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Original article

Significance of worsening renal function and nuclear cardiology for predicting cardiac death in patients with known or suspected coronary artery disease

Shunichi Yoda (MD, FJCC)*, Kanae Nakanishi (MD), Ayako Tano (MD), Yusuke Hori (MD), Yasuyuki Suzuki (MD), Naoya Matsumoto (MD), Atsushi Hirayama (MD, FJCC)

Department of Cardiology, Nihon University School of Medicine, Tokyo, Japan

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ABSTRACT

Background: Estimated glomerular filtration rates (eGFRs) at baseline are useful to determine the severity of renal function and to predict cardiac events. However, no studies aimed to demonstrate significance of eGFRs measured during follow-up and usefulness of combination with nuclear cardiology for prediction of cardiac death in patients with coronary artery disease (CAD).

Methods: We retrospectively investigated 1739 patients with known/suspected CAD who underwent myocardial perfusion single photon emission computed tomography (SPECT), who had eGFRs measured at baseline and after one year and who underwent a three-year follow-up. The SPECT images were analyzed with the visual scoring model to estimate summed defect scores. Reduction in eGFRs (ΔeGFR) was defined as the difference between eGFRs measured after one year and at baseline. The endpoint of the follow-up was cardiac deaths within three years after the SPECT, which were identified with medical records or responses to posted questionnaires.

Results: Cardiac death was observed in 54 of 1739 patients during the follow-up period (45.6 ± 9.1 months). The multivariate Cox regression analysis showed baseline eGFRs, ΔeGFR, and summed stress scores to be significant independent variables for prediction of cardiac death. The area under receiver operating characteristic curves for detection of cardiac death was 0.677 for the baseline eGFR and 0.802 for the follow-up eGFR. Sensitivity of detection of cardiac death was significantly higher in the follow-up eGFR than in the baseline eGFR ($p = 0.0002$). Combination of the best cut-off values, i.e. 9 for the summed stress scores and 10 for the ΔeGFR, which were suggested by receiver operating characteristic analysis, was useful for risk stratification of cardiac death both in patients with and without chronic kidney disease.

Conclusion: Baseline and follow-up eGFRs as well as nuclear variables are useful to predict cardiac death in patients with known/suspected CAD.

Introduction

Prediction of cardiac death is clinically significant in patients with chronic kidney disease (CKD) because cardiovascular disease is the leading cause of death among patients with CKD before starting hemodialysis therapy [1]. Myocardial perfusion single photon emission computed tomography (SPECT) has commonly been employed to predict cardiac events in patients with coronary artery disease (CAD) since the reports of Hachamovitch et al. [2–4]. In Japan, the multicentre prospective Japanese Assessment of Cardiac Events and Survival Study (J-ACCESS) has been conducted since 2001 to evaluate the prognostic value of stress myocardial perfusion SPECT in patients with suspected or confirmed CAD [5–8].

There are several studies demonstrating the prognostic value of myocardial perfusion SPECT for future cardiac events in CKD patients. The incidences of cardiac death, all-cause mortality, and non-fatal myocardial infarction (MI) were reported to be higher in patients with than without CKD who had known or suspected cardiovascular disease in a nuclear cardiology study [9]. Summed stress scores (SSS) derived from the SPECT image are considered to be a reliable predictor of cardiac events among 820 patients with

* Corresponding author at: Department of Cardiology, Nihon University School of Medicine, 30-1 Oyaguchi-Kamicho, Itabashi-Ku, Tokyo 173-8610, Japan.
Tel.: +81 3 3972 8111; fax: +81 3 3972 1098.
E-mail address: masteryoda@mf.point.ne.jp (S. Yoda).

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CKD extracted from the J-ACCESS database [10]. Recently, the SSS, left ventricular ejection fraction (LVEF), and estimated glomerular filtration rates (eGFRs) have been shown to be independent predictors of cardiac events in CKD patients in a one-year interim report of the J-ACCESS 3 [8]. We also have demonstrated that nuclear variables derived from myocardial perfusion SPECT and eGFRs are useful for predicting cardiac events and survival in 2243 patients at all stages of CKD including those on hemodialysis [11].

In those studies, eGFRs measured at baseline were used to determine the CKD stage and the severity of renal function, and to predict cardiac events. However, there is no report of studies demonstrating risk stratification of cardiac events and prediction of cardiac death by means of combination of eGFR reduction and nuclear cardiology. In addition, no Japanese large-scale nuclear cardiology studies referred to cardiac death as the primary endpoint.

We conducted a retrospective large-scale cohort study to evaluate significance of eGFR reduction during a follow-up for prediction of cardiac death in patients with known or suspected CAD.

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 1739 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 October 2010, who had eGFRs measured at baseline and after approximately one year, and who underwent a three-year follow-up after the SPECT. We excluded patients aged ≤20 years, those who developed acute MI or unstable angina pectoris within three months prior to the SPECT, those on hemodialysis, those with hypertrophic or dilated cardiomyopathy, serious valvular heart disease or heart failure with class III or higher New York Heart Association functional classification, those who underwent revascularization within 90 days of the SPECT, and those who had no data on the follow-up eGFR after one year. Patients were diagnosed as having hypertension if having systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg within the past three months or currently under medication to lower blood pressure; as having diabetes mellitus if having a fasting blood glucose ≥126 mg/dL, casual blood glucose ≥200 mg/dL within the past three months, or under medication to control hyperglycemia, or already diagnosed with diabetes mellitus; as having hyperlipidemia if having low-density lipoprotein cholesterol ≥140 mg/dL within the past three months or currently under medication to normalize hypercholesterolemia.

Evaluation of eGFRs

The GFR was calculated from serum creatinine levels at the time of SPECT for each patient in the final prognostic analysis population using the Modification of Diet in Renal Disease Equation for Japanese Patients proposed by the Japanese Society of Nephrology [17] as follows:

$$\mathrm{eGFR} = \mathrm{A} \times 194 \times (\mathrm{Serum\ \ Creatinine})^{-1.094} \times (\mathrm{Age})^{-0.287},$$

where A is 1 for men and 0.739 for women and eGFRs are expressed as mL/min/1.73 m^2.

Patients having baseline eGFRs < 60 mL/min/1.73 m^2 were diagnosed as having CKD. Reduction in eGFR (ΔeGFR) was defined as the difference between the eGFR measured in the follow-up period (follow-up eGFR) and the baseline eGFR. The follow-up eGFR was measured at 12.0 ± 2.4 months after the baseline.

Electrocardiogram-gated dual-isotope myocardial perfusion SPECT

The procedure of rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin electrocardiogram (ECG)-gated myocardial perfusion SPECT were performed as a protocol previously reported [11–16]. All patients received an intravenous (i.v.) injection of ^{201}Tl (111 MBq) and 16-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 27.5% of the patients or by adenosine triphosphate in 72.5% of them. Sixteen-frame gated SPECT image was initiated 30 min after exercise or 30–60 min after adenosine stress. 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 3 min after 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 (Philips North America, JETStream Workspace 3.0, Andover, MA, USA) combined with a Butterworth filter of ^{201}Tl (order 5; cut-off frequency 0.42 cycles/cm), and also 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 [12] 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 (normal, slight, moderate, and severe reduction of uptake, 0, 1, 2 and 3, respectively; absent uptake, 4) [18]. The sum total of the scores of 20 segments in the stress and rest images provided the SSS and the summed rest score (SRS), respectively. The summed difference score (SDS) was calculated as the difference between the SSS and SRS. Cohen's kappa (κ), which was calculated to determine the inter-observer variability for the perfusion score, was 0.92, indicating very good reproducibility.

Sixteen-frame quantitative gated SPECT data were analyzed using QGS^{TM} software (Cedars-Sinai Medical Center, Los Angeles, CA, USA) to calculate LVEF (%), end-diastolic volume (LVEDV, mL) and end-systolic volume (LVESV, mL) as described by Germano et al. [19].

Patient follow-up

All patients were followed up for approximately three years (45.6 ± 9.1 months) after the myocardial perfusion SPECT. The study endpoint was cardiac death defined as death due to any cardiac cause including fatal MI, sudden arrhythmic death, and congestive heart failure; identified with medical records or responses to a posted questionnaire within the follow-up period.

Statistical analysis

Continuous variables were calculated as means and standard deviations. Intergroup comparisons of continuous and categorical