Multimodality imaging in chronic coronary artery disease

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Chapter 6

Non-invasive evaluation with multi-slice computed tomography in suspected acute coronary syndrome: plaque morphology on multi-slice computed tomography versus coronary calcium score

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Abstract

Introduction: 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 acute coronary syndrome (ACS) are scarce. The aim of the present study was to evaluate the atherosclerotic plaque burden and morphology as determined by 64-slice multi-slice computed tomography (MSCT) coronary angiography in relation to the calcium score (CS) in patients presenting with suspected ACS.

Methods: In 40 patients (57±11 years, 26 men) presenting with suspected ACS, MSCT coronary angiography in combination with coronary calcium scoring was performed prior to 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 CS.

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

Conclusions: In patients presenting with suspected ACS, non-calcified plaques are highly prevalent and 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.

Introduction

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 >1000.[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 non-calcified 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 non-calcified plaques to the overall plaque burden as compared to 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 the recent years, multi-slice computed tomography (MSCT) has matured into a reliable imaging modality for non-invasive 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 also non-calcified atherosclerosis is 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 non-invasive 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 hours of each other. Patients presenting with ST elevation myocardial infarction were not included and were directly referred to conventional coronary angiography. However, patients with other ECG changes were enrolled. Contra-indications 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 presented results are observational findings.

MSCT

Data acquisition

MSCT examinations were performed with a 64-slice Toshiba Multi-slice Aquilion 64 system (Toshiba Medical Systems, Otawara, Japan). In all patients a non-contrast enhanced scan was performed prior to MSCT angiography to assess the total coronary calcium burden. Collimation was 4x3.0 mm and rotation time 500 ms. Tube current and voltage were 200 mA and 120 kV.

For the contrast enhanced scan, collimation was 64x0.5 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 90-110 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 prior to MSCT imaging if no contra-indications 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 15.6-16.2 mSv.

Data analysis

Coronary artery calcium score

All data were evaluated on a remote workstation using dedicated software (Vitrea 2, Vital Images, USA). In each patient coronary calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 HU, 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 two 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 one coronary plaque was assigned per coronary segment. Each plaque was subsequently visually classified as obstructive or non-obstructive 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 non-obstructive 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 non-calcified and calcified elements within a single plaque, or 3. non-calcified 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 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 considered as having single- or multi-vessel 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 the χ^2 test. Finally the prevalence of the different coronary calcium scores 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, 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 intermediate risk of ACS (TIMI III: 12 (30%) and TIMI IV: 9 (23%)), whereas 18 patients were classified as having low risk of ACS (TIMI I: 9 (23%) and TIMI II: 9 (23%)).[8] Only one patient had 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 ACS was confirmed by coronary angiography in 25 patients. Single- and multi-vessel disease (based on the presence of a significant stenosis or previous PCI in the corresponding coronary artery) was observed in respectively 12 and 16 patients. PCI was performed in 17 patients whereas 4 patients were referred for CABG. The remaining 4 patients were treated conservatively.

Table 1. Baseline characteristics of the study population.

Characteristic	
Nr. 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*	
Non-obstructive CAD	10 (25%)
Single vessel CAD	12 (30%)
Multiple vessel CAD	16 (40%)
Average nr. of segments with significant stenoses	1.6 ± 1.8
Average nr. of segments with any atherosclerotic plaques	5.6 ± 3.4

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

Coronary artery calcium score

In all 40 patients the coronary calcium score could be obtained. In 13 (33%) patients coronary calcium was absent. Coronary calcium was detected in 27 patients (67%) of whom 10 (37%) >400.
A CS of 1-9 was shown in 3 (8%) patients, whereas CS was 10-100 in 8 (20%) patients. In 6 (15%) patients, CS was 101-400, 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 was 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 non-obstructive (<50% luminal narrowing) in 159 (71%) segments, whereas lesions were deemed obstructive in 65 (29%) segments.
Non-calcified 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 (**Figure 1**). In total, 36 culprit lesions were identified. In these lesions, plaque morphology was non-calcified in 18 (50%), mixed in 16 (44%), whereas only 2 (6%) lesions were calcified.

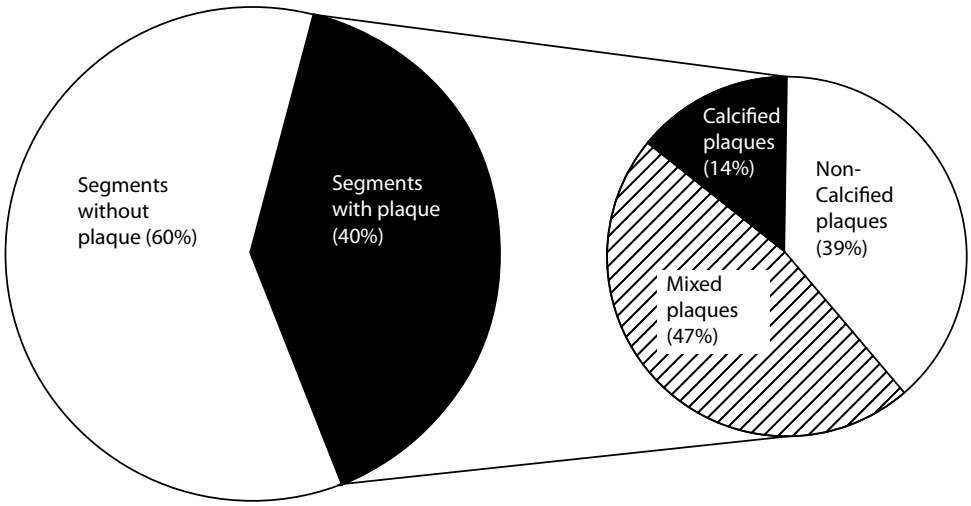

Figure 1. Percentage of segments with and without plaque, and prevalence of the different plaque types. Left panel: percentage of segments with plaque (black area) and segments without plaque (white area). Right panel: prevalence of the different plaques types: non-calcified plaque (white area), mixed plaque (hatched area), and calcified plaque (black area).

Patient characteristics

In 2 (5%) patients, complete absence of coronary plaques was demonstrated on MSCT. Non-obstructive 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 multi-vessel disease was present, confirmed by conventional coronary angiography in all patients.

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

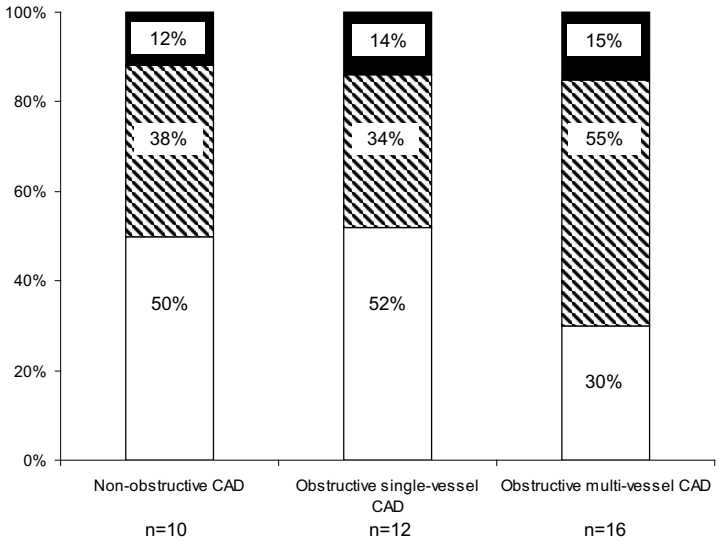

Figure 2. Presence of different plaque types in patients with non-obstructive CAD, in patients with single-vessel CAD, and in patients with multi-vessel CAD. Open bars = non-calcified plaques, hatched bars = mixed plaques, and black bars = calcified plaques. Patients with multi-vessel disease presented with relatively more mixed (55%) and less non-calcified plaques (30%) as compared with patients with non-obstructive CAD and patients with single-vessel CAD. The prevalence of calcified plaques remained constant between the 3 groups (non-obstructive CAD: 12% vs. single-vessel CAD: 14% vs. multi-vessel CAD: 15%).

Coronary calcium score versus the presence of significant stenosis and atherosclerotic plaque on MSCT angiography

In **Figure 3**, the relation between the presence of various coronary calcium scores 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 without coronary artery calcium, but with obstructive CAD is provided in **Figure 4** .

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

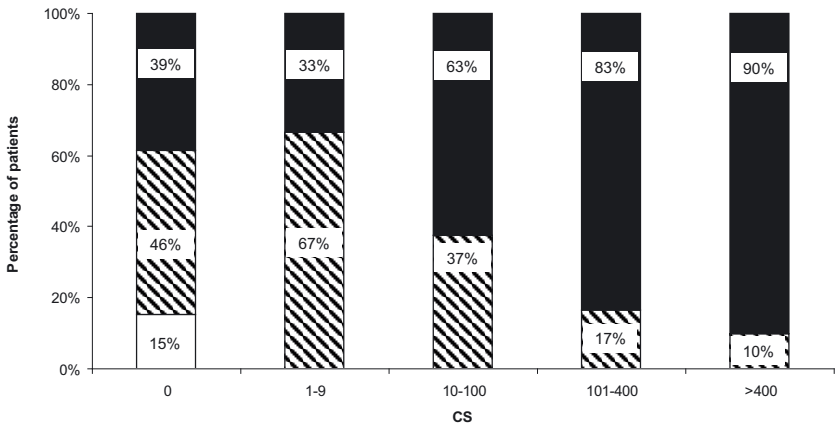

Figure 3. Presence of (non-)obstructive CAD and the presence of plaque for the different calcium score groups. Open bar = normal, hatched bars = plaque with non-obstructive CAD, and black bars = plaque with obstructive CAD. Note that a calcium score of 0 in only 15% corresponded with complete absence of CAD, whereas 39% presented with obstructive CAD.

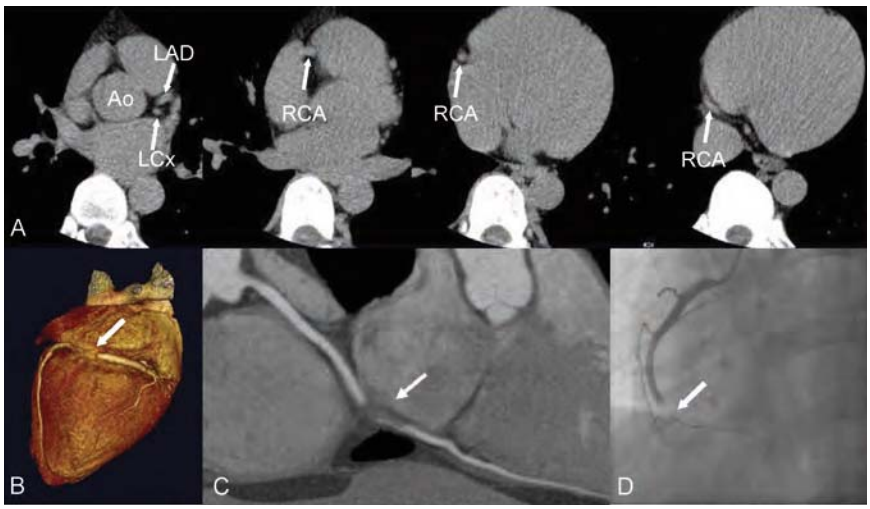

Figure 4. Example of a patient without coronary artery calcium but with obstructive CAD. This patient presented with suspected ACS. MSCT showed no coronary artery calcium (panel A, Ao = Aorta, LAD = left anterior descending coronary artery, RCA = right coronary artery, LCx = left circumflex coronary artery). However, obstructive non-calcified plaque and superimposed thrombus was observed in the distal segment of the right coronary artery on MSCT (panel B: volume rendered reconstruction, panel C: multiplanar reconstruction, white arrows indicating obstructive CAD in RCA). This finding was confirmed by conventional coronary angiography. Panel D: conventional coronary angiography showing obstructive CAD in RCA (white arrow).

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 non-calcified plaques was present in the whole study population. Even in multi-vessel disease (which may reflect more advanced CAD) still a large proportion of the atherosclerotic plaques were non-calcified with a similar amount of calcified plaques as compared to patients with either non-obstructive 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. demonstrated in a large cohort of 10377 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 to 95.0% for patients with CS >1000.[9] It is widely accepted that the coronary calcium score 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 calcium score 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 non-linear.[11] Moreover, non-calcified lesions are not detected; potentially further limiting the use of calcium scoring in ACS.

Indeed, in ACS, there appears to be a tendency towards a lower completely calcified plaque burden. In the present study, only 14% of the observed plaques were calcified, with 86% of lesions containing non-calcified 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 as compared to 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 patients presenting with ACS ($P < 0.001$). Similarly, Hoffmann et al.[12] showed that in culprit lesions of patients with ACS non-calcified 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 had calcified plaques (98 (61%)). Importantly, even in this cohort of patients with stable CAD and high prevalence of calcified plaques, non-calcified 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

either non-obstructive CAD, obstructive single-vessel CAD and obstructive multi-vessel CAD. A trend in plaque distribution between the 3 groups was observed. Patients with obstructive multi-vessel CAD appeared to have less non-calcified plaques (30%) and more mixed plaques (55%), as compared with patients with non-obstructive CAD (50%, 38% respectively) and obstructive single-vessel CAD (52%, 34% respectively). This progression from completely non-calcified to partially calcified could potentially be regarded as reflecting the development of atherosclerotic lesions over time. Interestingly, although one could assume that patients with multi-vessel 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 non-obstructive CAD, 14% in obstructive single-vessel CAD and 15% in obstructive multi-vessel 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 diagnostic work up in this population. Possibly, these observations may also have implications for the effectiveness of anti-atherosclerotic therapies. Of interest, Nicholls et al.[15] recently demonstrated that non-calcified 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 anti-atherosclerotic treatment. Possibly, non-invasive coronary angiography, which can provide a more reliable estimate of non-calcified and calcified plaque burden, may have incremental 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 non-calcified plaques. Accordingly, it appears that MSCT coronary angiography provides more information as compared to 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 and colleagues recently showed, non-invasive assessment of coronary anatomy by MSCT may be of use in the triage of patients presenting with acute chest pain in the emergency

department.[18] 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 as 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]

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 non-calcified, mixed and calcified plaque. However, this was not the purpose of the present study; previous studies have demonstrated that classification of plaque type into non-calcified, 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 prior to 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 15.6-16.2 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 CTA 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 CTA 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, non-calcified 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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