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Research paper

Incremental prognostic value of quantitative plaque assessment in coronary CT angiography during 5 years of follow up

Jonathan Nadjiri [a], Jörg Hausleiter [b], Christin Jähnichen [a], Albrecht Will [a], Eva Hendrich [a], Stefan Martinoff [a], Martin Hadamitzky [a, *]

[a] Institut für Radiologie und Nuklearmedizin, Deutsches Herzzentrum München, Technische Universität München, Munich, Germany
[b] Medizinische Klinik und Poliklinik I, Klinikum der Ludwig-Maximilians-Universität München, Munich, Germany

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ABSTRACT

Objective: We sought to assess the incremental prognostic value of quantitative plaque characterization beyond established CT risk scores.
Background: Several plaque characteristics detectable by coronary computed tomographic angiography (coronary CTA) are thought to be indicative of vulnerable plaques and subsequent cardiac events, particularly low attenuation plaque volume (LAPV), positive remodeling and the napkin-ring sign which is high density vascular adhesion with a small center of low density. It is unknown how quantitative plaque assessment can contribute to the long-term prediction of cardiovascular events in relation to established CT risk scores such as the calcium score or Segment Stenosis Score (SSS).
Methods: In 1168 consecutive patients with suspected coronary artery disease (CAD), calcium score measurement and coronary plaque characterization was performed comprising the presence of calcified, non-calcified, and partially calcified plaques on a per-segment basis. In all non-calcified or partially calcified plaques, semi-automated plaque analysis was performed to quantify low attenuation plaque volume (density <30HU), total non-calcified plaque volume (<150HU, TNCPV) and remodeling index. The presence of the napkin-ring sign was assessed visually. The study endpoint was the occurrence of major adverse cardiac events (MACE), a composite of cardiac death, myocardial infarction and coronary revascularization more than 90 days after coronary CTA.
Results: During a clinical follow up of 5.7 years, MACE was observed in 46 patients (3.9%). All plaque characteristics were associated with MACE. The strongest association was observed for LAPV (HR 1.12, $p < 0.0001$). LAPV showed incremental prognostic value in a stepwise multivariable model including the Morise Score for clinical risk, calcium score and SSS ($p = 0.036$).
Conclusion: LAPV, TPV, PR and presence of the napkin-ring sign are predictors of MACE independently of clinical risk presentation. LAPV carries slight additional prognostic information beyond the calcium score and conventional coronary CTA analysis. It may therefore improve risk prediction after CT imaging.

1. Introduction

In industrial nations, cardiovascular disease is the most common cause for death and morbidity.[1] Particularly myocardial infarction can lead to decreased life expectation and quality of life. Plaque rupture is a major cause for ischemic myocardial events.[2] It occurs not only in stenotic coronary lesions but also in plaques with mild lumen narrowing.[3,4] Coronary CTA as a non-invasive diagnostic tool may play an important role in assessing CAD over and above stenosis quantification. Several score based on routine evaluation of coronary CT such as the Agatston score to quantify coronary calcium and the Segment Involvement Score (SIS) to quantify calcified

Abbreviations: BMI, body mass index; Bpm, beats per minute; CAD, coronary artery disease; CI, confidence interval; HDL, high density lipoprotein; HR, hazard ratio; HU, hounsfield units; IVUS, intra vascular ultra sound; LAPV, low attenuation plaque volume; LDL, low density lipoprotein; LR, likelihood ratio; MACE, major adverse cardiac events; MI, myocardial infarction; mV, millivolt; NYHA, New York Heart Association classification; OCT, optical coherence tomography; RI, remodeling index; SIS, segment involvement score; SSS, segment stenosis score; TCFA, thin cap fibroatheroma; TNCPV, total non-calcified plaque volume.

* Corresponding author. Deutsches Herzzentrum, Lazarettstrasse 36, 80636 München, Germany.
E-mail address: mhy@dhm.mhn.de (M. Hadamitzky).

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as well as non-calcified plaque burden (SIS) – provide prognostic value beyond assessing degree of vessel narrowing.[5,6]

As opposed to invasive modalities for plaque characterization like Intravascular Ultrasound (IVUS) and Optical Coherence Tomography (OCT), coronary CTA noninvasively covers the entire coronary system and allows for evaluation of the total extent of calcified and non-calcified plaques including both obstructive and non-obstructive lesions. Although it is well known that non-calcified plaques are more common in patients suffering from acute coronary syndrome,[7] the prognostic value of the presence of non-obstructive plaques in an unselected study population seems to be limited.[8] The exact reason for this finding is not completely understood, but it seems likely that the presence of non-calcified plaque is not specific for a vulnerable lesion. Therefore, more elaborated plaque characterization methods are needed to improve the prognostic value of coronary CTA. It has been previously shown that characterization of plaque types from coronary CTA is possible and can predict adverse cardiac events.[9] However it is not clear whether characterization of plaques is superior to merely quantifying ("counting") plaques.[10,11] As another limitation, the duration of follow-up in all previous studies was relatively short.[9,10] Additionally, it is necessary to analyze the incremental value of any new form of coronary CTA evaluation beyond conventional assessment in order to justify the considerable effort of elaborate plaque analysis. Therefore, the aim of this study was to assess the incremental prognostic value of a detailed plaque analysis protocol – with combined analysis of low attenuation plaque volume (LAPV), total non-calcified plaque volume (TNCPV), remodeling index (RI) and presence of the napkin-ring sign - in addition to conventional analyses such as the calcium score and determination of SIS and SSS on major cardiac events during 5 years of follow-up in an unselected patient population undergoing calcium scoring and coronary CTA for the assessment of suspected CAD.

2. Methods

2.1. Study population

All consecutive patients with suspected CAD who underwent calcium scoring and coronary CTA at our institution between October 1st, 2004 and September 15th, 2006 were eligible for the study. The study design was prospective, but advanced plaque analysis was retrospectively added. All patients gave written informed consent. Patients were excluded if they had acute life-threatening conditions or no stable sinus rhythm at the time point of coronary CTA.

A structured questionnaire was completed for every patient prior to coronary CTA and it captured patient information such as age, height, weight, symptoms and cardiac history. Furthermore, the questionnaire documented cardiac risk factors:[1] extent and presence of arterial hypertension (for binary analysis hypertension was defined as a systolic blood pressure of 140 mmHg or prescribed antihypertensive medication),[2] diabetes mellitus (defined as fasting blood glucose level of 7 mmol/l or oral and insulin-based anti-diabetic therapy, respectively),[3] smoking (defined as current or smoking within the last year) and[4] positive family history (defined as presence of CAD in first-degree relatives younger than 55 years in male or 65 years in female). Laboratory values of total cholesterol, LDL and HDL, and triglycerides were documented additionally. From these data, the Morise Score was obtained. The Morise Score represents extended risk stratification as it includes both risk factors and current symptoms.[12] The study was approved by the local institutional ethics committee.

2.2. Computed tomography procedure

The scan procedure has been previously described in detail.[13,14] All examinations were performed on a 64-slice single source CT system (Somatom 64, Siemens Healthcare, Erlangen, Germany). In case of heart rates higher than 60 bpm, up to four doses of 5 mg of metoprolol were administered intravenously immediately before scanning. If systolic blood pressure was higher than 100 mmHg, 0.8 mg nitroglycerin was administered sublingually just before image acquisition to achieve coronary vasodilatation.

Collimation was $2 \times 32 \times 0.6$ mm. Using an ECG-gated half-scan reconstruction algorithm, the temporal resolution was 164 ms. In patients with heart rates above 65 bpm, a bi-segmental reconstruction algorithm was applied, reducing the effective reconstruction interval per heart cycle to 83 ms. In patients with stable sinus rhythm, the tube current was modulated according to the ECG, with a maximum current of 850–950 mAs during a time period of 330 ms centered at 675 ms after the R-wave and reduction by 80% during the remaining cardiac cycle.

Coronary calcium was quantified through the Agatston score, based on a non-contrast-enhanced sequential scan and evaluated with a commercially available software package (Siemens CalciumScore, Siemens, Erlangen, Germany). The contrast-enhanced scan was obtained using 80–140 ml of contrast individually adapted to the selected table feed and scan range at a rate of 4–6 ml/s followed by 50 ml of saline chaser bolus. Data sets of axial slices, multiplanar reformations, and three perpendicular sets of thin-slab maximum intensity projections oriented along the heart axis (5 mm thickness, 1 mm increment) were reconstructed and investigated for the presence of plaque composition and luminal stenosis. Segments with artefacts were assigned to the group that seemed most appropriate, whenever possible.

The coronary artery tree was segmented according to a simplified American Heart Association classification using the first 15 segments of the original 18.[15] Each vessel segment with a diameter of more than 1.5 mm was evaluated visually by two experienced readers with an experience of having read more than 400 cardiac CT studies at the time the scan was performed. Disagreements were settled by consensus. The degree of stenosis was assessed visually categorizing either no relevant stenosis (<25%), mild (25–49%), moderate (50–74%), and severe ($\geq$75%) stenosis. In addition, for each segment the presence of calcium and the presence of non-calcified plaque was assessed. Non-calcified plaques were defined as a structure of at least 1 mm^2 size adjacent to the vessel lumen, having a signal intensity lower than the vessel lumen and being clearly distinguishable from the surrounding tissue.[16] Plaques meeting these criteria, but additionally showing calcification, were classified as partially calcified plaques. From the primary analysis the following coronary CTA scores were calculated: CAD severity as proposed by Chow et al.[10] with the categories 'normal', 'non-obstructive', 'one-vessel obstructive', 'two-vessel obstructive' and 'three-vessel obstructive'. Segment Involvement Score (SIS): Number of segments with any calcified, partially calcified or non-calcified plaques, irrespective of the degree of stenosis or a stenosis >25% not fulfilling the aforementioned plaque criteria.

The Segment Stenosis Score (SSS) combines number and degree of stenoses by assigning a score ranging from 0 (normal) to 3 (>70% stenosis) to each segment and summarizing them across all segments.[6]

For all segments containing non-calcified or partially calcified plaques, cross-sectional reconstructions of 1 mm slice thickness were created covering the whole lesion and at least 3 slices of the adjacent unaffected coronary artery. In these reconstructions, the