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Quantitative baseline CT plaque characterization of unrevascularized non-culprit intermediate coronary stenosis predicts lesion volume progression and long-term prognosis: A serial CT follow-up study

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ABSTRACT

Aims: To investigate the quantitative baseline CT plaque characterization of unrevascularized non-culprit intermediate coronary stenosis and its association with lesion volume progression and long-term prognosis.
Methods: Patients with baseline coronary CT angiography (CCTA) and invasive coronary angiography (ICA) and at least one unrevascularized non-culprit intermediate coronary stenosis were prospectively enrolled for this study. All patients were followed up by a second CCTA at 1-year to 1.5-year interval. High-risk plaque features as well as other quantitative plaque measurements were recorded.
Results: 140 patients with 165 unrevascularized non-culprit intermediate lesions were selected. Lesion volume progression was identified in 18 lesions (10.9%, 18/165) at follow-up CCTA and 15 patients experienced major adverse cardiac events (MACE) during a mean follow-up period of 51.5 months. Low attenuation plaque (LAP) was more frequently present in the lesion-progression subgroup and MACE subgroup (lesion-progression VS. non-lesion progression: 55.6% VS. 8.8% and MACE VS. MACE free: 40% VS. 12.8%, both $p < 0.05$), while other parameters showed no significant differences. Based on stepwise multivariable logistic regression analysis, LAP was an independent predictor (OR = 16.74, 95%CI = 5.02 to 55.84, $p < 0.001$) for lesion volume progression and MACE (OR = 4.25, 95%CI = 1.03 to 17.53, $p = 0.046$).
Conclusions: The presence of LAP of unrevascularized non-culprit intermediate stenosis is associated with lesion volume progression and an independent predictor for MACE occurrence.

1. Introduction

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality across the world [1]. The plaque phenotypes are clinically significant as vulnerable plaques may result in rupture and lead to devastating acute coronary syndrome (ACS) [2]. Early detection and intervention of high-risk plaques is hence clinical significant. Invasive imaging modalities, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), are able to differentiate high-risk plaques and predict future cardiac events [3–5].

Although the spatial resolution is limited, coronary computed tomography angiography (CCTA) has been validated as a non-invasive imaging modality for characterization of high risk plaque features, such as positive remodeling (PR), low-attenuation plaque (LAP), Napkin-ring sign (NRS) and spotty calcification. These high risk plaque features are associated with cardiovascular events and unfavorable clinical outcomes [6–10].

Percutaneous coronary intervention (PCI) and medical therapy are two major treatment options for intermediate coronary stenosis. Based on published guidelines, the clinical decision is made based on comprehensive evaluation of the patients' symptoms, lesion locations and hemodynamical status [11,12]. However, plaque risk features evaluated by CCTA are currently not taken into consideration when deciding on treatment strategies for intermediate coronary stenosis. In addition, the association between those high-risk features and plaque progression of unrevascularized borderline lesions has not been investigated. In this study we aimed to evaluate the clinical benefit of quantitative baseline CT plaque characterization for predicting lesion progression of unrevascularized non-culprit intermediate coronary stenosis as well as future cardiovascular events.

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2. Materials and methods

2.1. Patient population

Institutional review board approval was obtained for this prospective study, and informed consent was obtained from all patients. Between January 2011 and December 2015, patients with stable angina or atypical chest pain were referred for CCTA and ICA (if baseline CCTA revealed at least one obstructive lesion with diameter stenosis ≧ 50% in one epicardial vessel). Patients with at least one unrevascularized intermediate coronary stenosis (determined by ICA) were prospectively enrolled for this study. All patients were referred for second CCTA at 1-year to 1.5-year interval for follow up of the unrevascularized lesions. The inclusion criteria were: 1) Patients had baseline CCTA and ICA which revealed at least one unrevascularized intermediate coronary stenosis which was considered as a non-culprit lesion; and 2) Patients underwent follow-up CCTA at 1-year to 1.5-year interval. The exclusion criteria were: 1) The image quality of baseline/follow-up CCTA was compromised and not feasible for accurate plaque analysis; 2) Patients who refused to undergo follow-up CCTA; and 3) The target lesions were severely calcified (defined as calcium covering ≧ 50% of any vessel cross-section within lesion).

2.2. Imaging protocol of CCTA

A 128-slice single source multi-detector CT (Definition AS+; Siemens Medical Solutions, Forchheim, Germany) was used for scanning. Patients with a pre-scan heart rate > 65 bpm were orally administered 25–75 mg of a β-blocker (Betaloc ZOK; AstraZeneca, China) 1 h prior to the scan. Sublingual nitroglycerin was administered to all patients. A bolus of contrast media, i.e. iopamidol 370 mg iodine/ml (Isovist; Schering AG, Berlin, Germany) was injected into the antecubital vein at the rate of 4.5–5 ml/s, followed by injection of a 20–40 ml saline flush using a dual-barrel power injector (Tyco-Mallinckrodt, Cincinnati, OH, US). The amount of contrast media was determined based on the patient's body weight and the scanning time. A test bolus was first injected and the region of interest was placed within the ascending aorta to determine the accurate delay time, which was defined as 4 s plus the peak time of the ascending aorta. Retrospective ECG-gated CTA was performed in patients with a final heart rate ≧ 70 bpm, with a section thickness of 0.6 mm and a rotation time of 300 ms. The pitch varied between 0.2 and 0.5 depending on the heart rate and patient size. The tube current was automatically adjusted according to the patients' body habitus using the automatic exposure control system (CareDose 4D, Siemens Medical Solutions, Forchheim, Germany) and electrocardiographically modified (an electrocardiographically dependent dose modulation technique was applied with a full dose during the R-R interval of 40%–70%). The tube voltage was also automatically determined from 80 kVp to 120 kVp according to patients' body habitus by using the automatic exposure control system (Care KV). The images were reconstructed with a slice thickness of 0.6 mm, a reconstruction increment of 0.5 mm using a medium soft-tissue convolution kernel (B26F), and reconstructed matrix size of 512 * 512. ECG-triggered CTA was performed in patients with a final heart rate < 70 bpm, with the center of the triggering window set at 70% of the RR interval. The rest of the parameters for prospective acquisition were similar to the retrospective acquisition.

2.3. Imaging reconstruction and analysis

Data generated was transferred to an offline workstation (Syngo.Via; Siemens Medical Solutions) for further analysis. Axial, cross-sectional, curved planar reformation (CPR), multiplanar reformation, and three-dimensional maximum intensity projection (MIP) images were then generated.

The image quality was assessed using a 4-point Linkert scale: 4 = excellent (absence of artifacts), 3 = good (presence of mild artifacts), 2 = sufficient (presence of moderate artifacts, but still diagnostic), 1 = poor (presence of severe artifacts, non-diagnostic). Only patients with image quality scans of grade 4 were included for further analysis.

All unrevascularized non-culprit intermediate lesions (diameter stenosis determined by ICA: 50%–69%) detected by baseline CCTA were considered for analysis. The plaque characterization was performed according to baseline CCTA findings and included the following parameters listed below. 1) A remodeling index was defined as a maximal lesion vessel diameter divided by proximal reference vessel diameter, with PR defined as a remodeling index ≥ 1.1; 2) LAP was defined as any voxel < 30 HU within a coronary plaque, using a dedicated plaque analysis software (Coronary Plaque Analysis, version 2.0, Siemens, Germany); 3) spotty calcification was defined by an intra-lesion calcific plaque < 3 mm in length that comprised <90° of the lesion circumference; 4) NRS was characterized by a plaque core with low computed tomography attenuation surrounded by a rim-like area of higher attenuation as previous reported [10]; 5) lesion length was measured on CPR at the best projection view, from the proximal shoulder of plaque to the distal shoulder; 6) plaque volume was automatically measured using a dedicated plaque analysis software as mentioned above. Plaque borders were manually adjusted if needed; 7) Plaque burden was measured on cross-sectional images and defined as the ratio of the plaque cross sectional area to the vessel cross sectional area; 8) The minimal lumen area (MLA) and the minimal lumen diameter (MLD) were all measured manually using a digital caliper at the narrowest level of the lesion on the cross-sectional images. The proximal and distal vessel diameter/area was measured manually with a digital caliper on cross-sectional images, immediately proximal or distal to the lesion where no plaques could be detected. The reference diameter and reference area were determined as an average of the proximal and distal vessel diameter/area, respectively. The MLD and proximal/distal vessel diameters were determined as the shortest diameters in eccentric lesions; 9) Diameter stenosis was defined as (reference diameter − MLD) / reference diameter; the area stenosis was defined as (reference area − MLA) / reference area; plaque burden was defined as (vessel cross-sectional area − MLA) / cross-sectional area.

Two experienced radiologists (with 10-years and 8-years of cardiac imaging experience) independently analyzed the lesions. The mean values of quantitative parameters measured by the two radiologists were used for further analysis.

2.4. ICA procedure and analysis

The ICA was performed using standard techniques, with at least 2 different views obtained for each main vessel. Two skilled cardiologists (with combined 32 years of interventional cardiology experience), who were blinded to the results of the CCTA, evaluated all the segments. The extent of stenosis for every lesion was evaluated and recorded based on visual assessment at best projection with least vessel foreshortening.

The extent of stenosis for every calcified lesion was classified into 5 subgroups: minimal (<25% stenosis), mild (25% to 49% stenosis), moderate (50%–69% stenosis), severe (70% to 99% stenosis) and occluded [13]. PCI was performed for culprit lesions, which were considered to be responsible for the patients' symptoms. Non-culprit intermediate lesions were defined as moderate coronary stenosis, which did not cause myocardial ischemia as revealed by myocardial perfusion imaging or invasive fractional flow reserve (FFR) measurement, or had minimal lumen area ≥ 4 mm^2 as revealed by IVUS. Non-culprit intermediate lesions were deferred for PCI and treated medically. Disagreements in findings between the two cardiologists were resolved by discussions to reach a final consensus.

2.5. Clinical follow-up

Clinical follow-up was initiated on admission and lasted at least 1 year or until patients met the primary endpoint. The primary endpoint was major adverse cardiac events (MACE), which was defined as composite of death from cardiac causes, ACS, or unplanned late coronary revascularization (3 months later than the index ICA) due to progression of unrevascularized non-culprit intermediate lesions.

Follow-up CCTA was performed at 1-year to 1.5-year interval after ICA. The scanning protocol and image analysis were similar to those mentioned previously. Plaque volume was used to assess lesion progression. Plaque volume progression was defined as the follow-up plaque volume that increased ≥10% compared to baseline volume. Plaque volume regression was defined as the follow-up plaque volume that decreased ≥10% compared to baseline volume.

2.6. Statistical analysis

Statistical analysis was performed using commercially available statistical analysis software (MedCalc Statistical Software version 15.2.2, MedCalc Software bvba, Ostend, Belgium and SPSS Statistical Software version 17.0, Chicago, IL, USA). One-sample Kolmogorov-Smirnov test was used to determine normal distribution. Quantitative variables with normal distribution were expressed as means ± standard deviations while median and quartiles were used otherwise. Student *t*-test was used for normally distributed data, and the Mann-Whitney *U* test was used for data that were not normally distributed. Categorical variables were reported as counts (%) and compared by using the Fisher exact test or chi-square test, according to the data cell size. Inter-observer and intra-observer variability of CCTA-derived plaque features was assessed by intra-class correlation coefficient (ICC). The effects of the variables on native lesion progression and MACE were investigated by univariable and multivariable logistic regression analyses. Multivariable regression analysis was used to determine the independent predictors of clinical outcome, which was performed using the "stepwise" method. The model included variables with p value < 0.20 in the univariable analysis. Kaplan-Meier analysis was used to estimate the cumulative event rates of MACE based on the presence or absence of LAP or lesion progression. Differences in time-to-event curves were compared using the log-rank test. A two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics

A total of 172 patients were prospectively enrolled in our study. Of these patients, 13 refused to undergo follow-up CCTA at 1-year to 1.5-year interval, and were excluded from the study. Eight patients with severe calcified target lesions and 11 patients with impaired image quality were also excluded (Online supplement Fig. E1). Ultimately, 140 patients [mean age: 67.2 ± 8.9 (range, 43–92) years; 86 males (mean age: 68.4 ± 9.1 (range, 45 to 91) years, and 54 females (mean age: 65.1 ± 8.6 (range 49 to 79) years; $p = 0.66$) were selected for the study.

The dose length product (DLP) of CCTA was 443.5 ± 92.2 mGy * cm (range 177 to 738 mGy * cm) and the effective dose was 6.2 ± 1.3 mSv (range 2.5 to 10.3 mSv). The mean amount of contrast material used for CCTA was 85.4 ± 7.2 ml (range 70 to 105 ml). Follow-up CCTA was

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