Thus, within-patient effects did not influence the outcome of the test results significantly.

DISCUSSION

Our data suggest that the newly developed CT technology does offer the possibility to differentiate plaque configura-

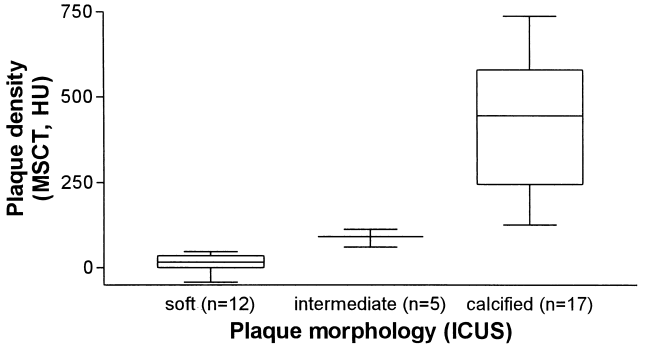

Figure 5. Comparison of plaque configuration (ICUS) and plaque density (MSCT). Box-and-whiskers plot showing range and quartiles. The box extends from the 25th percentile to the 75th percentile, with a line at the median (the 50th percentile). The whiskers extend above and below the box to show the highest and lowest values. HU = Hounsfield unit; ICUS = intracoronary ultrasound; MSCT = multislice computed tomography.

tion noninvasively with a high accuracy. We found a strong correlation of tissue density measurements within the plaque and the qualitative ultrasound classification "soft, intermediate and calcified" (Fig. 2 to 4). By determining plaque density, an accurate classification of the plaques can be achieved. Our findings appear to be of special interest with regard to risk assessment in patients with known or suspected CAD. In particular, the early detection of rupture-prone soft plaques, which are known to be of crucial importance for the occurrence of acute coronary syndromes (1,2,22,23), is obviously possible. Thus, adequate therapy may be initiated before plaque rupture occurs (4,24).

Plaque configuration score. The determination of plaque echogenity as derived from ICUS corresponded well to plaque density as measured by MSCT. Recently published data on density measurements, performed with a conventional single-slice CT scanner in plaques located in carotid arteries, confirm our results: plaque densities of soft plaques (39 ± 12 HU) and fibrous plaques (90 ± 24 HU) were within comparable ranges. Furthermore, the density measurements in both groups showed statistically significant differences (25).

There was no overlap in the mean density values among the three groups of plaques. Thus, especially soft plaques with a presumably lipid-rich core might be identified by density values <50 HU. Intermediate plaques showed a density ranging from 50 to 119 HU. Lesions with a density >120 HU correlated to calcified plaques in the ICUS studies. A more precise view by MSCT on plaque configuration by visualizing lipid cores, fibrous caps or calcified sprinkles is at present restricted due to limited spatial resolution. Further clinical studies are necessary to confirm the relevance of a plaque score that is based on these initial findings.

Comparison with other imaging techniques. Electron beam CT and MRI have been shown to be capable of some configurational assessment in the coronary system. However, the limitations of EBCT to reliably differentiate plaque configuration include limited spatial resolution of three-dimensional visualizations of the coronary arteries and the fact that only sequential ECG-triggered 3-mm slices can be obtained, resulting in poorer image quality (26). Further technical improvements are on their way, but clinical data on this issue are still missing.

Promising results have been reported for MRI (8–11,27). The most important advantage of MRI is the avoidance of radiation exposure. However, major limitations are the low signal-to-noise ratio and lower spatial resolution (>1 mm) when compared with MSCT scanning. This results currently in poorer image quality and less reproducibility.

Study limitations. In the presented series, special attention was focused on LAD and RCA, and no left circumflex artery was studied. Thus, further studies should additionally focus on the differentiation of plaque configuration within this vessel. Intracoronary ultrasound was used as a gold standard for in vivo tissue analysis within the coronary arteries. Limitations of this technology in the detection of soft plaques have been reported (28). However, just recently, Yamagishi et al. (29) reported about the correlation between soft plaques as assessed and classified by ICUS and the occurrence of major cardiac events. New MSCT criteria for the noninvasive assessment of plaque configuration and composition by determining plaque density were evaluated. Further prospective studies in larger patient cohorts are needed to validate the presented data. Additionally, our MSCT findings need to be confirmed by histopathologic studies.

CONCLUSIONS

Our results indicate that the characterization of coronary lesion configuration, which is at present a domain of ICUS, might be reliably performed by noninvasive MSCT. Since also rupture-prone soft plaques can be detected by MSCT, this noninvasive method might become an important diagnostic tool for risk stratification in patients with known or suspected CAD. In addition, this technology holds promise to offer the possibility to monitor plaque stabilization in patients receiving, for example, lipid-lowering therapy noninvasively.

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