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Cardiac Imaging

Noninvasive Evaluation With Multislice Computed Tomography in Suspected Acute Coronary Syndrome

Plaque Morphology on Multislice Computed Tomography Versus Coronary Calcium Score

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Objectives Our aim was to evaluate the atherosclerotic plaque burden and morphology as determined by 64-slice multislice computed tomography (MSCT) coronary angiography in relation to the calcium score in patients presenting with suspected acute coronary syndrome (ACS).

Background The absence of coronary calcium during coronary calcium scoring has been proposed to rule out significant coronary artery disease (CAD). However, data in patients presenting with suspected ACS are scarce.

Methods In 40 patients (age 57 ± 11 years, 26 men) presenting with suspected ACS, MSCT coronary angiography in combination with coronary calcium scoring was performed before conventional coronary angiography. MSCT angiograms were evaluated for the presence or absence of coronary atherosclerotic plaque and the presence or absence of obstructive (≥50% luminal narrowing) CAD. In addition, plaque type was determined, and findings were related to the calcium score.

Results Coronary artery disease was observed in 38 patients, of whom 10 patients had nonobstructive and 28 patients had obstructive CAD, confirmed by conventional coronary angiography in all patients. In patients with CAD, plaques were distributed as follows: 39% noncalcified plaques, 47% mixed plaques, and 14% calcified plaques. Coronary calcium was detected in 27 patients, of whom 10 had a score >400. In 13 (33%) patients, no coronary calcium was observed, but in 11 (85%), atherosclerotic plaques were detected on MSCT angiography.

Conclusions In patients presenting with suspected ACS, noncalcified plaques are highly prevalent and the absence of coronary calcium does not reliably exclude the presence of (significant) atherosclerosis. This information may be of value to improve our understanding of the potential role of MSCT in this patient population. (J Am Coll Cardiol 2008;52:216–22) © 2008 by the American College of Cardiology Foundation

Coronary artery calcium score (CS) has been demonstrated to have an excellent prognostic value in asymptomatic individuals (1). A very low rate of cardiac death and myocardial infarction (0.4%) over 3 to 5 years has been reported for individuals without detectable calcium. In contrast, event rates as high as 7.1% have been reported for individuals with extensive calcium, reflected by a CS >1,000 (1). The positive relationship between a high CS and an elevated cardiac event rate may be explained by the fact that an increase in coronary calcium reflects an increase in overall coronary plaque burden. However, the presence of coronary calcium is considered to represent a more advanced and stable stage of atherosclerosis, and noncalcified plaque burden, which may represent the more initial stages of atherosclerotic disease, is not appreciated with calcium scoring. Moreover, preliminary data in patients with acute coronary syndrome (ACS) suggest a larger contribution of noncalcified plaques to the overall plaque burden compared with that in patients with stable coronary artery disease (CAD) (2,3). As a consequence, a low CS may significantly underestimate the overall coronary plaque burden in the setting of ACS.

Over recent years, multislice computed tomography (MSCT) has matured into a reliable imaging modality for

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noninvasive evaluation of the coronary arteries. With this technique, the coronary arteries are directly visualized; not only the degree of atherosclerosis but also the degree of stenosis can be evaluated with high accuracy (4). Accordingly, the technique may be of interest in the diagnostic work-up of patients presenting with suspected ACS in the emergency department (5). A particular advantage is the fact that noncalcified atherosclerosis is also identified, thus providing a more accurate evaluation of the underlying atherosclerotic plaque burden. However, this is at the cost of contrast administration and a higher radiation dose. At present, data on how the CS relates to observations obtained with MSCT coronary angiography in patients presenting with suspected ACS are scarce.

The aim of the present study, therefore, was to assess the presence of coronary calcium in patients with suspected ACS, and to evaluate the overall atherosclerotic burden and plaque morphology in relation to the CS.

Methods

Study population. Forty consecutive patients who were admitted in our hospital with suspected ACS were included in the study. All patients underwent noninvasive coronary angiography with MSCT to evaluate the presence or absence of obstructive (≥50% luminal narrowing) CAD, before conventional invasive coronary angiography was performed. Both investigations were performed within 24 h of each other. Patients presenting with ST-segment elevation myocardial infarction were not included and were directly referred to conventional coronary angiography. However, patients with other electrocardiographic (ECG) changes were enrolled. Contraindications to MSCT included known allergy to iodine contrast media (supra)ventricular arrhythmias and renal insufficiency (serum creatinine >120 mmol/l). MSCT was performed within the clinical diagnostic work-up of patients, and the results presented are observational findings.

MSCT, data acquisition. MSCT examinations were performed with a 64-slice Toshiba multislice Aquilion 64 system (Toshiba Medical Systems, Otawara, Japan). In all patients, a noncontrast enhanced scan was performed before MSCT angiography to assess the total coronary calcium burden. Collimation was 4 × 3.0 mm and rotation time 500 ms. Tube current and voltage were 200 mA and 120 kV.

For the contrast-enhanced scan, collimation was 64 × 0.5 mm and rotation time was 400 or 450 ms, depending on heart rate. Tube current and voltage were 300 mA (range 250 to 400 mA) and 120 kV (range 100 to 135 kV), respectively. Total amount of contrast (Iomeron 400, Altana, Konstanz, Germany) was 90 to 110 ml, followed by a saline flush of 50 ml, both injected at 5 ml/s. Automated detection of peak enhancement in the aortic root was used to time the scan. In all patients, imaging was performed during an inspiratory breath hold and electrographic gating. In patients with a heart rate >65 beats/min, beta-blocking agents were administered before MSCT imaging if no contraindications for beta-blockade were present. No additional nitroglycerin was given for MSCT imaging. Although no ECG X-ray modulation was applied, care was taken to minimize radiation dose by using lower kV and mA values in patients with either normal or small posture. The average radiation dose for MSCT was 15.6 to 16.2 mSv.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CABG = coronary artery bypass graft surgery
CAD = coronary artery disease
CS = calcium score
MSCT = multislice computed tomography
PCI = percutaneous coronary intervention

MSCT, data analysis. CORONARY ARTERY CS. All data were evaluated on a remote workstation using dedicated software (Vitrea 2, Vital Images, Plymouth, Minnesota). In each patient, coronary calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 HUs, and the total CS was calculated based on Agatston (6).

CORONARY ANGIOGRAPHY. In all patients, the complete coronary arterial tree was assessed for the presence of coronary plaques (regardless of their severity) by 2 experienced observers, by consensus. Segments with previously implanted stents were excluded from the analysis. The location of each plaque was documented according to the segmentation model of the American Heart Association/American College of Cardiology (7), and 1 coronary plaque was assigned per coronary segment. Each plaque was subsequently visually classified as obstructive or nonobstructive using a 50% threshold of luminal narrowing. For each patient, the total number of diseased coronary segments (segments containing plaques) and the number of coronary segments with nonobstructive as well as obstructive plaques were determined.

PLAQUE MORPHOLOGY. Subsequently, each interpretable plaque was classified as follows: 1) calcified plaque = plaque with a high density compared with the contrast-enhanced vessel lumen; 2) mixed plaque = plaque with noncalcified and calcified elements within a single plaque; or 3) noncalcified plaque = plaque having a lower density compared with the contrast-enhanced vessel lumen.

CONVENTIONAL CORONARY ANGIOGRAPHY. Conventional coronary angiography was performed according to the standard techniques. To obtain vascular access, the femoral approach with the Seldinger technique was used. An experienced observer blinded to the MSCT data performed a visual evaluation of the coronary angiograms. Coronary arteries were divided in 17 segments according to the guidelines of the American Heart Association/American College of Cardiology (7). Obstructive CAD was defined as ≥50% luminal narrowing of ≥1 coronary segment. In addition, patients with previous coronary stenting were

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considered as having single-vessel or multivessel CAD as appropriate.

Finally, based on electrocardiographic findings, left ventricular wall motion abnormalities, angiographic lesion morphology, and revascularization strategy, culprit lesions were identified.

Statistical analysis. Results are presented as mean values ± SD. Categorical data were compared with the chi-square test. Finally, the prevalence of the different coronary CS was compared with the presence of (non)obstructive CAD. A p value <0.05 was considered as statistically significant.

Results

Study population. In total, 40 consecutive patients (26 men, age 57 ± 11 years) with suspected ACS were included in this study. The baseline characteristics of the patients are summarized in Table 1. All patients presented to the emergency department with suspected ACS. The majority of patients were diagnosed as having an intermediate risk of ACS (Thrombolysis In Myocardial Infarction [TIMI] III: 12 [30%] and TIMI IV: 9 [23%]), whereas 18 patients were classified as having a low risk of ACS (TIMI I: 9 [23%] and TIMI II: 9 [23%]) (8). Only 1 patient had a high risk of ACS (TIMI V: 1 [2%]). In total, 6 patients with positive enzymes were included of whom 3 patients had no abnormalities on their ECG, whereas 3 patients presented with negative T waves on their ECG. An additional 2 patients showed positive troponin values during serial testing after MSCT. In total, 11 (28%) patients presented with previous percutaneous coronary intervention (PCI) (in 9 patients in combination with stent implantation). The diagnosis of ACS was confirmed by coronary angiography in 25 patients. Single- and multivessel disease (based on the presence of a significant stenosis or previous PCI in the corresponding coronary artery) was observed in 12 and 16 patients, respectively. PCI was performed in 17 patients whereas 4 patients were referred for coronary artery bypass grafting (CABG). The remaining 4 patients were treated conservatively.

Table 1 Baseline Characteristics of the Study Population

Number of patients	40
Gender (M/F)	26/14
Age (yrs)	57 ± 11
Risk factors for CAD	
Average body mass index (kg/m^2)	27 ± 3
Diabetes mellitus	6 (15%)
Hypertension	20 (50%)
Hypercholesterolemia	18 (45%)
Family history of CAD	17 (43%)
Current smoking	19 (48%)
History	
Previous PCI	11 (28%)
Previous MI	10 (25%)
(Non)obstructive CAD as observed on CAG*	
Nonobstructive CAD	10 (25%)
Single-vessel CAD	12 (30%)
Multiple-vessel CAD	16 (40%)
Average number of segments with significant stenoses	1.6 ± 1.8
Average number of segments with any atherosclerotic plaques	5.6 ± 3.4

*In 2 patients, no coronary plaques could be demonstrated.

CAD = coronary artery disease; CAG = conventional coronary angiography; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Coronary artery CS. In all 40 patients, the coronary CS could be obtained. In 13 (33%) patients, coronary calcium was absent. Coronary calcium was detected in 27 patients (67%), in whom 10 (37%) there was a score >400. A CS of 1 to 9 was shown in 3 (8%) patients, whereas CS was 10 to 100 in 8 (20%) patients. In 6 (15%) patients, CS was 101 to 400, and in 10 (25%) patients a CS >400 was identified.

MSCT coronary angiography. LESION CHARACTERISTICS. On a segmental basis, a total of 565 coronary segments were available for analysis after exclusion of 10 segments due to previous coronary stenting.

In the remaining segments, coronary plaques were identified in 224 (40%) segments. Lesions were nonobstructive (<50% luminal narrowing) in 159 (71%) segments, whereas lesions were deemed obstructive in 65 (29%) segments. Noncalcified plaque was identified in 87 (39%) of the 224 diseased coronary segments on MSCT. In 105 (47%) diseased segments, mixed plaque was observed, whereas calcified plaque was present in 32 (14%) segments (Fig. 1). In total, 36 culprit lesions were identified. In these lesions, plaque morphology was noncalcified in 18 (50%), mixed in 16 (44%), whereas only 2 (6%) lesions were calcified.

PATIENT CHARACTERISTICS. In 2 (5%) patients, complete absence of coronary plaques was demonstrated on MSCT. Nonobstructive CAD was observed in 10 (25%) and obstructive CAD was present in 28 (70%) patients, respectively.

In 12 (30%) patients, single-vessel disease was demonstrated, whereas in 16 (40%) patients multivessel disease was present, confirmed by conventional coronary angiography in all patients.

Patients with multivessel disease presented with relatively more mixed (55%) and less noncalcified plaques (30%) as compared with patients with nonobstructive CAD and patients with single-vessel CAD. However, the percentage of calcified plaques remained fairly constant between the 3 groups (12% in nonobstructive CAD vs. 14% in single-vessel CAD vs. 15% in multivessel CAD). The relative distribution of plaque types for patients with nonobstructive CAD, single-vessel CAD, and multivessel CAD is illustrated in Figure 2.

Coronary CS versus the presence of significant stenosis and atherosclerotic plaque on MSCT angiography. In Figure 3, the relation between the presence of various coronary CS and the presence of CAD is illustrated. Importantly, in 5 (39%) of the 13 patients without coronary calcium, obstructive CAD was present despite the absence of any calcium. In all of these patients, revascularization by means of PCI was performed. An example of a patient

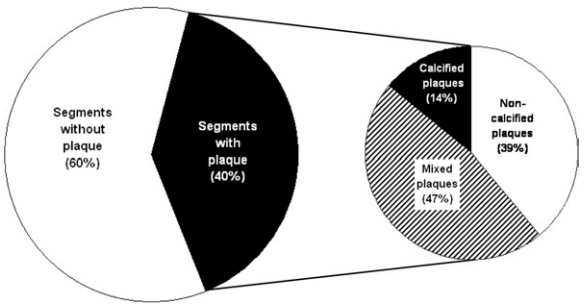

Figure 1 **Percentage of Segments With and Without Plaque, and Prevalence of the Different Plaque Types**

(Left) Percentage of segments with plaque **(solid area)** and segments without plaque **(open area)**. **(Right)** Prevalence of the different plaque types: noncalcified plaque **(open area)**, mixed plaque **(hatched area)**, and calcified plaque **(solid area)**.

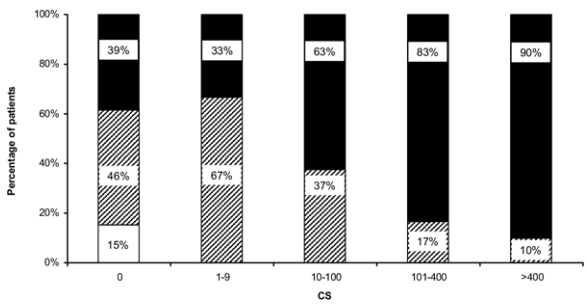

Figure 3 **Presence of (Non)Obstructive CAD and the Presence of Plaque for the Different CS Groups**

Note that a calcium score (CS) of 0 in only 15% of patients corresponded with complete absence of coronary artery disease (CAD), whereas 39% presented with obstructive CAD. **Open bar** = normal; **hatched bars** = plaque with nonobstructive CAD; **solid bars** = plaque with obstructive CAD.

without coronary artery calcium, but with obstructive CAD, is provided in Figure 4.

Considering patients with elevated coronary CS, the majority showed obstructive CAD on MSCT; significant stenosis was detected in 5 (83%) of the 6 patients with CS 101 to 400 and in 9 (90%) of the 10 patients with CS >400. All of the patients with CS 101 to 400 and significant stenosis underwent subsequent revascularization (3 patients underwent PCI and 2 patients underwent CABG). Of the patients with CS >400 and significant stenosis, revascularization was performed in 7 (78%) (PCI: n = 5 patients, CABG: n = 2 patients). The remaining patients were treated conservatively with optimal medical treatment.

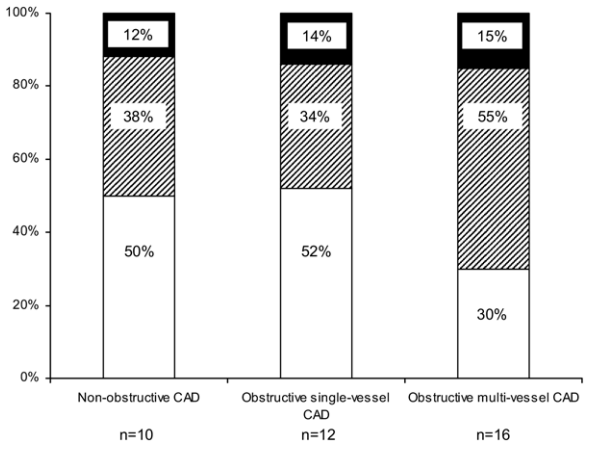

Figure 2 **Presence of Different Plaque Types in the Various Patient Groups**

Patients with multivessel disease presented with relatively more mixed (55%) and less noncalcified plaques (30%) as compared with patients with nonobstructive coronary artery disease (CAD) and patients with single-vessel CAD. The prevalence of calcified plaques remained constant between the 3 groups (nonobstructive CAD: 12% vs. single-vessel CAD: 14% vs. multivessel CAD: 15%). **Open bars** = noncalcified plaques; **hatched bars** = mixed plaques; **solid bars** = calcified plaques.

Discussion

The main finding of the present study is that a considerable proportion of patients with suspected ACS present without coronary calcium on MSCT. In 13 (33%) of the 40 patients with suspected ACS, no coronary calcium was observed. However, in 11 (85%) of these patients, coronary artery plaques could be observed, causing a significant stenosis in 5 (39%) of these patients.

Indeed, in line with this observation, a high proportion (39% of total plaque burden) of noncalcified plaques was present in the whole study population. Even in multivessel disease (which may reflect more advanced CAD) a large proportion of the atherosclerotic plaques were still noncalcified with a similar amount of calcified plaques compared with that seen in patients with either nonobstructive CAD or single-vessel disease.

In the last decade, the prognostic value of CS assessment has been extensively investigated in mainly asymptomatic cohorts. Indeed, Shaw et al. (9) demonstrated in a large cohort of 10,377 asymptomatic patients who underwent electron-beam computed tomography for CS screening that the 5-year risk-adjusted survival for patients with CS ≤10 was 99.0% compared with 95.0% for patients with CS >1,000 (9). It is widely accepted that the coronary CS is related to the total atherosclerotic burden and can, therefore, provide long-term prognostic information in asymptomatic patients (10).

However, in patients presenting with suspected ACS, the goal is to establish the presence of significant stenoses as the cause of acute chest pain. Accordingly, the CS may be less reliable in this setting since the presence of coronary calcium is not specific for obstructive CAD. Although a positive relation exists between the amount of coronary calcium at a site and the severity of stenosis at that site, this relation is nonlinear (11). Moreover, noncalcified lesions are not detected, potentially further limiting the use of calcium scoring in ACS.

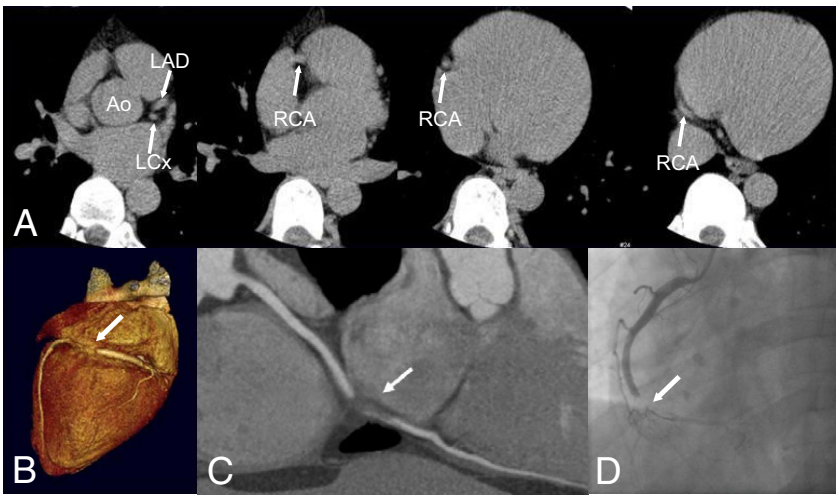

Figure 4 **Example of a Patient Without Coronary Artery Calcium but With Obstructive CAD**

This patient presented with suspected acute coronary syndrome. Multislice computed tomography showed no coronary artery calcium **(A)**. However, obstructive noncalcified plaque and superimposed thrombus was observed in the distal segment of the right coronary artery on multislice computed tomography. **(B)** Volume-rendered reconstruction. **(C)** Multiplanar reconstruction, **arrow** indicating obstructive coronary artery disease (CAD) in right coronary artery (RCA). This finding was confirmed by conventional coronary angiography. **(D)** Conventional coronary angiography showing obstructive CAD in RCA **(arrow)**. Ao = aorta; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery.

Indeed, in ACS, there appears to be a tendency toward a lower completely calcified plaque burden. In the present study, only 14% of the plaques observed were calcified, with 86% of lesions containing noncalcified tissue. This finding is in line with previous studies. Recently, similar findings were reported by Schuijf et al. (2), who studied differences in plaque composition and distribution as assessed with MSCT in 46 patients presenting with ACS compared with that in patients with stable CAD. It was demonstrated that in patients with stable CAD a significantly larger portion of the plaques was calcified as compared with that seen in patients presenting with ACS ($p < 0.001$). Similarly, Hoffmann et al. (12) showed that in culprit lesions of patients with ACS, noncalcified tissue was constantly present while none of the culprit lesions was exclusively formed by calcified plaque. In contrast, Mollet et al. (13) showed that completely calcified plaques tend to be more frequently encountered in patients with stable CAD, with calcified lesions contributing to 65% of the total plaque burden. Similar results were found by Hausleiter et al. (14), who investigated plaque morphology in a stable population consisting of 161 patients with an intermediate risk for significant CAD. The authors showed that the majority of patients (98 [61%]) had calcified plaques. Importantly, even in this cohort of patients with stable CAD and a high prevalence of calcified plaques, noncalcified plaques were present in 16% of patients without any coronary calcium.

In our study, we also explored the prevalence of the different plaque types among patients with nonobstructive CAD, obstructive single-vessel CAD, or obstructive multivessel CAD. A trend in plaque distribution between the 3 groups was observed. Patients with obstructive multivessel CAD appeared to have less noncalcified plaques (30%) and more mixed plaques (55%) as compared with patients with nonobstructive CAD (50% and 38%, respectively) and obstructive single-vessel CAD (52% and 34%, respectively). This progression from completely noncalcified to partially calcified could potentially be regarded as reflecting the development of atherosclerotic lesions over time. Interestingly, although one could assume that patients with multivessel CAD would have more advanced disease and, therefore, more completely calcified plaques, the percentage of calcified plaques appeared to remain constant among the 3 groups (12% in nonobstructive CAD, 14% in obstructive single-vessel CAD, and 15% in obstructive multivessel CAD). Accordingly, calcifications appear to contribute to only a relatively small portion of coronary plaque burden over the whole range from subclinical to more advanced disease in ACS, indicating that mere CS is not sufficient for a diagnostic work-up in this population. Possibly, these observations may also have implications for the effectiveness of antiatherosclerotic therapies. Of interest, Nicholls et al. (15) recently demonstrated that noncalcified plaque components may be more susceptible to regression by medical therapies that target atherosclerotic risk factors. In contrast, calcified plaques were less likely to reduce in size in this study. These observations suggest that assessment of coronary calcium alone may not be optimal to identify patients likely to derive the greatest benefit from aggressive antiatherosclerotic treatment. Possibly, noninvasive coronary angiography, which can provide a more reliable estimate of noncalcified and calcified plaque burden, may have incre-

mental value. Importantly, however, thus far no prospective data are available to support this hypothesis.

Clinical implications. In the current study, obstructive CAD was present in 11 (46%) of the 24 patients with low CS (CS <100). Similar findings have been reported by Rubinshtein et al. (16), who examined the extent of CAD, using 64-slice MSCT, in 231 (predominantly stable) patients with a zero or low (<100) CS. In the patients without detectable calcium (n = 125), CAD was observed in 25 (20%) patients, with obstructive lesions in 9 (36%). Expanding the analysis to patients with low CS (defined as CS <100), significant CAD was observed in 18 (32%). Accordingly, the authors concluded that the absence of coronary calcium or a low CS in symptomatic patients does not reliably exclude (significant) CAD (16). The precise role of MSCT in patients presenting with suspected ACS is at present still unclear. However, our study shows that these patients frequently present with noncalcified plaques. Accordingly, it appears that MSCT coronary angiography provides more information as compared with calcium scoring and may be preferred. Evidently, the use of MSCT in the setting of suspected ACS needs further study, although the recently published appropriateness criteria have indicated that MSCT may provide a suitable alternative in patients with low-to-intermediate pre-test likelihood of ACS (17).

Indeed, as Hoffmann et al. (18) recently showed, noninvasive assessment of coronary anatomy by MSCT may be of use in the triage of patients presenting with acute chest pain in the emergency department. In 89 patients, ACS was ruled out by standard clinical care, whereas 14 patients were diagnosed with ACS. High negative predictive values of 100% for both the absence of significant stenosis and for the absence of coronary atherosclerotic plaque were demonstrated. Similar observations have been reported recently by other groups (5,19,20). Accordingly, MSCT may have the potential to facilitate early discharge of patients with acute chest pain but with inconclusive evaluation (18).

Study limitations. Several limitations need to be addressed. First, the patient population described in this study is relatively small, and the results will need to be confirmed in larger populations of symptomatic patients. Also, only conventional coronary angiography was performed, and no comparison between MSCT and intravascular ultrasound was available for the classification of noncalcified, mixed, and calcified plaque. However, this was not the purpose of the present study; previous studies have demonstrated that classification of plaque type into noncalcified, mixed, and calcified with MSCT is both accurate and reproducible (21–23).

Finally, more general limitations inherent to MSCT need to be mentioned. The radiation burden of MSCT is still high, and, at the moment, the technique remains limited to patients with low heart rate, making administration of beta-blocking agents necessary before MSCT (24). However, administration of beta-blocking agents is part of the treatment of ACS in general, and the need for heart rate control is, therefore, not an important limitation in this patient population. In this study, the average radiation dose for MSCT was 15.6 to 16.2 mSv. Accordingly, the currently used protocol still required a substantial radiation dose. Particularly in younger female patients, use of MSCT should be treated with caution due to a higher lifetime cancer risk, as recently emphasized by Einstein et al. (25). Extensive effort, therefore, is currently invested in the development of dose-reduction protocols. Recently, Husmann et al. (26) described the feasibility of low-dose computed tomographic angiography with prospective ECG gating. In this study, the authors were able to obtain good image quality at an average dose of 1.1 to 3.0 mSv. Other developments include the introduction of 320-slice computed tomographic angiography, which allows prospective image acquisition without any overlap in a single rotation (27). Accordingly, substantial dose reduction may be achieved in the near future using novel acquisition protocols.

Finally, due to blooming artifacts, diagnostic accuracy of MSCT imaging is currently limited in patients with severe coronary calcifications and previous coronary stenting.

Conclusions

In patients presenting with acute chest pain, noncalcified plaques are highly prevalent. As a result, the absence of coronary calcium does not reliably exclude the presence of atherosclerosis or even obstructive CAD. This information may be of value to improve our understanding of the potential role of MSCT in this patient population.

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