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Prognostic value of coronary computed tomography angiography in stroke patients

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ABSTRACT

Objective: The predictive value of coronary computed tomography angiography (CCTA) in stroke patients has not yet been established. We investigated the prognostic value of coronary artery disease (CAD) detection by CCTA, and determined the incremental risk stratification benefit of CCTA findings as compared to coronary artery calcium scores (CACS) in ischemic stroke patients without chest pain. **Methods**: Among 914 consecutive ischemic stroke patients, 317 (68.5% were male with a mean age of 64 years) who had at least one clinical risk factor for CAD without chest pain were prospectively enrolled to undergo CCTA. CT images were assessed for CAC, presence of CAD and extent of CAD. The primary endpoint was major adverse cardiac events (MACEs) defined as cardiac death, non-fatal myocardial infarction, unstable angina requiring hospitalization, or revascularization after 90 days from index CCTA. **Results**: The prevalence of CAC $\geq$1 was 73.1% (232/317) and the average CACS was 346.6 $\pm$ 693.5 (Agatston unit). During the median follow-up period of 409 days, there were a total of 26 MACEs. Both CACS [CAC (101–400, and >400)] and CCTA findings [presence of obstructive CAD, 1-vessel disease (VD), 2-VD, and 3-VD] independently stratified risk of future MACEs (all $p < 0.05$). The time-dependent receiver operating characteristic curve analysis revealed that CAD findings (presence of obstructive CAD and number of involved vessels) based on CCTA improved risk stratification beyond clinical risk factors and CACS (iAUC: 0.863 vs 0.752, $p < 0.05$). **Conclusion**: In ischemic stroke patients without chest pain, CCTA findings of CAD provide additional risk-discrimination over CACS.

1. Introduction

Coronary artery disease (CAD) is the major cause of mortality in patients with stroke [1]. Several studies demonstrated that the prevalence of CAD is substantial in stroke patients [2–4]. Knowledge of the absolute risk of coronary events and the detection of occult CAD in patients with stroke is important for assessing their prognosis and may affect decisions regarding further diagnostic testing and preventive strategies. Whether stroke patients should be screened for occult CAD remains a matter of debate. Current American Heart Association (AHA) and American Stroke Association (ASA) guidelines suggest that only those individuals with carotid artery disease or who are at high risk based on Framingham risk scoring (FRS) warrant further CAD evaluation [1].

The advance of noninvasive imaging techniques, such as coronary artery calcium scoring (CACS) and coronary computed tomography angiography (CCTA) has provided new options for CAD evaluation in various populations [5–9]. CCTA provides comprehensive information regarding the location, severity and characteristics of atherosclerotic plaque, and has been validated against conventional coronary angiography [10–14]. However, there is no available data on the prognostic value of CCTA in stroke patients and no consensus guideline for screening for occult CAD in this population.

We investigated the prognostic value of CAD detection by CCTA and determined the incremental risk stratification benefit of CCTA findings as compared to CACS in ischemic stroke patients without chest pain.

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2. Materials and methods

2.1. Patient selection

Our institutional review board approved this study and all patients provided written informed consent to undergo CCTA. From January 2010 to December 2011, 914 consecutive ischemic stroke patients were admitted to Severance hospital for a recent stroke (onset within the previous seven days). Of these patients, we prospectively enrolled 350 ischemic stroke patients without chest pain to undergo CCTA for evaluation of CAD. The inclusion criteria were as follows: 1) age >20 years; 2) presence of ≥1 risk factor for CAD including hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, or obesity; 3) no known chest pain. The remaining 564 patients were excluded who 1) had unknown symptom status or chest pain ($n = 208$), 2) had no risk factors for CAD ($n = 158$), 3) had poor general condition or poor cooperation ($n = 112$), 4) had renal dysfunction or contrast agent allergy ($n = 27$), or 5) had failed to provide informed consent ($n = 59$).

Of 350 patients, 33 patients who had history of myocardial infarction, percutaneous coronary intervention, or coronary bypass surgery; ($n = 12$), had uninterpretable CCTA ($n = 11$) or had insufficient medical records or no follow-up data ($n = 10$) were excluded. Finally, a total of 317 ischemic stroke patients (217 men and 100 women, aged from 21 to 89 years (mean age, 64.0 ± 13.1 years)) remained for final analysis.

Clinical data were collected at the time of the index visit. Hypertension was defined by current use of anti-hypertensive medications or a blood pressure ≥140/90 mmHg. Diabetes mellitus was defined as receiving anti-diabetic treatments or a fasting plasma glucose ≥126 mg/dL. Smoking was defined as patients with former and current smokers. Current smoker was defined as any cigarette smoking in the past month and former smoker was defined as patients who stopped smoking for more than 3 months prior to the study. Dyslipidemia was defined as a total serum cholesterol ≥200 mg/dL, a low-density lipoprotein of ≥130 mg/dL, a high-density lipoprotein of <40 mg/dL, and/or treatment with a lipid-lowering agent. Obesity was defined as having a body mass index (BMI, kg/m^2) ≥ 30.

All patients underwent brain computed tomography (CT) and/or brain magnetic resonance imaging (MRI) to confirm and characterize the stroke type and to exclude hemorrhages and other pathology. Subtypes of ischemic stroke were classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system [15]. The stroke subtypes of 317 patients were the following: stroke of undetermined etiology ($n = 135$, 42.6%), large artery atherosclerosis ($n = 106$, 33.4%), cardioembolism ($n = 44$, 13.9%), small-vessel occlusion ($n = 28$, 8.8%), and stroke of other determined etiology ($n = 4$, 1.3%).

2.2. Cardiac computed tomography examination

Cardiac CT scans were performed with a second-generation dual-source CT (DSCT) scanner (Somatom Definition Flash; Siemens Medical Solutions, Erlangen, Germany) in the craniocaudal direction during a single breath-hold. The mean heart rate was 64 ± 15 beats per minute (range 43–97 beats/min) during the CT examination. Among the 317 stroke patients, 49 patients (15.5%) had atrial fibrillation during cardiac CT examinations. However, the image quality of all of the cardiac CT examinations was considered acceptable for the evaluation of CAD.

First, a non-enhanced prospective electrocardiography (ECG)-gated sequential scan was performed to measure coronary artery calcium (CAC) with a tube voltage of 120 kV and a tube current of 50 mAs. The scan was reconstructed at 70% of the R–R interval using a slice thickness of 3 mm and an increment of 3 mm. Next, contrast-enhanced CCTA was performed using prospective ECG-gating. A bolus of 70 ml of iopamidol (370 mg of iodine per milliliter, Iopamiro; Bracco, Milan, Italy) was administered using a power injector (Envision CT, Medrad, USA) at a rate of 5 ml/s via an 18-gauge needle placed into the right antecubital vein. Following contrast agent administration, 50 ml of saline was administered at a flow rate of 5 ml/s through the same venous access. Start delay was defined by test bolus technique before image acquisition in each patient. The scan parameters were as follows: detector collimation, 2 × 64 × 0.6 mm; slice acquisition, 2 × 128 × 0.6 mm by means of a z-flying focal spot; gantry rotation time, 280 ms; tube voltage, 100–120 kV; tube current, 280–380 mAs; and pitch, 0.2–0.43 adapted to the heart rate. In patients with heart rate less than 75 beats per minute, prospectively ECG-triggered studies were centered at 70% of the R–R interval, whereas, in patients with heart rate more than 75 beats per minute, prospectively ECG-triggered studies were centered at 40% of the R–R interval. In patients with atrial fibrillation, scan was performed with prospective ECG-triggered acquisition targeting end-systolic phase using the absolute delay method (a fixed time delay after the R wave). Images were reconstructed with a slice thickness of 0.6 mm and a reconstruction increment of 0.4 mm, using a soft-tissue convolution kernel (B36f). Radiation exposure was estimated from the dose-length product (DLP). The calculated mean radiation dose was 5.51 mSv (DLP range, 93–1388 mGy*cm) depending on the scan range and the patient's body weight.

2.3. Data and image analysis

The 10-year cardiovascular risks were calculated using the equations derived from the Framingham Heart Study and Framingham Offspring Study [16]. Framingham risk score (FRS) were categorized into 4 groups: low (<10), low intermediate [10–15], high intermediate [16–20] and high (>20).

Coronary artery calcium score (CACS) was quantified by means of the Agatston method [17]. CACS were categorized into 4 groups: group 1 (0–10), group 2 (11–100), group 3 (101–400), and group 4 (>400).

All CCTA images were evaluated using a dedicated clinical workstation (Aquarious Workstation; TeraRecon, Inc, San Mateo, CA). The CCTA images were evaluated independently by two experienced cardiac radiologists who were unaware of the clinical histories of the patients. Differences in assessments were resolved by consensus.

The coronary arteries were evaluated according to a 16-segment coronary artery model modified from the American Heart Association (AHA) classification [18]. In each coronary segment, coronary atherosclerotic plaques were defined structures >1 mm^2 within and/or adjacent to the vessel lumen, which could be clearly distinguished from the lumen and surrounding pericardial tissue or epicardial fat. CAD was defined as presence of any plaque. CAD extent and severity were graded by various methods. First, obstructive CAD was defined when coronary artery segments exhibited plaque with a luminal diameter stenosis ≥50%, and non-obstructive CAD was defined when coronary artery segments exhibited plaque with a luminal stenosis less than 50%. CAD was categorized into 2 groups as either obstructive CAD or non-obstructive CAD. Individuals manifesting obstructive CAD were further categorized as having 1-vessel disease (VD), 2-VD, or 3-VD. Three-vessel disease was defined as either obstructive CAD in all 3 of the major epicardial vessels (right coronary, left anterior descending, and left circumflex arteries) or right coronary artery and left main artery disease.