Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

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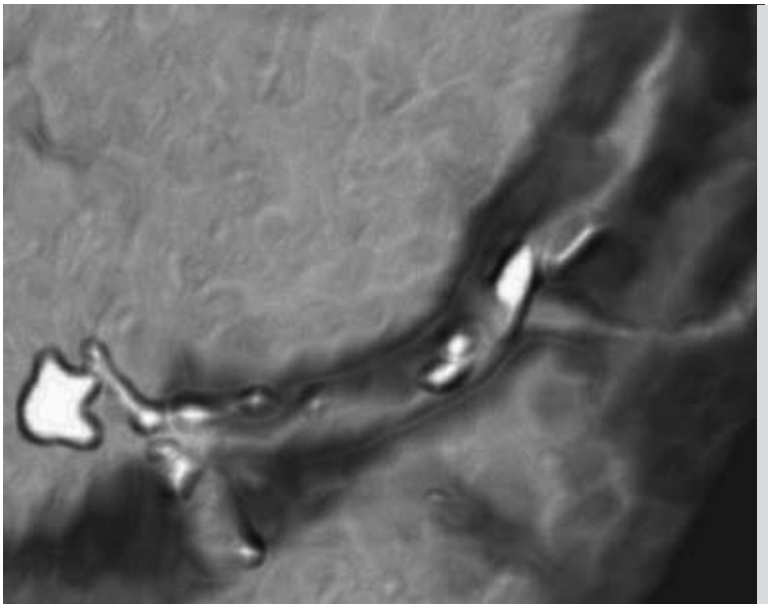

Part IV

Coronary Plaque Imaging and Prognostification

Chapter 18

Differences in Plaque Composition and Distribution in Stable Coronary Artery Disease versus Acute Coronary Syndromes; Non-Invasive Evaluation with Multi-Slice Computed Tomography

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Acute Cardiac Care 2007; 9: 48-53

Abstract

Background

Plaque composition rather than degree of luminal narrowing may be predictive of acute coronary syndromes (ACS). The purpose of the study was to compare plaque composition and distribution with multi-slice computed tomography (MSCT) between patients presenting with either stable coronary artery disease (CAD) or ACS.

Methods

MSCT was performed in 22 and 24 patients presenting with ACS or stable CAD, respectively. Coronary lesions were classified as calcified, non-calcified or mixed while signal intensity (SI) was measured.

Results

In patients with stable CAD, the majority of lesions were calcified (89%). In patients with ACS, less calcifications were observed with a greater proportion of non-calcified (18%) or mixed (36%) lesions ($P<0.001$). Accordingly, mean SI of plaques was significantly less in ACS (320 ± 201 HU versus 620 ± 256 HU in stable CAD, $P<0.001$). Dividing lesions in the ACS group according to culprit versus non-culprit vessel location resulted in no significant difference in average SI between these 2 groups while still lower as compared to stable CAD ($P<0.001$).

Conclusions

In patients with ACS, significantly less calcifications were present as compared to stable CAD. Moreover, even in non-culprit vessels, multiple non-calcified plaques were detected, indicating diffuse rather than focal atherosclerosis in ACS.

Introduction

Non-ST-elevation acute coronary syndromes (ACS) are recognized as among the most frequent and important manifestations of coronary artery disease (CAD) and contribute to a considerable percentage of both morbidity and mortality. In addition, the occurrence of an ACS is associated with an elevated risk of further coronary incidents within the subsequent year [1].

It is widely acknowledged that local thrombus formation due to plaque rupture or erosion plays a pivotal role in the pathogenesis of ACS. Consequently, plaque composition rather than the degree of luminal narrowing may be predictive of the patient's risk for further coronary events. Extensively calcified lesions most likely represent atherosclerosis at later stages of remodeling and may reflect more stable lesions [2]. On the other hand, earlier stages of atherosclerosis that lack the presence of calcium deposits may be more prone to rupture with subsequent occurrence of acute events. Recent studies indicate a higher degree of inflammation in patients presenting with unstable clinical conditions, resulting in diffuse destabilization of atherosclerotic plaques in the entire coronary tree [3;4]. Indeed, multiple sites of rupture-vulnerable plaque may be present rather than one site of complex plaque or thrombus, explaining the increased incidence of recurrent ACS, repeat intervention and coronary bypass grafting in the subsequent year [5].

During the past few years, MSCT has emerged as a new modality to evaluate the presence of significant CAD through direct visualization of the coronary arteries. Besides the assessment of coronary artery stenoses, the technique allows visualization of atherosclerotic plaques. As a result, the technique may potentially be used to assess plaque composition. Indeed, few recent studies have demonstrated the feasibility of differentiation between calcified, non-calcified or mixed plaques based on differences in signal intensity (SI) [6]. Since the availability of non-invasive coronary angiography with MSCT is continuously expanding, the technique will increasingly be used to identify patients at either low- or high- risk for developing coronary events. Accordingly, its potential to differentiate between various patterns of atherosclerotic lesions needs to be explored. Eventually, this may prove to provide additional information useful for refinement of risk stratification and may allow early institution of appropriate therapy to prevent further events.

The purpose of the present study was to compare plaque composition and distribution between patients presenting with either stable CAD or non-ST-elevation ACS.

Methods

Study populations

The study group consisted of 22 patients presenting with ACS and 24 age- and gender matched patients with known, stable CAD; all underwent MSCT and invasive coronary angiography. Referral for coronary angiography was based on the presence of symptoms, abnormal or inconclusive previous exercise ECG and/or nuclear testing. Only patients in sinus rhythm without contraindications to MSCT

were included. Exclusion criteria were: (supra-) ventricular arrhythmia, renal insufficiency (serum creatinine >120 mmol/L), known allergy to iodine contrast media, severe claustrophobia and pregnancy. All patients gave written informed consent to the study protocol, which was approved by the local ethics committees.

MSCT data acquisition

Data acquisition was performed at 2 centers (the Eberhard-Karls-University, Tübingen, Germany and the Leiden University Medical Center, Leiden, the Netherlands). 16-slice MSCT was performed using either a Sensation Siemens (Siemens, Germany) or Toshiba Aquilion (Toshiba Medical Systems, Japan) scanner. In all patients, imaging was performed during electrocardiographic gating and the administration of a bolus of non-ionic contrast agent with a flow rate of 4 ml/s, as previously described [7-9].

Data evaluation

Data were evaluated on a remote workstation using dedicated software (Vitrea, Vital Images, USA). For each patient, the entire coronary arterial tree was inspected for the presence of coronary plaques (regardless of their severity). For this purpose, knowledge from invasive coronary angiography was used in order to ensure most optimal lesion detection. Lesions identified on the MSCT were recorded and classified as being interpretable or not. Interpretable lesions were subsequently visually classified as calcified, non-calcified or mixed plaques. Examples of each type of lesion are provided in Figure 1.

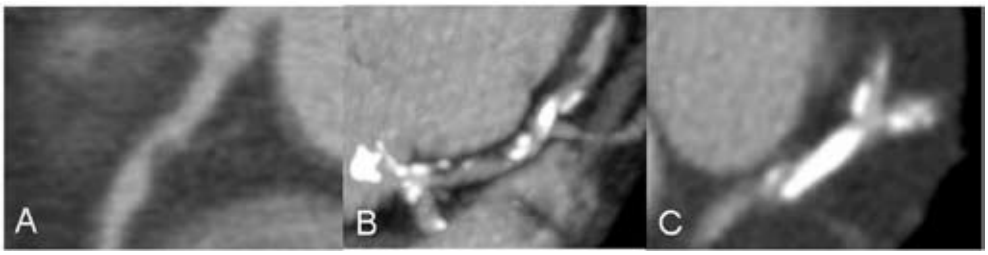

Figure 1. Example of the different lesion types as visually assigned on the MSCT images. Panel A: non-calcified lesion; Panel B: mixed plaque; Panel C: dense calcified lesion.

In each plaque, SI was measured in 3 regions of interest of each 2-3 mm^2, placed in subsequent axial slices. Subsequently, the average SI was calculated. The location of each lesion was documented according to the American Heart Association-American College of Cardiology segmentation [10]. Lesions observed in segments 1, 2, 5, 6 and 11 (proximal and mid right coronary artery, left main, proximal left anterior descending coronary artery and proximal left circumflex coronary artery) were considered to be located proximally in the coronary arteries. In patients presenting with ACS, further distinction was made between lesions located in the culprit coronary artery versus elsewhere. Culprit vessels were identified using electrocardiographic findings, left ventricular wall motion abnormalities, angiographic lesion morphology, as previously described [11;12].

Statistical analysis

Continuous variables were described by their means and standard deviations. Comparisons between patient groups were performed using 1-way ANOVA for continuous variables and the χ^2 test with Yates' correction for categorical variables. Nonparametric Mann-Whitney and Kruskall-Wallis tests were used to compare the means of the plaque SI between the different groups. All statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, Il, USA). A P-value <0.05 was considered to indicate statistical significance.

Results

Patient characteristics

The baseline characteristics of the patients are summarized in Table 1. No significant differences in risk factors were present between the 2 groups. By invasive angiography, the average number of coronary arteries with a ≥50% stenosis was 1.5 ± 1.4 and 2.1 ± 1.0 in patients with respectively stable CAD and ACS, and was not significantly different between the 2 groups. By MSCT, the average number of vessels with any evidence of atherosclerotic lesions (including coronary arteries with both ≥50% as well as coronary arteries with only lesions <50% diameter narrowing) however, was

Table 1. Baseline characteristics of the study population.

	Stable CAD	ACS
Nr. patients	24	22
Gender (M/F)	22/2	21/1
Age (yrs)	62 ± 11	61 ± 12
Risk factors for CAD		
Average Body Mass Index (kg/m^2)	29 ± 4	26 ± 3
Diabetes mellitus type 2	11 (46%)	10 (46%)
Hypertension	20 (83%)	15 (68%)
Hypercholesterolemia	20 (83%)	19 (86%)
Family history of CAD	7 (29%)	12 (56%)
Current smoking	12 (50%)	13 (59%)
History		
Previous PCI/CABG	6/2	6/6
Previous MI	6	13
Significant CAD as observed on CAG		
No significant CAD	9 (38%)	2 (9%)
Single vessel CAD	3 (13%)	5 (23%)
Multiple vessel CAD	12 (50%)	12 (55%)
Average nr. of coronary arteries with significant stenoses	1.5 ± 1.4	2.1 ± 1.0
Average nr. of coronary arteries with any atherosclerotic plaques	2.0 ± 1.0	2.6 ± 0.7

Abbreviations: ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CAG: conventional coronary angiography; PCI: percutaneous intervention; MI: myocardial infarction.

significantly higher in the ACS patients (2.6 ± 0.7 as compared to 2.0 ± 1.1, P<0.05). In patients with ACS, 57 diseased coronary arteries were identified, with a total of 106 diseased segments. In patients with stable CAD, atherosclerotic lesions were present in 101 segments (in 48 coronary arteries).

Spatial distribution of calcified, mixed or non-calcified lesions

In total, 207 segments with a total 258 coronary lesions were identified, of which 228 (88%) lesions (in 175 evaluable segments) were of sufficient image quality to assign plaque type and measure average SI.

In patients with ACS, 73 (58%) of 125 lesions were located proximally as compared to a slightly lower percentage (72 of 133 lesions, 54%) in patients with stable CAD (P=NS). The majority of non-calcified and mixed lesions (81% and 62%, respectively) tended to be located in the proximal part of the coronary arteries. Calcified lesions were more equally distributed between the proximal and more distal parts of the coronary arteries with 56% of calcifications located proximally (P<0.05).

Table 2. Distribution of plaque types, as visually assessed using MSCT, between patients with stable and unstable angina pectoris.

Plaque type	Stable CAD	ACS patients
Non-calcified	3 (2%)	18 (18%)
Mixed	11 (9%)	36 (36%)
Calcified	114 (89%)	46 (46%)
Total	128	100

Abbreviations: ACS: acute coronary syndrome; CAD: coronary artery disease.

Distribution of plaque types between ACS and stable CAD patients

In patients presenting with stable CAD, 128 of 133 (96%) identified lesions were interpretable. The majority of observed lesions, 114 (88%), were calcified, whereas only 3 (2%) and 11 (9%) lesions were either completely non-calcified or mixed, respectively. On the contrary, a larger part of demonstrated lesions were non-calcified or mixed in patients with ACS. A total of 100 (80%) lesions were interpretable, of which 18 (18%) and 36 (36%) were respectively non-calcified or mixed. Forty-six percent of plaques were calcified (P<0.001). Results are summarized in Table 2 and Figure 2.

As a result of the relatively lower number of calcifications, mean SI of the observed plaques was significantly lower in the ACS patients as compared to the stable CAD patients (320 ± 201 HU versus 620 ± 256 HU, P<0.001).

Culprit vessels versus non-culprit vessels

In the patients with ACS, we compared culprit with non-culprit vessels. In the 22 culprit vessels, a total of 50 plaques were present, of which 42 could be identified and evaluated with MSCT. The relative distribution of non-calcified, mixed and calcified lesions, as shown in Table 3, were respectively 9

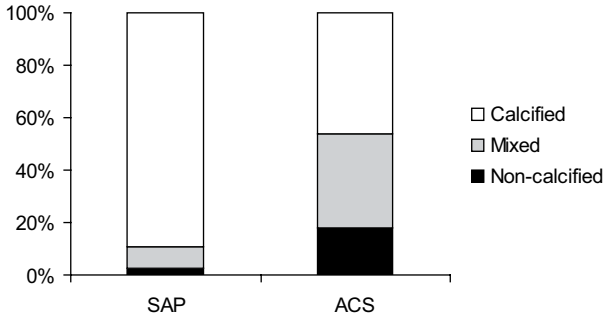

Figure 2. Bar graph demonstrating the relative distribution of the different lesion types in patients with ACS and stable CAD (P<0.001).
Abbreviations: ACS: acute coronary syndrome; CAD: coronary artery disease.

(21%), 19 (45%) and 14 (33%). In the 35 remaining, non-culprit vessels with atherosclerotic lesions, 75 plaques were present, of which 58 could be evaluated with MSCT. In these vessels, relatively more calcified lesions were observed, 32 (55%, P=NS). In the remaining lesions, calcium was absent in 9 (16%), whereas a mixture was observed in 17 (29%) plaques.

Although mean signal intensity was higher in plaques located in non-culprit vessels (346 ±196 HU) as compared the average value observed in culprit vessels (284 ± 205 HU), no statistical difference was reached (P=NS). Still, as depicted in Figure 3, SI of both culprit and non-culprit vessels in the ACS patients were significantly lower as compared to the SI of plaques in coronary vessels of the patients with stable CAD.

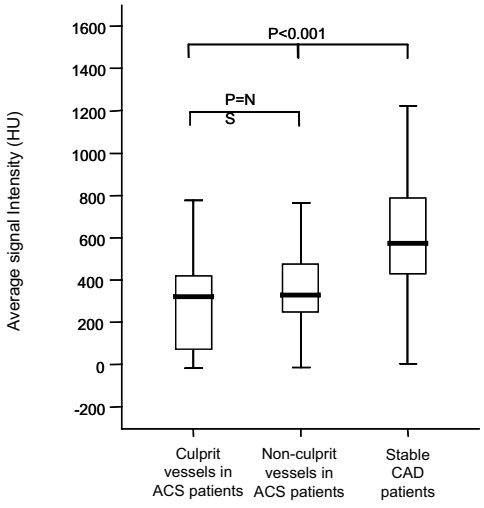

Figure 3. Box plot of average signal intensities of lesions in culprit vessels, non-culprit vessels of acute coronary syndrome (ACS) patients and signal intensities of lesions in stable coronary artery disease (CAD) patients. The box extends from the 25th percentile to the 75th percentile, with a line at the median (the 50th percentile). The whiskers extend above and below the box to show the highest and lowest values. No significant difference was observed between the average lesion signal intensity in culprit and non-culprit vessel of ACS patients whereas a significantly higher average signal intensity was observed in patients with stable CAD.

Discussion

Comparison of contrast-enhanced MSCT coronary angiograms of patients with stable CAD and ACS revealed the following findings. Firstly, non-calcified plaques tended to cluster in the proximal portion of the coronary arteries, whereas calcified lesions were more equally distributed. The second observation was that in patients presenting with ACS, a significantly lower percentage of observed lesions were completely calcified as compared to lesions in the patients with stable CAD. Accordingly, average plaque SI was significantly lower in the ACS patients as compared the patients with stable CAD. Finally, even in non-culprit vessels, multiple non-calcified lesions were noted. Accordingly, average lesion SI was lower in both culprit and non-culprit vessels in ACS patients as compared to lesions in stable CAD patients.

Table 3. Distribution of plaque types between culprit and non-culprit lesions of ACS patients as compared to plaques in stable CAD patients.

Plaque type	Culprit vessels	Non-culprit vessels	Vessels in stable CAD
Non-calcified	9 (21%)	9 (16%)	3 (2%)
Mixed	19 (45%)	17 (29%)	11 (9%)
Calcified	14 (33%)	32 (55%)	114 (89%)
Total	42	58	128

Abbreviations: ACS: acute coronary syndrome; CAD: coronary artery disease.

The spatial distribution of non-calcificied lesions

In the present study, the majority of non-calcified lesions were located in the proximal regions of the coronary arteries. Although this finding may have been influenced by the possibility that smaller non-calcified plaques located more distally are more difficult to detect, previous studies underline the current observation. Wang et al recently studied the spatial distribution of acute myocardial infarction occlusions in 208 patients and observed that the majority of acute coronary occlusions, caused by unstable plaque erosions or ruptures, were located in the proximal third of the coronary artery tree [13].

The incidence of calcified lesions

A relative lack of calcified lesions in patients with ACS has been reported previously with most observations based on angiographic or intravascular ultrasound (IVUS) findings [14-17]. In a recent study by Beckman et al. the extent of coronary calcifications was measured by the angle of its arc in 43 and 18 patients with respectively unstable angina and myocardial infarction, while 17 patients with stable CAD served as a control group [15]. The authors observed a significant decrease in the average calcium arc from 32 ±7° in the stable CAD patients to an average of 15±4° in the patients with unstable angina.In other angiographic studies, similar results have been reported [14;16;17].

Although the presence and extent of coronary calcifications can be evaluated with MSCT, data obtained with MSCT are currently still scarce. In a recent study, plaque morphology and composition

was evaluated using MSCT in 37 patients presenting with either ACS or stable CAD. In line without our observations, the authors found relatively more non-calcified plaques in culprit lesions in patients with ACS as compared to patients with stable CAD (100% versus 77%) [18]. In contrast, the prevalence of calcified plaques in culprit lesions in ACS patients was considerably lower (71% versus 85%). These findings underline the notion that the presence of coronary calcium more likely represents a feature of advanced obstructive CAD rather than the typical substrate for acute coronary events. Accordingly, identification of patients at risk based on merely coronary calcium scoring, as has been proposed, may be insufficient in the setting of ACS.

The incidence of non-calcified lesions in culprit and non-culprit vessels

Another finding of the current study was that the non-calcified and mixed plaques were equally distributed among culprit and non-culprit vessels of ACS patients, resulting in an average SI of lesions located in non-culprit vessels that was still significantly lower than that of lesions in stable CAD patients. Although the number of significantly stenosed vessels was comparable between populations, lesions tended to be more diffuse in patients with ACS, reflected by a significantly higher average number of diseased coronary arteries per patient.

A surge of coronary events has been observed in ACS patients in the months following their initial presentation [5]. Even within a year, a large portion of patients will present with recurrent ACS or infarction and may require intervention [5]. Not only worsening of the originally treated culprit lesions may be the cause of recurrent complaints in these patients but also worsening of lesions that were initially deemed insignificant. Indeed, evidence is accumulating that multiple sites of rupture-vulnerable plaque are present in patients presenting with ACS rather than one site of complex plaque or thrombus [5]. Plaque instability may result from generalized inflammation that affects the entire coronary tree rather than a single site, a finding that is underlined by the elevated inflammation markers circulating in patients presenting with unstable symptoms. Thus, although one single lesion may be clinically active at the time of ACS, multiple, potentially unstable, lesions may be present throughout the entire coronary tree.

(Non-invasive) imaging

Accordingly, conventional coronary angiography may be suboptimal in patients presenting with ACS, particularly with regard to prognosis. Invasive angiography may identify only the most severe lesions rather than assessing the presence of widespread but non-significant lesions and as a consequence overall plaque burden may be underestimated. Although the additional use of IVUS during coronary angiography may be extremely useful for depicting the coronary artery wall, it is an invasive technique with inherent limitations. MSCT on the other hand, has the advantage that it permits direct and non-invasive visualization of coronary artery lumen with corresponding plaques. Accordingly, MSCT may allow identification of patients at risk for ACS, but larger studies are needed to confirm this hypothesis.

Limitations

The current study has several limitations. First, only conventional coronary angiography was performed and no comparison between MSCT and IVUS was available. Accordingly, observed plaques were classified as calcified, mixed or non-calcified whereas identification of fibrotic or lipid-rich material was not possible. Also, data were acquired using 2 different MSCT scanners, which may hamper the reproducibility of our results. Second, whether lesions with low SI on MSCT actually reflect potentially unstable lesions has not been established yet and prospective studies are needed to determine whether these plaques are indeed associated with an increased incidence of coronary events.

Finally, several limitations need to be acknowledged that are inherent to MSCT. The radiation burden of MSCT is still high and the technique remains limited to patients with low heart rate, making administration of beta-blocking agents necessary prior to MSCT [19].

Conclusion

MSCT revealed that significantly less calcified lesions were present in ACS patients as compared to patients with stable CAD. Moreover, even in non-culprit vessels, multiple non-calcified plaques, which may represent high-risk lesions, were detected, indicating diffuse disease rather than focal atherosclerosis in ACS. Future studies are warranted to determine whether assessment of plaque type and distribution with MSCT may indeed allow identification of patients at increased risk for coronary events.

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