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Research paper

Quantification of coronary low-attenuation plaque volume for long-term prediction of cardiac events and reclassification of patients

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ABSTRACT

Background: To investigate the incremental prognostic value of low-attenuation plaque volume (LAPV) from coronary CT angiography datasets.

Methods: Quantification of LAPV was performed using dedicated software equipped with an adaptive plaque tissue algorithm in 1577 patients with suspected CAD. A combination of death and acute coronary syndrome was defined as primary endpoint. To assess the incremental prognostic value of LAPV, parameters were added to a baseline model including clinical risk and obstructive coronary artery disease (CAD), a baseline model including clinical risk and calcium scoring (CACS) and a baseline model including clinical risk and segment involvement score (SIS).

Results: Patients were followed for 5.5 years either by telephone contact, mail or clinical visits. The primary endpoint occurred in 30 patients. Quantified LAPV provided incremental prognostic information beyond clinical risk and obstructive CAD (c-index 0.701 vs. 0.767, $p < .001$), clinical risk and CACS (c-index 0.722 vs. 0.771, $p < .01$) and clinical risk and SIS (c-index 0.735 vs. 0.771, $p < .01$. A combined approach using quantified LAPV and clinical risk significantly improved the stratification of patients into different risk categories compared to clinical risk alone (categorical net reclassification index 0.69 with 95% CI 0.27 and 0.96, $p < .001$). The combined approach classified 846 (53.6%) patients as low risk (annual event rate 0.04%), 439 (27.8%) patients as intermediate risk (annual event rate 0.5%) and 292 (18.5%) patients as high risk (annual event rate 0.99%).

Conclusion: Quantification of LAPV provides incremental prognostic information beyond established CT risk patterns and permits improved stratification of patients into different risk categories.

1. Introduction

Despite advances in therapy, coronary artery disease (CAD) and myocardial infarction (MI) are leading causes of mortality in western societies and identification of patients at risk for future MI in clinical routine remains challenging.[1,2] Coronary computed tomography angiography (CTA) is an established imaging technique providing excellent negative predictive values to rule out CAD at reasonable radiation dose levels.[3–5] Patients with a negative coronary CTA scan have an excellent prognosis, while detection and severity of CAD by coronary CTA are associated with adverse outcome.[6–8] In addition, coronary CTA is able to detect coronary atherosclerosis at earlier disease stages than other non-invasive imaging techniques.[9] Consequently, there is a lot of effort in identifying patients at risk for mortality and future coronary events such as myocardial infarction (MI) from coronary CTA scans.[6–8,10] An interesting concept is the identification of the vulnerable plaque in coronary CTA. Retrospective histopathology studies characterized the vulnerable plaque as thin-cap fibrous atheroma (TCFA) filled with a large necrotic core containing lipids and macrophages and covered with a thin fibrous cap measuring < 65 µm.[11,12] Due to limited spatial resolution of coronary CTA the visualization of the thin cap covering the TCFA itself is not feasible, but the visualization of the necrotic core inside the TCFA seems to be a promising concept. This type of plaque presents itself as non-calcified plaque with low attenuation values (LAPV) in coronary CTA.[13,14] Its presence has been associated with future adverse cardiac events.[15,16]

Recently, dedicated software platforms have been developed by different vendors to automatically detect localized but also diffuse

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Abbreviations

CACS	Calcium Scoring
CAD	Coronary artery disease
CTA	CT angiography
CI	Confidence interval
LAPV	Low-attenuation Plaque Volume
MI	Myocardial infarction
NRI	Net reclassification Improvement
ROC	Receiver-operating curve
SIS	Segement Involvement Score
TCFA	thin-cap fibrous atheroma

atherosclerotic changes of the entire coronary artery tree and further differentiate plaque tissue based on attenuation values.[13,14,16,17] This concept allows for quantification of coronary LAPV.[18] The objective of this analysis was to investigate the incremental predictive value of quantified coronary LAPV and its potential for risk reclassification in a large consecutive patient population with a long follow-up.

2. Methods

2.1. Patient population

The patient population, the coronary CTA procedures as well as the clinical outcome have been described in detail elsewhere.[7] In brief, consecutive patients undergoing coronary CTA between December 2003 and November 2006 were prospectively enrolled. Patients were eligible for this study, if CAD was suspected, but not previously known. The study design was approved by the local ethics committee and written informed consent was obtained from all the patients before the investigation. Patients investigated in an acute life-threatening condition or without stable sinus rhythm were excluded.

Individual patient data and cardiac risk factors were collected with a structured interview. Cardiac risk factors were obtained in a binary fashion. Arterial hypertension was defined as systolic blood pressure > 140 mm Hg or prescription of antihypertensive medication. Diabetes mellitus was defined as fastening blood glucose levels > 7 mmol/l or prescription of antidiabetic medication including insulin. Hyperlipoproteinemia was defined as elevated total or LDL cholesterol or use of any lipid-lowering medication. Smoking was defined as former or active smoking. Positive family history was defined as presence of CAD in first-degree relatives younger than 55 years in male or 65 years in female relatives. The Morise score, which incorporates age, gender, CAD risk factors, and symptoms at presentation, was used to calculate overall patient risk for presence of CAD.[19]

2.2. Image acquisition

Image acquisition was performed using established institutional standards including administration of oral nitroglycerine to achieve coronary vasodilatation whenever systolic blood pressure was > 100 mmHg and administration of intravenous metoprolol (up to four 5 mg doses) to achieve target heart rates < 60 bpm. The contrast-enhanced scan was obtained using 80–140 ml of contrast agent (Iomeprol, Imeron 350, Bracco Altana Pharma GmbH, Konstanz, Germany, iodine content 350 mg/ml) individually adapted to the selected table feed and scan range injected at a rate of 4–6 ml/s and followed by a 50 ml saline chaser. Established dose saving strategies were used whenever appropriate and available at the time of scanning. Patients were scanned with a 16-slice single source, a 64 slice single source or a 64 slice dual source CT system (all Siemens Healthcare, Erlangen, Germany). All images were reconstructed using filtered back projection algorithms. The detailed image acquisition protocols are described elsewhere.[20–22]

For calcium scoring (CACS), non-contrast-enhanced images were obtained using sequential scan technique for 64 slice single and dual source CTs and retrospective low pitch helical scanning scan technique with dose pulsing for 16 slice CT. Images were analysed with a commercially available software package (Siemens Calcium Score, Siemens, Erlangen, Germany) using the Agatston score with a threshold of 130 HU.

2.3. Image analysis

Axial datasets were transferred to a commercially available personal computer equipped with dedicated software to perform automatic coronary plaque quantification (QAngio CT Research Edition V2.1.16.1, Medis medical image systems bv, Leiden, The Netherlands). All datasets were analysed by one of the two experienced readers and then cross-checked by the other reader. In case of disagreement a third reader was consulted. Prior studies revealed high inter- and intra-observer agreement.[13,23]

After coronary tree extraction from the datasets, the software detects the vessel lumen and outer vessel wall. The coronary artery tree including all proximal and mid coronary segments (left main, proximal 8 cm of left anterior descending and right coronary artery, proximal 6 cm of left circumflex coronary artery) was analysed. Segments with a diameter below 1.5 mm were excluded from analysis because there is strong evidence that proximal and mid coronary segments have the strongest impact on patient's outcome.[6]

The software initially measures the entire vessel wall including the normal coronary vessel wall and the coronary PV. Afterwards an algorithm is used to remove the media volume. Coronary plaques are automatically detected by the software, but can also be marked or deleted by the observer. Manual corrections to contours were applied only when necessary. Further plaque differentiation is then based on a dedicated algorithm using adaptive attenuation thresholds (measured as Hounsfield units), that incorporate for different enhancement patterns, for instance in lesions or distal parts of vessels. Total LAPV on a per-patient base was obtained by summing up LAPV from every plaque and was used for further analysis. The technical principles of the software have been described in more detail elsewhere.[13,14,17] Fig. 1 illustrates plaque volume quantification and differentiation. Obstructive CAD was assessed visually and defined as any stenosis above 50% luminal obstruction. The segment involvement score (SIS) represents the number of coronary segments with any plaque or stenosis as proposed by Min et al.[24]

2.4. Endpoints and follow-up

The primary endpoint comprised hard cardiac events (cardiac death and ACS). Acute coronary syndrome was defined as either myocardial infarction according to current guidelines or unstable angina leading to prompt revascularisation occurring at least 90 days after coronary CTA.[25] Follow-up was obtained either by telephone contact, a questionnaire sent by mail or clinical visits. All reported events were verified by contact with the attending physician or hospital records.

2.5. Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as median with interquartile ranges or means with standard deviations. Comparison of the groups was performed using student's t-test, Fisher's exact test or Kruskal-Wallis test as appropriate. Event-free survival was evaluated with the Kaplan-Meier method. Hazard ratios were obtained from univariate or