Incremental Prognostic Value of Cardiac Function Assessed by ECG-Gated Myocardial Perfusion SPECT for the Prediction of Future Acute Coronary Syndrome

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Background The prognostic value of ECG-gated rest 201TI/stress 99mTc-tetrofosmin myocardial perfusion single-photon emission computed tomography for the prediction of acute coronary syndrome (ACS: myocardial infarction (MI) and unstable angina (UA)) and the implications of ejection fraction (EF) has not yet been defined in Japanese.

Methods and Results The 1,895 patients were followed up for the occurrence ACS. The mean follow-up interval was 26.9±15.5 months. The 142 patients with revascularization within 60 days were censored. Summed stress score (SSS) and summed difference score (SDS) were calculated. The 19 MI and 29 UA occurred (1.1% and 1.6%, respectively). Univariate Cox analysis showed that hypertension (Wald 5.09, p<0.05), poststress EF (Wald 10.9, p<0.01), SSS (Wald 12.4, p<0.001) and SDS (Wald 18.7, p<0.001) were significant predictors of ACS. Multivariate Cox analysis showed that hypertension (Wald 4.27, p<0.05) and SDS (Wald 8.59, p<0.01) were independent predictors. When multiple clinical risk factors (number of coronary risk factors ≥2), significant ischemia (SDS ≥4) and low EF (EF <45%) were applied to multivariate Cox analysis, the combination of significant ischemia and low EF showed the highest predictive value (Wald 11.9; p<0.001) for future ACS.

Conclusion Poststress EF added incremental prognostic value for the prediction of ACS. (Circ J 2008; 72: 2035–2039)

Key Words: Acute coronary syndrome; Coronary artery disease; Gated SPECT; Prognosis; Single-photon emission computed tomography

Myocardial perfusion single-photon emission computed tomography (SPECT) has been shown to provide incremental prognostic value over clinical data and improves stratification of patients into different levels of risk in American populations1–3 as well as in Japanese patient populations4 However, the predictive value of poststress ejection fraction (EF) provided by electrocardiogram (ECG)-gated rest 201TI/stress 99mTc-tetrofosmin dual-isotope myocardial perfusion SPECT for future acute coronary syndrome (ACS) events has not yet been reported in a large Japanese population. Furthermore, the incremental prognostic value of poststress EF to myocardial perfusion parameters is unclear. The goal of this study was to define the prognostic value of ECG-gated myocardial perfusion SPECT for the prediction of ACS.

Study Population We prospectively identified 2,170 consecutive patients with known or suspected coronary artery disease who underwent dual isotope SPECT with either exercise or pharmacological stress between November 2001 and December 2005, at Nihon University Surugadai Hospital. Exclusion criteria were as follows: unstable angina (UA) or acute myocardial infarction (AMI) within 2 weeks from onset; hypertrophic or dilated cardiomyopathies, age less than 20 years; refusal to participate in the study. From the 1,988 patients without exclusion criterion, those with atrial fibrillation or atrial flutter (total 93 patients) were also excluded because arrhythmia might have affected the ECG-gated parameters. The total follow-up group consisted of 1,895 patients (follow-up rate 92.5%). Of this initial population, 142 patients revascularized in the first 60 days after nuclear testing were excluded from the prognostic portion of the analyses, and the prognostic data presented here are based on a subset of 1,753 patients.

Stress Myocardial Perfusion SPECT Protocol All patients underwent stress dual-isotope myocardial perfusion SPECT as previously described2–5 Initially, 201TI (111 MBq) was injected intravenously and rest 201TI imaging was initiated 5 min after injection of the isotope. Patients then performed bicycle ergometer stress or had
pharmacological (adenosine triphosphate) stress induced. Exercise was stopped when the patient’s heart rate reached more than 85% of the maximum predictive heart rate (220−age). When a patient’s heart rate did not reach 85% of the maximum predictive heart rate, or there was severe chest pain on ergometer stress, pharmacological stress by adenosine triphosphate took over as the mode of stress. Low level (25 W) ergometer exercise was added during adenosine triphosphate stress whenever possible to minimize the side-effects related to adenosine triphosphate. 99mTc-tetrofosmin was injected 1 min prior to the end of exercise stress. 99mTc-tetrofosmin was also injected 3 min after the start of adenosine triphosphate injection (120 µg·kg⁻¹·min⁻¹, total 6 min). Stress acquisition was started within 30 min after stress 99mTc-tetrofosmin injection (740 MBq). Patients were asked to discontinue β-blockers for 48 h, and nitrates and caffeine for 24 h prior to the study.

** Acquisition Protocol and Image Reconstruction**

Rest and stress scans were acquired on a dual detector gamma camera in the 90° detector configuration (E-CAM, Siemens Medical Solutions, Erlangen, Germany), using a high-resolution, low-energy collimator, pseudo-continuous detector rotation, 64 projections over an 180° arc from the horizontal axis images were generated.⁶

Filtered raw projection images were automatically reconstructed into transverse datasets. The 3-dimensional location of the long axis of the left ventricle was determined automatically, and the short-, vertical long- and horizontal long-axis images were generated.⁶

** Image Interpretation**

SPECT images were scored semiquantitatively by an experienced nuclear cardiologist (N.M) using a 20-segment model of the left ventricle with a 5-point scale (0=normal uptake, 1=mild hypoperfusion, 2=moderate hypoperfusion, 3=severe hypoperfusion and 4=no uptake).⁴,⁵ The interobserver reproducibility of scoring in our laboratory, determined by Cohen’s kappa analysis, has been reported to be excellent (kappa=0.92).⁶ In this model, the left anterior descending artery distribution territory comprised 10 segments (segments 1–3, 7–9, 13, 14, 19, and 20), the left circumflex artery comprised 5 segments (segments 5, 6, 11, 12, 17 and 18) and the right coronary artery comprised 4 segments (segments 4, 10, 15 and 16) (Fig 1). Summed stress score (SSS) and summed rest score were calculated by adding the scores of 20 segments in the stress and rest images, respectively. Summed difference score (SDS) was derived as the difference between the stress and rest scores. Non-reversible segments (stress-rest score combinations of 4–4, 4–3, 3–3, 3–2, or 2–2) were judged as infarcted myocardium.⁴,⁸

** ECG-Gated Parameters**

Poststress EF using 8-frame ECG-gating was automatically calculated by QGSTM software (Cedars-Sinai Medical Center, Los Angeles, CA, USA).⁹ When the mitral valve plane or left ventricle contour was inappropriate for visual interpretation, manual fitting was applied. As previously described, poststress EF <45% was recognized as low left ventricular (LV) function.¹⁰,¹¹

** Patient Follow-up**

Patient follow-up was performed by checking the medical records or by mail interview by individuals who were unaware of the patients’ test results. Cardiac events were defined as follows: (1) nonfatal AMI as evidenced by an elevation of creatine kinase and creatine kinase-MB more than twice the normal values, (2) UA defined as Braunwald severity class II and III (acute and subacute angina at rest), and clinical circumstance B (primary UA) angina.¹² All patients included in this report were followed for at least 1 year. The mean follow-up interval was 26.9±15.5 months.

The protocol was approved by the hospital’s ethical committee, and written informed consent was given by all patients.

** Statistical Analysis**

Continuous variables are expressed as the means±standard deviation. A p-value <0.05 was considered statistically significant. The Cox proportional hazard regression model (Dr SPSS II, ver.11) was applied in a forward stepwise fashion to define models with ACS (AMI and UA) as separate endpoints. The threshold for entry of variables into all models was p<0.05. A statistically significant increase in the Wald value of the model after the addition of the nuclear variables defined incremental prognostic value. The probability of survival without ACS was estimated using the Kaplan-Meyer method.
Results

Patient Population

Patients' characteristics are listed in Table 1; 837 patients were designated to exercise stress alone, 916 patients to pharmacological stress or a combination of low-grade exercise and pharmacological stress. Comparison of the patients undergoing exercise to those who underwent pharmacological stress revealed that the patients undergoing pharmacological stress more frequently had hypertension, diabetes mellitus, smoking and previous myocardial infarction (MI). The pharmacological stress group also had advanced age and higher SSS and SDS than the exercise group. Patients who underwent pharmacological stress also showed lower post-stress EF than patients who underwent exercise (Table 1).

Outcome Events

Revascularization cases within the first 60 days after nuclear testing numbered 142 (7.5%). Among 1,753 patients, 19 cases of AMI (1.1%) and 29 (1.6%) of UA occurred.

Prediction of Cardiac Events

Univariate Cox proportional hazard regression analysis of age, gender, history of prior MI, cardiac risk factors, SSS, SDS and poststress EF showed that the predictors of ACS were history of hypertension (Wald 5.09; p<0.05), SSS (Wald 12.4; p<0.001), SDS (Wald 18.7; p<0.001) and poststress EF (Wald 10.9; p<0.01) (Table 2). Multivariate Cox proportional hazard regression analysis showed that SDS (Wald 8.59; p<0.01) and hypertension (Wald 4.27; p<0.05) were the independent predictors of ACS (Table 3).
Annual Event Rates and Event Survival Rates in Subgroups

Annual event rates of ACS in subgroups are depicted in Fig. 2. There was statistical significance (p<0.05) of the annual ACS rate between the group with SDS <4 (0.9%/year) and the group with SDS ≥ 4 (2.6%/year). There was also statistical significance (p<0.05) of the annual ACS rate between the group with EF ≥ 45% (0.9%/year) and the group with EF <45% (2.9%/year).

Fig 3 shows the probability of survival without ACS in patients with SDS <4 and those with SDS ≥ 4. These groups were separated significantly (log rank <0.01). The probability of survival without ACS in the group with a normal EF (≥45%) and the group with low poststress EF (<45%) is shown in Fig 3, and these groups were also separated significantly (log rank <0.001).

Combined Assessment of Myocardial Perfusion and EF for Predicting ACS

The predictive value of the cumulative clinical risk factors (number of coronary risk factors ≥ 2), significant myocardial ischemia (SDS ≥ 4), low poststress EF (<45%) and the combination of significant myocardial ischemia and low poststress EF for predicting ACS are shown in Fig 4. The cumulative clinical risk factors alone was not a significant predictor (Wald 0.66; p=0.41), but significant myocardial ischemia (Wald 9.0; p<0.01) and low poststress EF (Wald 7.4; p<0.01) were significant predictors of ACS. However, the combined assessment of significant myocardial ischemia and low poststress EF was the best predictor (Wald 11.9; p<0.001) than myocardial ischemia alone or low EF alone.

Discussion

We previously described the prognostic value of myocardial perfusion SPECT for the prediction of nonfatal AMI, UA and cardiac death in a Japanese population. However, the prognostic significance and incremental value of poststress EF by ECG-gated myocardial perfusion SPECT for the prediction of ACS, which includes nonfatal MI and UA, has not been investigated in the Japanese population. Sharir et al showed in 1,680 patients that poststress EF is a strong and independent predictor of cardiac death and cardiac death or nonfatal MI in an American population. They further analyzed the data in which cardiac death and nonfatal MI were separated, and demonstrated that poststress EF was the best predictor of cardiac death, whereas SDS was the best predictor of nonfatal MI. However, poststress EF was not an independent predictor of nonfatal MI. On the other hand, our data from a univariate Cox proportional hazard regression analysis suggested that SDS and low poststress EF were significant predictors of not only AMI, but also UA. Similar to the results of Sharir et al, our data from the multivariate Cox proportional hazard regression analysis indicated that independent predictors for predicting ACS were SDS (Wald 8.59, p<0.01) and hypertension (Wald 4.27, p<0.05), whereas poststress EF was not.

We previously documented that a normal SSS group (SSS, 0–3) had a low annual ACS event rate (0.9%/year). The present study showed that the probability of future ACS events defined by SDS and annual ACS rates in a group of patients with a minimum amount of stress-induced ischemia (SDS<4) was significantly lower than that in the patients with significant myocardial ischemia (Fig 2). This finding suggests that the indication for revascularization for eliminating future ACS events would be defined by the SDS. For patients who show a minimum amount of ischemia (SDS<4), medical therapy would be recommended because their annual ACS event rate is less than 1%. Conversely, patients who have a large amount of ischemia (SDS ≥ 8) may benefit from revascularization.

Multivariate Cox proportional hazard regression analysis showed that the addition of functional data (poststress EF <45%) to significant myocardial ischemia (SDS ≥ 4) re-
sulted in a significant increase in the Wald value in predicting ACS. These finding were also in good agreement with previous reports in American populations.\textsuperscript{13,14}

Previous prognostic research in a multicenter study in Japan (J-ACCESS)\textsuperscript{5–18} which combined cardiac death, nonfatal MI and severe heart failure requiring hospitalization as major cardiac events, demonstrated that the combination of rest EF and SSS is a strong predictor of major cardiac events. However, this combination failed to predict hard cardiac events such as ACS and cardiac death. The discrepancy between the J-ACCESS study and ours might be the difference in the study design used. The J-ACCESS study did not gather the images to a core center, instead they were interpreted at 117 participating hospitals, and this may have resulted in non-uniformity of image interpretation.

Study Limitations
First, we used an 8-frame ECG-gating method for calculating poststress EF by QGS\textsuperscript{TM}, but this method has been found to underestimate LVEF by 3.7–4.0% because of undersampling of the time–volume curve.\textsuperscript{19} The 16-frame gating method should provide more accurate poststress EF and prognostic value in comparison to the 8-frame gating method. Second, our SPECT protocol used rest 201Tl/stress \textsuperscript{99m}Tc-tetrofosmin separate acquisition, and so the results of our study may not be applicable to other laboratories that use a single isotope protocol where myocardial perfusion parameters are concerned. Third, although the diagnoses of nonfatal MI and UA were firmly established in most of the patients, the exact cause of sudden death could not be known in each patient. However, previous clinical trials that concern prospective analysis of patients’ prognoses have included these endpoints as separate outcomes.\textsuperscript{13,14} Fourth, the prolonged time between stress and poststress image acquisition (30–50 min) might have resulted in an overestimation of poststress EF\textsuperscript{20,21} and the poststress EF might not represent the amount of stress-induced ischemia because of the inclusion of 476 (27.1%) patients with prior MI, in whom the difference between rest and poststress EF is not as much as in those without MI.

Conclusions
Our data indicate that SDS is a strong and independent predictor of the future occurrence of ACS, whereas poststress EF alone is not. However, when low poststress EF (<45%) is combined with significant myocardial ischemia (SDS ≥4), it provides valuable prognostic information for predicting future ACS events.

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References