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Original article

Prognosis of anatomic coronary artery disease without myocardial ischemia: Coronary computed tomography angiography detects high-risk patients even in cases of negative single-photon emission computed tomography findings

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ABSTRACT

Background: While coronary computed tomography angiography (CCTA) provides comprehensive anatomic evaluation of coronary artery disease (CAD) with prognostic implications, clinically, the focus is usually placed on presence or absence of functionally significant CAD. Herein, we aimed to suggest a new risk stratification strategy using CCTA in patients with anatomic CAD but without myocardial ischemia on single-photon emission computed tomography (SPECT).

Methods: Consecutive patients (n = 798) with CAD on CCTA who underwent SPECT for evaluation of myocardial ischemia were retrospectively evaluated. The primary outcome was the occurrence of adverse cardiac events, including cardiac death, nonfatal myocardial infarction, unstable angina, and late revascularization.

Results: Of the enrolled patients, 542 (68%) showed no perfusion defect (PD) on SPECT. During the follow-up (median, 22.6 months), adverse cardiac events occurred in 23 patients without PD (4.6%). Presence of plaque in ≥4 coronary segments, plaque in the left main or proximal left anterior descending coronary artery, and partially calcified plaque presence were independent predictors of adverse events. When we defined the CCTA score based on these 3 predictors (0–3 points), the annualized event rates increased with increasing CCTA scores. Patients with a CCTA score of 3 were associated with a 23-fold risk increase (adjusted HR 23.18; p = 0.003) and showed unfavorable event-free survival, comparable to those with PD on SPECT (p = 0.191).

Conclusion: Anatomic CAD patients without evidence of myocardial ischemia on SPECT but with high-risk characteristics on CCTA showed unfavorable outcomes, comparable to those with PD. CCTA allows further risk stratification even in patients with negative SPECT findings.

Introduction

Coronary computed tomography angiography (CCTA) has been widely used as a noninvasive modality to evaluate coronary artery disease (CAD) [1,2]. Compared to traditional approaches to assessing CAD, which build on the evaluation of myocardial

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ischemia, CCTA directly visualizes coronary atherosclerosis and provides anatomic information, including on the presence, severity, and extent of CAD [1,2]. While the anatomic information provided by CCTA is valuable for risk stratification [1,3,4], clinically, the focus is mainly placed on the presence of functionally significant CAD that requires revascularization [5–7]. Anatomic CAD without evidence of myocardial ischemia is often regarded as "insignificant CAD" [5–7], and the ability of CCTA to detect CAD regardless of its functional significance raises the concern that widespread use of CCTA may precipitate unnecessary referral for invasive angiography and revascularization. However, not only obstructive stenosis (either functionally or anatomically), but also nonobstructive stenosis is associated with the risk of adverse cardiac events [8–11]. Moreover, considering recent studies that demonstrated improved outcomes in patients with nonobstructive CAD upon treatment with statins [12,13], the presence of anatomic CAD itself provides valuable information to guide the management. In addition, the coronary atherosclerotic burden and distribution evaluated by CCTA are important determinants of long-term prognosis [14–18]. The plaque composition, which cannot be evaluated by invasive angiography, is also expected to have prognostic implications [8,10,15].

Herein, we aimed to stratify the risk of CAD patients with negative single-photon emission computed tomography (SPECT) results according to the plaque extent, distribution, and composition, as well as the presence of luminal stenosis, and suggest a novel risk stratification strategy based on CCTA characteristics to detect high-risk patients comparable to those with evidence of myocardial ischemia on SPECT.

Materials and methods

Study population

Consecutive adult patients undergoing CCTA for the evaluation of coronary artery stenosis at Seoul National University Hospital and Seoul National University Bundang Hospital between 2004 and 2012 were retrospectively assessed for eligibility. The inclusion criteria were as follows: (1) patients with coronary atherosclerotic plaque on CCTA and (2) patients who underwent SPECT for evaluation of the hemodynamic significance of CAD within 90 days from CCTA. Patients were excluded from the study if any of the following was present: (1) prior history of CAD or (2) uninterpretable CCTA images. Consequently, 798 patients were included in the analysis. The primary indication of CCTA and SPECT was chest pain (n = 398, 49.9%), followed by dyspnea (n = 126, 15.8%) (Table 1). The study protocol conforms to the guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's human research committee, and the requirement for written informed consent was waived due to the retrospective nature of the study.

CCTA image acquisition and analysis

CCTA images were acquired using either a retrospectively electrocardiogram (ECG)-gated or prospectively ECG-triggered protocol using a 64-detector row CT scanner (SOMATOM Definition; Siemens Medical Solutions, Forchheim, Germany, or Brilliance 64; Philips Medical Systems Inc., Cleveland, OH, USA). Image acquisition, post-processing, and interpretation were performed according to the guideline of the Society of Cardiovascular Computed Tomography [19]. All images were independently analyzed by two experienced radiologists who were blinded to the clinical data. The coronary artery calcium score (CACS) was measured using the Agatston scoring system (in units), and graded as follows: 0, 1–399, and ≥400 [20]. A coronary atherosclerotic plaque was defined as any clearly distinguishable lesion >1 mm^2, distinct from the coronary artery, in at least two independent image planes. The presence, severity, location, and composition of coronary atherosclerotic plaques were evaluated by per-segment analysis according to the modified 15-segment criteria [21,22]. The severity of coronary stenosis was quantified by visual estimation and divided into diameter stenosis (DS) <50%, and ≥50%. Plaque composition was classified as non-calcified (<30% calcified plaque volume), partially calcified (30–70%), or calcified (>70%), according to the calcified component (>130 Hounsfield Units) [23,24].

SPECT image acquisition and analysis

Myocardial SPECT (CardioMD, ADAC Vertex V60; Philips Medical Systems Inc.) was performed with pharmacologic stress, using technetium-99m tetrofosmin or sestamibi as the radiotracer. Stress images were obtained at peak stress in sequence with a continuous infusion of adenosine (0.14 mg/kg/min) or dipyridamole (0.142 mg/kg/min) and subsequent radiotracer (25 mCi technetium-99m) injection 3 min after stress initiation [25,26]. The rest-stress images were interpreted by the consensus of two well-trained nuclear physicians who were blinded to the clinical data. The patients were categorized according to the presence or absence of any perfusion defect (PD), as determined on the stress image (segmental tracer activity <75% of maximum), and included both fixed (irreversible change on the resting phase) and reversible (≥10% increase in tracer uptake on the resting phase) PDs [27].

Clinical follow-up

Follow-up information was obtained by either clinical visits or telephone interview. All reported events were verified by hospital records or direct contact with the attending physicians. The primary endpoint was the occurrence of adverse cardiac events, including cardiac death, nonfatal myocardial infarction (MI), unstable angina, and late revascularization [22,28]. Late revascularization was defined as any revascularization, by either percutaneous coronary intervention or coronary artery bypass graft, after 90 days from the last CCTA or SPECT. Coronary revascularizations within 90 days were excluded to subtract any examination-driven revascularization from the clinical events. For the outcome analysis, patients undergoing early revascularization were censored at the time of intervention.

Statistical analysis

All statistical analyses were performed using SPSS 22.0 (IBM, Chicago, IL, USA) and MedCalc for Windows, version 13.1.2.0 (MedCalc Software, Ostend, Belgium). To estimate the risk of a given variable in patients with negative SPECT findings, univariate and multivariate Cox proportional hazard analyses were performed. The risk of adverse cardiac events was expressed as the hazard ratio (HR) and corresponding 95% confidence interval (CI). To identify the cut-off for the number of involved segments for better prediction of adverse cardiac events, receiver-operating characteristic (ROC) curves were plotted. The optimal cut-off values were determined according to the maximum sum of the sensitivity and specificity. To identify the high-risk group among the patients without PD on SPECT, we proposed a new scoring system based on the CCTA findings. The HRs of the final multivariate Cox regression model were used to estimate the contribution of each variable to the risk estimation. This resulted in a CCTA score calculated as the number of CCTA parameters significantly and independently associated with adverse cardiac events. The predictive accuracies of the Framingham Risk Score

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