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Original article

Usefulness of automated assessment of nuclear cardiology for prediction of major cardiac events in Japanese patients with known or suspected coronary artery disease: Comparison with conventional visual assessment in a large-scale prognostic study

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ABSTRACT

Background: There are no reports indicating that automated quantification with a total perfusion deficit (TPD) is used to predict future cardiac events in Japanese patients. We, therefore, aimed to determine the prognostic value of the automated assessment with the TPD for risk stratification of major cardiac events (MCEs) in Japanese patients with known or suspected coronary artery disease (CAD).

Methods: We retrospectively investigated 2848 patients who underwent rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin myocardial perfusion single photon emission computed tomography (SPECT) between October 2004 and March 2008. The follow-up period was 25.8 ± 11.0 months. The TPD was automatically derived from the SPECT image through the QPS software with the Japanese normal database. Twenty segments of SPECT images were analyzed with the 5-point visual scoring model to estimate summed scores. The endpoint of the follow-up was the occurrence of MCEs within 1 year after the SPECT, which were identified with medical records or responses to a posted questionnaire.

Results: During the first year of the follow-up, 62 patients had MCEs, which comprised cardiac death (n = 30), non-fatal myocardial infarction (n = 13), and unstable angina pectoris (n = 19). The MCE rates positively correlated with the stress TPD and the summed stress score. Sensitivity of the automated quantification with the TPD for detection of the MCEs was high and similar to that of the visual semi-quantification. Multivariate Cox regression analysis indicated that significant independent predictors for the MCEs were an estimated glomerular filtration rate and the ischemic variables both in the automated quantification and visual semi-quantification.

Conclusion: The automated quantification with the TPD is useful for prognostic risk stratification of MCEs in Japanese patients with known or suspected CAD. Its predictive power is similar to that of the visual semi-quantification by expert interpreters.

Introduction

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 coronary artery disease (CAD) since the reports of Hachamovitch et al. [1,2]. The quantification of myocardial perfusion SPECT has originally been based on a semi-quantitative analysis including visual segmental scoring by expert interpreters. The visual scoring requires a special skill or knowledge of image interpretation, gained as a result of training or experience. Therefore, the ideal assessment should be based on objective quantitative measurements but not the visual interpretation with subjective nature. Slomka et al. [3] proposed a total perfusion deficit (TPD) as an objective parameter substituted for the visual scoring, which is automatically calculated by quantitative perfusion SPECT (QPS) software [4] to represent both severity and extent of a defect. The automated quantitative assessment with the TPD has been confirmed to provide highly correlated results with visual interpretation by three expert readers and to be more reproducible than the

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visual semi-quantitative assessment for defect extent [5]. The automated quantitative assessment with the TPD has been employed as a reliable technique detecting CAD in the multicenter studies of the COURAGE (clinical outcomes utilizing revascularization and aggressive drug evaluation) trial [6] in the USA. The American Society of Nuclear Cardiology (ASNC) imaging guideline 2010 for SPECT also describes the automated quantification with the TPD as a useful assessment for ischemia [7].

In Japan, myocardial perfusion SPECT has also commonly been used to predict cardiac events in patients with CAD. Risk stratification of cardiac events by nuclear cardiology is 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) [8], in asymptomatic patients with type 2 diabetes (J-ACCESS 2) [9], and in patients with chronic kidney disease (J-ACCESS 3) [10], and another single-center large-scale prospective study [11]. In these large studies, the diagnostic assessment of nuclear cardiology has been based on the semi-quantitative analysis with visual segmental scoring systems including a summed stress score (SSS) and a summed rest score (SRS). Up to now, the visual semi-quantitative assessment has widely been used in Japanese nuclear cardiology.

We have already reported that the automated quantitative assessment of SPECT images using the TPD derived from the Japanese normal database is consistent with the conventional visual semi-quantitative assessment with the segmental defect scores for detection of CAD in Japanese patients [12] and that the quantitative assessment with the TPD is reproducible [13]. Our results demonstrate that the assessment with the TPD has a diagnostic power for CAD equal to that of the visual assessment. Those results suggest that the TPD may be a useful parameter for prognostic assessment of CAD. However, there are no reports indicating that the automated quantification with the TPD is used to predict future cardiac events in Japanese patients. We, therefore, have conducted a single-center large-scale study to determine the prognostic value of the automated assessment with the TPD of myocardial perfusion SPECT images for risk stratification of major cardiac events (MCEs) in Japanese patients.

Materials and methods

The institutional review board of Nihon University Itabashi Hospital approved this study, which proceeded in accordance with the ethical standards established in the 1964 Declaration of Helsinki. All study participants provided written informed consent prior to inclusion in this study.

Patient population

We retrospectively investigated 2848 patients with known or suspected CAD who underwent rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin myocardial perfusion SPECT [11–16] at Nihon University Itabashi Hospital between October 2004 and March 2008. We excluded patients aged ≤20 years, those who developed acute myocardial infarction (MI) or unstable angina pectoris (UAP) within 3 months prior to the SPECT, those with hypertrophic or dilated cardiomyopathy, those with serious valvular heart disease, and those with heart failure with class III or higher New York Heart Association (NYHA) functional classification. 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. The follow-up was complete for 2592 (91%) patients. Of these, 368 patients were excluded from prognostic analyses because they had undergone revascularization within 3 months of the SPECT examination. Data from the remaining 2224 patients were finally analyzed.

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 [11–16]. All patients received an intravenous (i.v.) injection of ^{201}Tl (111 MBq) and a sixteen-frame gated SPECT image was initiated 10 min after injection during rest. Then an i.v. injection of ^{99m}Tc-tetrofosmin (740 MBq) was performed under stress induced by ergometer exercise in 30% of the patients or by adenosine triphosphate in 70% of them. 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 the stress tests. Heart rate and blood pressure were recorded at baseline and every minute for at least 3 min 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).

Visual assessment of perfusion images

The SPECT images were divided into 20 segments 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. An abnormal criterion for the SSS was defined as 4 or more [5]. The visual semi-quantitative scoring was performed by two independent expert interpreters who were not provided with patients' clinical information. Cohen's kappa (κ), which was calculated to determine the inter-observer variability for the summed defect score, was 0.92, indicating very good reproducibility.

Automated quantification of perfusion images

The quantitative perfusion variable used was a TPD, which is a parameter representing both defect extent and severity of myocardial abnormality, and was automatically computed. TPD scores were calculated as the percentage of the total surface area of the left ventricle below the predefined uniform average deviation threshold using QPS software. A normal database used was the Japanese one developed by the Japanese Society of Nuclear Medicine [17], which is based on exercise-rest myocardial perfusion images accumulated from 80 subjects with a low likelihood of cardiac disease. The TPD scores were measured at stress and rest, and ischemic TPD was calculated from the difference between the stress and rest TPD scores (stress TPD minus rest TPD). An abnormal criterion for the stress TPD was defined as 5% or more [6].

Patient follow-up

All patients were followed up for at least 1 year (25.8 ± 11.0 months) after the stress myocardial perfusion gated SPECT. The study endpoints comprised MCEs within 1 year including cardiac death, non-fatal MI, and UAP identified from medical records or