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Original article

Correlation between early revascularization and major cardiac events demonstrated by ischemic myocardium in Japanese patients with stable coronary artery disease

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ABSTRACT

Background: There is no report on correlation between early revascularization and the occurrence of major cardiac events (MCEs) except severe heart failure in Japanese patients with stable coronary artery disease (CAD). This study aimed to determine whether early revascularization affected the incidence of MCEs in Japanese patients with stable CAD.

Methods: We retrospectively investigated 3581 stable CAD patients who underwent rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin myocardial perfusion single-photon emission computed tomography (SPECT) and provided three-year-prognostic data. The endpoint was the onset of MCEs consisting of cardiac death, non-fatal myocardial infarction, and unstable angina pectoris. On the basis of estimated propensity scores, patients who underwent revascularization within the first 60 days after the SPECT and those who did not were matched in a 1:1 ratio (n = 450 per group). We compared MCE rates in relation to the amount of ischemic myocardium detected with the SPECT between the two groups.

Results: The overall incidence of MCEs was not significantly different between the early-revascularization and no-early-revascularization groups (6.7% vs. 8.7%, p = 0.2598). Nevertheless, the incidence of MCEs in the patients with ≤5% ischemia was significantly higher in the early-revascularization group than in the no-early-revascularization group (5.8% vs. 0.8%, p = 0.0226). In contrast, the incidence of MCEs in the patients with >10% ischemia was significantly lower in the early-revascularization group than in the no-early-revascularization group (7.0% vs. 16.8%, p = 0.0036). The incidence of MCEs in the patients with 6–10% ischemia, however, was not significantly different between the early-revascularization and no-early-revascularization groups (6.9% vs. 4.1%, p = 0.3235).

Conclusions: Early revascularization possibly leads to the occurrence of MCEs related to the treatment procedure but may be a therapeutic strategy leading to improvement in prognosis in patients with moderate to severe ischemia.

Introduction

Coronary revascularization is an established therapy used worldwide to improve anginal symptoms associated with coronary stenoses in patients with coronary artery disease (CAD). Improvement in prognosis following percutaneous coronary intervention (PCI), however, is restricted to stable CAD patients having a stenosis in the proximal region of the left anterior descending artery (LAD). Therefore, PCI is impossible to use in all stable CAD patients and the indication should be limited according to the guidelines of the American College of Cardiology and the American Heart Association (ACC/AHA) [1,2] and the European Society of Cardiology (ESC) [3].

Myocardial perfusion single photon emission computed tomography (SPECT) has been well recognized as a useful imaging methodology for prediction of future cardiac events in patients with known or suspected CAD [4,5]. Ischemic evaluation with SPECT is useful in the wide range of medical management including diagnosis, risk stratification, and prognosis in stable CAD patients and is highly recommended by the ACC/AHA guideline [1]. Also, in Japan, myocardial perfusion SPECT has

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commonly been used to predict cardiac events in patients with CAD. Risk stratification of cardiac events by nuclear cardiology has been demonstrated in some large-scale prognostic studies including the multicenter prospective Japanese Assessment of Cardiac Events and Survival Study in patients with ischemic heart disease (J-ACCESS) [6] in asymptomatic patients with type 2 diabetes (J-ACCESS 2) [7] and patients with chronic kidney disease (J-ACCESS 3) [8], and another single-center large-scale prospective study [9]. Therefore, it is important to re-evaluate the benefit of early revascularization under consideration of SPECT findings.

Studying the relation of early revascularization to a prognosis in 632 patients with stable CAD having propensity score matching in the J-ACCESS database, Moroi et al. reported that coronary revascularization within 60 days after SPECT study for stable CAD failed to decrease major cardiac events (MCEs) in all patients but might do in patients with moderate to severe ischemia [10]. In their report, more than half of the MCEs observed were associated with severe heart failure. In general, MCEs defined in other studies [4,5] included no severe heart failure requiring hospitalization unlike those defined in the J-ACCESS [5].

We, therefore, have conducted this retrospective prognostic study in Japanese patients with stable CAD to evaluate the relation between early revascularization and the occurrence of MCEs excluding severe heart failure under consideration of amount of ischemic myocardium detected with SPECT using risk-adjusted techniques of propensity score matching to minimize bias like a randomized design.

Methods

Patient population

We retrospectively investigated 3581 patients with known or suspected CAD who underwent rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin myocardial perfusion SPECT [9,11–19] at Nihon University Itabashi Hospital between October 2004 and March 2011 and who had data on a three-year follow-up. We excluded patients aged ≤20 years, those with hypertrophic or dilated cardiomyopathy, those with serious valvular heart disease, those with heart failure being class III or higher New York Heart Association (NYHA) functional classification, and those with onset of acute coronary syndromes within three months [6,10]. We separated the patients into groups according to whether they underwent revascularization (n = 583) or not (n = 2998) within the first 60 days after the SPECT [5,10]. Follow-up examinations were based on medical records for patients who periodically attended the hospital and responses to a posted questionnaire for patients who did not attend.

Electrocardiogram-gated dual-isotope myocardial perfusion SPECT

The procedure of rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin electrocardiogram (ECG)-gated myocardial perfusion SPECT was performed according to a protocol previously reported [9,11–19]. All patients received an intravenous (i.v.) injection of ^{201}Tl (111 MBq) and a 16-frame gated SPECT image was initiated 10 minutes after injection during rest. Then an i.v. injection of ^{99m}Tc-tetrofosmin (740 MBq) was performed under stress induced by ergometer exercise in 25% of the patients or by adenosine triphosphate in 75% of those. Sixteen-frame gated SPECT image acquisition was initiated 30 min after the exercise or 30–60 min after the adenosine stress. The acquisition was performed in a supine position and subsequently in a prone position. No attenuation or scatter correction was used. Twelve-lead ECG was monitored continuously during stress tests. Heart rate and blood pressure were recorded at baseline and every minute for at least three minutes after the stress.

The projection data over 360° were obtained with 64 × 64 matrices and a circular orbit. A triple-detector SPECT system equipped with low-energy high-resolution collimators was used (Toshiba, GCA9300A, Tokyo, Japan). SPECT images were reconstructed from the data with a data processor (JETStream Workspace 3.0, Philips North America, Andover, MA, USA) combined with a Butterworth filter of ^{201}Tl (order 5; cut-off frequency 0.42 cycles/cm), that of ^{99m}Tc (order 5; cut-off frequency 0.44 cycles/cm) and a ramp filter.

SPECT image interpretation

The SPECT images were divided into 20 segments [18] on three short-axis (distal, mid, basal) and one vertical long-axis (mid) slices, and the tracer uptake of each segment was visually scored using a 5-point scale (0: normal; 1: slight reduction of uptake; 2: moderate reduction of uptake; 3: severe reduction of uptake; and 4: absence of uptake). The sum total of the scores of 20 segments in the stress and rest images provided the summed stress score (SSS) and the summed rest score (SRS), respectively. The summed difference score (SDS) was calculated as the difference between the SSS and SRS. The respective summed scores were converted to percent of the total myocardium (visual % myocardium). Visual % myocardium was derived from a summed score divided by the maximum potential score (4 × 20) and multiplied by 100. When the SDS score was 8, the visual ischemic % myocardium was 10%. Minimal or no, mild, and moderate-to-severe ischemia was defined as ≤5%, 6–10%, and >10% ischemic myocardium, respectively [20].

The visual semi-quantitative scoring was performed by two independent expert interpreters who were not provided with patient's clinical information. Cohen's kappa (κ), which was calculated to determine the inter-observer variability for the summed defect score, was 0.92, indicating good reproducibility.

Sixteen-frame quantitative gated SPECT data were analyzed using QGS^{TM} software (Cedars-Sinai Medical Center, Los Angeles, CA, USA) to calculate left ventricular ejection fraction (LVEF, %), end-diastolic volume (LVEDV, mL), and end-systolic volume (LVESV, mL) as described by Germano et al. [21].

Patient follow-up

The study endpoint was the onset of MCEs during the follow-up, consisting of cardiac death, non-fatal myocardial infarction (MI), and unstable angina pectoris (UAP) identified with medical records or responses to a posted questionnaire. A diagnosis of UAP was provided for a patient who required unscheduled hospitalization for the management of UAP, occurring within 24 hours of the most recent symptoms, and who had worsening ischemic discomfort, ischemic ECG changes without ST elevation, and negative troponins. Angiographic evidence after early revascularization included atherosclerotic plaque rupture and stent and graft thromboses for non-fatal MI and were target, adjacent, remote, and new lesion failures and graft failure for UAP. All patients were followed up for three years (36.5 ± 9.6 months) after the initial stress myocardial perfusion gated SPECT. When a patient had multiple MCEs, only the first event was taken as the study endpoint.

Statistical analysis

Continuous variables were calculated as means and standard deviations. Intergroup comparisons of continuous and categorical variables were achieved with an unpaired t test and the chi-square test, respectively.

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