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Original article

Prediction of cardiovascular events in pre-dialysis chronic kidney disease patients with normal SPECT myocardial perfusion imaging

Tatsuhiko Furuhashi (MD)[a], Masao Moroi (MD, FACP, FJCC)[a,*], Nobuhiko Joki (MD)[b], Hiroki Hase (MD, FJCC)[b], Megumi Minakawa (MD)[a], Hirofumi Masai (MD)[a], Taeko Kunimasa (MD)[a], Hiroshi Fukuda (MD)[a], Kaoru Sugi (MD, FJCC)[a]

[a] Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan
[b] Department of Nephrology, Toho University, Ohashi Medical Center, Tokyo, Japan

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ABSTRACT

Purpose: Patients with normal stress myocardial perfusion imaging (MPI) results generally have an excellent prognosis with <1% cardiovascular events/year. Chronic kidney disease (CKD) is an established risk factor for cardiovascular events. However, the estimated glomerular filtration rate (eGFR) varies considerably among patients with CKD. We evaluated the prognostic value of eGFR for patients with CKD who did not undergo hemodialysis and had no evidence of coronary artery disease (CAD).

Methods and subjects: Patients with CKD ($n = 108$; 58 males; mean age: 74 years) with no CAD [no previous CAD and normal stress MPI results; summed stress score (SSS) <4] and with no history of hemodialysis were followed-up (mean duration: 24 months). CKD was defined by eGFR of <60 ml/min/1.73 m^2 and/or persistent proteinuria. Cardiovascular events included cardiac death, non-fatal myocardial infarction, and unstable angina.

Results: Cardiovascular events were observed in 8 patients with CKD (7%). The following were determined as significant predictors of these events: age (hazard ratio = 1.14; $p = 0.019$), hemoglobin levels (hazard ratio = 0.69; $p = 0.021$), eGFR (hazard ratio = 0.94; $p = 0.008$), SSS (hazard ratio = 2.31; $p = 0.012$), and summed difference score (hazard ratio = 2.33; $p = 0.014$).

Conclusions: Patients with CKD and with no previous CAD and normal stress MPI results (SSS < 4) may not exhibit an excellent cardiovascular prognosis. Further, a lower eGFR and stress MPI results may be the predictors of cardiovascular events. Thus, patients with a lower eGFR and/or normal stress MPI results (SSS < 4) may require continuous follow-up.

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Introduction

Stress myocardial perfusion imaging (MPI) is useful for predicting cardiovascular events such as mortality because of cardiac failure and acute coronary syndrome [1–3]. In general, normal stress MPI results are associated with an excellent cardiovascular prognosis with <1% cardiovascular events/year [4]. In addition, associations between chronic kidney disease (CKD) and adverse cardiovascular prognosis were established in large community-based studies [5–10]; however, few previous reports indicated that even for patients with normal stress MPI results an excellent prognosis for cardiovascular events could not be guaranteed [11–13].

The estimated glomerular filtration rate (eGFR) varies considerably among the patients with CKD. In this study, we assessed the prognostic value of eGFR for patients with CKD who did not undergo hemodialysis and had no evidence of coronary artery disease (CAD), as assessed by clinical history and stress MPI results.

Materials and methods

Patients and study protocol

This was a retrospective prognostic study for patients who underwent stress MPI. A total of 1002 consecutive patients with suspected or prior CAD underwent thallium-201 stress MPI between 2008 and 2010. The following patients were excluded from this study: 144 patients for whom no prognostic data could be obtained after stress MPI; 15 with a summed difference score (SDS) of >2 on stress MPI and in whom revascularization was achieved within 2 months of percutaneous coronary intervention

* Corresponding author at: Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, 2-17-6 Ohashi, Meguro-ku, Tokyo 153-8515, Japan. Tel.: +81 3 3468 1251; fax: +81 3 3468 1269.
E-mail address: moroi@med.toho-u.ac.jp (M. Moroi).

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(performed to manage significant ischemia) [14]; 8 with severe valvular disease requiring surgery; 3 with severe aortic disease requiring surgery; 297 without CKD; 67 receiving dialysis; 348 with a history of CAD; and 12 with abnormal stress MPI results [summed stress scores (SSS) ≥4].

Finally, 108 CKD patients were followed up (Fig. 1). All the patients provided informed consent to participate in this study. Our study protocol was approved by the Committee on Human Investigation of the Toho University Ohashi Medical Center (approval No. 12-62). This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki (as revised in Tokyo, 2004) and subsequent revisions.

The following patient data had been recorded during previous stress MPI: age, gender, use of medication, and other coronary risk factors. The following were considered as possible risk factors for this study: cigarette smoking and history of hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, and/or anti-hypertensive therapy); diabetes (fasting blood glucose >126 mg/dl, glycosylated hemoglobin >6.5% based on the National Glycohemoglobin Standardization Program definition, currently undergoing treatment with insulin or oral anti-diabetic drugs), hyperlipidemia [hypercholesterolemia (total cholesterol >220 mg/dl), hypertriglyceridemia (serum triglycerides >150 mg/dl), and/or currently undergoing lipid lowering therapy]; and history of CAD incidence among first-degree relatives at <60 years of age.

Exercise or pharmacological stress tests were performed. All the exercise stress tests were performed using a treadmill. None of the patients underwent ergometer exercise stress testing. The treadmill exercise test (Bruce protocol) was considered adequate if patients achieved >85% of their maximum predicted heart rate and/or developed chest pain. Further, patients with limited exercise capacity (who failed to achieve at least 85% of their predicted heart rate during the treadmill test) underwent a pharmacological stress test comprising intravenous adenosine infusion. Adenosine infusion and thallium-201 injection were administered in separate arms. An automated infusion pump was used to deliver the intravenous adenosine infusion (0.120 mg/kg/min) over 6 min. Thallium-201 (111 MBq; FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan) was injected into a peripheral vein approximately 1 min before cessation of the treadmill stress test or 3 min after initiating the adenosine infusion.

Myocardial perfusion single-photon emission computed tomography

All myocardial perfusion single-photon emission tomographic data were acquired using a 3-headed gamma camera (MS-3; Siemens, Chicago, IL, USA) equipped with a low-energy cardiofocal collimator and a computer interface (ICON; Siemens). Stress single-photon emission computed tomography (SPECT) was performed 10 min after stress testing, and resting SPECT was performed 4 h after stress imaging. Ninety projections were acquired for 20 s each in 4/360° intervals and stored in 64 × 64 matrices. A 15% symmetrical energy window, centered on the 70-keV peak, was used. Tomographic reconstruction was performed by the standard filtered back-projection technique using a Butterworth filter with a cutoff frequency of 0.5 cycles/pixel and an order of 5. No corrections were made for attenuation or scatter.

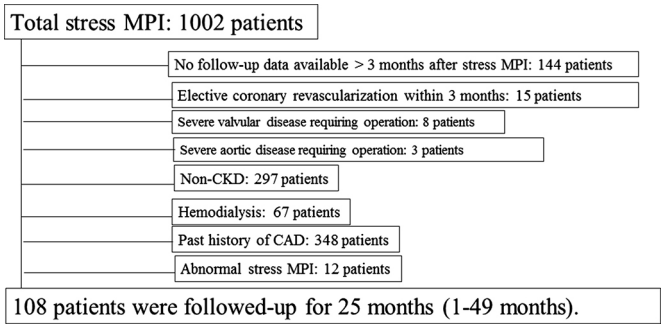

Fig. 1. Flow diagram for the study population. MPI, myocardial perfusion imaging; CAD, coronary artery disease; CKD, chronic kidney disease.

SPECT images were reoriented along the short, horizontal, and vertical long axes for analysis. SPECT data analysis was performed on the basis of agreement among 2 or more experienced radiologists, who were blinded to patient identity and clinical information. Defects were classified as reversible (including partially reversible) or fixed (irreversible). SPECT images were assessed to determine the presence, location, and severity of any perfusion defects. The left ventricle was divided into 17 segments, and each segment was assigned a score using a 5-point scoring system (0 = normal; 1 = mildly reduced; 2 = moderately reduced; 3 = severely reduced; and 4 = uptake absent). The sum of SSS, scores at rest (summed rest score; SRS), and the difference between stress and resting scores (SDS) were calculated. The score for each myocardial segment on the images was calculated, and a stress score for each segment was determined. As demonstrated in previous studies, based on an excellent cardiovascular prognosis, patients with SSS of <4 were considered to be normal [3,15,16]. Quantitative gated SPECT (QGS) was not usually performed at our institution. Therefore, only 18 patients were assessed by QGS.

CKD classifications

eGFR was calculated using the 4-variable Modified Diet in the Renal Disease equation [17]: eGFR = 175 × serum creatinine (mg/dl) − 1.154 × age − 0.203 × 0.741 (Japanese) × 0.742 (if female).

eGFR was determined at a mean of 30 ± 23 days from the time of conduction of MPI. CKD was defined according to National Kidney Foundation criteria [18] as eGFR of <60 ml/min/1.73 m^2 and/or persistent proteinuria for >3 months. CKD was categorized into the following stages depending on the basis of eGFR: Stage I > 90 ml/min/1.73 m^2 (n = 7); Stage II 60–90 ml/min/1.73 m^2 (n = 27); Stage III 30–60 ml/min/1.73 m^2 (n = 51); Stage IV 15–30 ml/min/1.73 m^2 (n = 16); and Stage V < 15 ml/min/1.73 m^2 (n = 7). None of the patients in this study suffered acute renal failure (defined by >0.5 mg/dl increase in serum creatinine levels in <2 weeks, or an increase of >20% over baseline if serum creatinine levels were >2.5 mg/dl).

Echocardiography and ankle brachial index

The left ventricular ejection fraction (LVEF) was measured by M-mode echocardiography within 1 month of MPI. Peripheral arterial disease (PAD) was defined on the basis of previous medical history and/or an ankle brachial index of <0.9 [19,20] and/or previous angioplasty for peripheral arteries.

Endpoints and follow-up

Follow-up commenced after assessing cardiac function and stress MPI. Endpoints were cardiac death, nonfatal myocardial infarction (MI), and Braunwald class III unstable angina requiring hospitalization. Cardiac deaths included sudden cardiac death, fatal MI, death due to heart failure, or death due to arrhythmia. Sudden cardiac death was defined as witnessed cardiac arrest, death within 1 h of onset of acute symptoms, or unexpected death for those who had been considered well for the previous 24 h. Braunwald class III

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