Combined Assessment of Myocardial Perfusion and Function by ECG-Gated Myocardial Perfusion Single-Photon Emission Computed Tomography for the Prediction of Future Cardiac Events in Patients With Type 2 Diabetes Mellitus

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Background: The mid-term prognostic significance of ECG-gated single-photon emission computed tomography (SPECT) remains unclear in Japanese patients with type 2 diabetes mellitus (DM). In the present study rates of future cardiac events (nonfatal acute myocardial infarction (AMI), cardiac death (CD) and severe heart failure (HF) requiring hospitalization) were compared in patients with and without DM.

Methods and Results: 1,810 patients (563 DM and 1,247 non-DM) we followed for a mean of 26.3±15.5 months. Summed stress score (SSS), summed difference score (SDS), poststress ejection fraction (EF) and resting end-diastolic volume (EDV) were calculated. In total, 20 cases of AMI (9 in DM (1.59%) and 11 in non-DM (0.88%)), 20 of CD (7 in DM patients (1.24%) and 13 in non-DM (1.04%)) and 54 of severe HF (31 in DM (5.5%) and 23 in non-DM (1.84%)) occurred. Univariate Cox analysis showed that, in DM patients, predictors of total cardiac events were poststress EF (Wald 60.4; P<0.001), resting EDV (Wald 53.8; P<0.001), SSS (Wald 39.6; P<0.001), SDS (Wald 26.1; P<0.001), history of prior MI (Wald 4.32; P<0.05) and hemoglobin A1c value (Wald 4.30; P<0.05). Multivariate Cox analysis showed that poststress EF (Wald 9.85; P<0.01) and SDS (Wald 6.19; P<0.01) were independent predictors of total cardiac events.

Conclusions: Combined assessment of perfusion and function by ECG-gated SPECT may predict future cardiac events in type 2 DM patients. (Circ J 2011; 75: 376–382)

Key Words: Coronary artery disease; Diabetes mellitus; Gated single-photon emission computed tomography; Prognosis

Cardiovascular complications, especially coronary artery disease (CAD), are the leading cause of death or acute myocardial infarction (AMI).1-5 The cardiovascular mortality rate in male patients with diabetes mellitus (DM) has been reported to be more than twice that of male patients without DM and 4-fold in female DM patients as compared with female patients without DM.6 Kang et al6 compared the accuracy of detecting significant CAD using myocardial perfusion single-photon emission computed tomography (SPECT) in patients with and without DM, and they concluded it is comparable for the diagnosis of coronary disease in diabetic and non-diabetic patients. We have previously documented that myocardial perfusion SPECT could be used to predict future cardiac events (nonfatal AMI and cardiac death (CD)) in a Japanese population.7-9 In the present study we investigated whether ECG-gated SPECT can still give prognostic information for patients with DM in terms of those major cardiac events. Recently, a Japanese assessment of cardiac events and survival by quantitative gated SPECT (J-ACCESS 2) in patients with asymptomatic DM documented the short-term cardiac event rates (ie, in 1 year).10 Therefore, we also compared the cardiac event rates in J-ACCESS 2 and the present study.11,12

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Methods

Study Population
We prospectively identified 2,239 consecutive patients with known and suspected CAD who had undergone dual isotope SPECT with either exercise or pharmacological stress between November 2001 and March 2006, at Nihon University Surugadai Hospital. Exclusion criteria were as follows: AMI within 2 weeks of onset; hypotrophic and dilated cardiomyopathies; age less than 20 years; refusal to participate. From the 2,057 patients satisfying the criteria, those with atrial fibrillation and atrial flutter (total, 93 patients) were also excluded because the arrhythmia might have affected the ECG-gated parameters. Therefore, the initial follow-up population was 1,964 patients (follow-up rate 95.4%). Of this initial population, 154 patients who were 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 1,810 patients. The definitions of type 2 DM were hemoglobin A1c (HbA1c) ≥6.5% or abnormal type with 75 g oral glucose tolerance test or the patient undergoing pharmacological (adenosine triphosphate) stress. Exercise was stopped when the patient’s heart rate reached more than 85% of the maximum predictive heart rate (220–age). If the patients’ heart rate did not reach 85% of the maximum predictive heart rate, or if the patient complained of severe chest pain (CP) on ergometer stress, pharmacological stress by adenosine triphosphate replaced exercise 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. 99m-technetium (99mTc)-tetrofosmin was injected 1 min prior to the end of exercise stress and was also injected 3 min after the start of adenosine triphosphate injection (120 μg·kg⁻¹·min⁻¹, total 6 min). Stress image acquisition was started within 30 min after 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, pseudocontinuous detector rotation, 64 projections over an 180° arc from the right anterior oblique (RAO) to the left posterior oblique (LPO), and a noncircular orbit. Poststress images were acquired in the supine and prone positions. ECG-gated rest 201TI images were acquired for 23 s/projection for 64 stops (32 stops/head), an acquisition time of 16 min. ECG-gated 99mTc-tetrofosmin poststress images in the supine position were acquired for 20 s/projection (14 min) and non-ECG-gated 99mTc-tetrofosmin prone poststress images were acquired for 18 s/projection (9 min). For prone-position imaging, patients lay on the table and the detectors rotated underneath the table from the RAO to the LPO. 201TI images at rest were acquired with a 30% symmetrical window over the 80 keV 201TI photopeak. All 99mTc-tetrofosmin images were acquired with a 15% symmetrical window over the 140 keV 99mTc photopeak. The raw projection datasets were filtered with a Butterworth filter (order 10 and cutoff frequency 0.38 cycles/cm for rest images; order 5 and cutoff frequency 0.5 cycles/cm for stress supine images; order 5 and cutoff frequency 0.42 cycles/cm for stress prone images). Neither scatter nor attenuation correction was applied. 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 then the short-, vertical long- and horizontal long-axis images were generated. All patients underwent stress image acquisitions in the supine and prone positions. Interpretation of the inferior walls was considered with prone-position imaging because it can decrease the frequency of attenuation artifacts in the inferior walls.

Image Interpretation
SPECT images were semiquantitatively scored by an experienced nuclear cardiologist (M.K. or 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). The interobserver reproducibility of scoring determined by Cohen’s κ analysis has been reported as excellent (κ=0.92). In this model, the distribution territory of the left anterior descending artery comprises 10 segments (segments 1–3, 7–9, 13, 14, 19 and 20), that of the left circumflex artery comprises 6 segments (segments 5, 6, 11, 12, 17 and 18) and the right coronary artery comprises 4 segments (segments 4, 10, 15 and 16) (Figure 1). Summed stress score (SSS) and summed rest score (SRS) were calculated by adding the scores of the 20 segments in the stress and rest images, respectively. The 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.

ECG-Gated Parameters
Poststress ejection fraction (EF) and resting end-diastolic volume of the left ventricle (EDV) using 8-frame ECG-gating were automatically calculated by QGS software (Cedars-Sinai Medical Center, LA, USA). When the mitral valve plane or left ventricular contour was inappropriate for visual interpretation, manual fitting was applied.

Follow-up
Follow-up of the patients was performed by checking the medical records or a mail interview by individuals who were unaware of the patients’ test results. Cardiac events were defined as follows: AMI as evidenced by an elevation of the creatine kinase and creatine kinase-MB levels more than twice the normal values; CD as noted and confirmed by the review of hospital chart or physician’s records; severe heart failure (HF) requiring hospitalization as noted and confirmed by review of hospital chart. All patients included in this study were followed for at least 1 year. The mean follow-up interval was 26.3±15.5 months.

The protocol was approved by the hospital’s ethics committee, and written informed consent was given by all patients.
Statistical Analysis
All continuous variables are expressed as means ± standard deviation. We used the unpaired t-test to compare the mean of the continuous variables. The chi-square test was used to compare categorical variables. A threshold <0.05 was considered statistically significant. The Cox proportional hazard regression model (SPSS v11.0, Chicago, IL, USA) was applied to the DM group in a forward stepwise fashion to define models with total cardiac events (AMI, CD and severe HF requiring hospitalization) as combined endpoints. The proportionality of the Cox hazard model was validated by log-minus-log function. The threshold for entry of variables into all models was P<0.05. The probability of survival without major cardiac events was estimated using the Kaplan-Meier method.
Results

Patient Population
The patients' characteristics are listed in Table 1. The DM group consisted of 563 patients and the non-DM group of 1,247 patients. In the DM group, the average HbA1c was 7.06%. The prevalences of hypertension, dyslipidemia, smoking habit, history of prior MI and history of percutaneous coronary intervention (PCI) or coronary artery bypass graft were higher in the DM group than in the non-DM group. Body mass index, resting EDV, SSS and SDS were also higher in the DM group than in the non-DM group. Poststress EF was lower in the DM group than in the non-DM group.

According to our cardiac symptomatic criterion, asymptomatic patients and those with typical CP were more frequent, but non-anginal and atypical CP, were less frequent in the DM group than in the non-DM group. The frequency of shortness of breath was identical in both groups (Table 1).

Outcome Events
Revascularization cases within the first 60 days after nuclear imaging numbered 154 (7.8%). Among 1,810 patients, 20 (1.1%) cases of AMI (9 in DM group, 11 in non-DM group) and 20 (1.1%) of CD (7 in DM group, 13 in non-DM group) occurred, and 54 patients (2.9%) were admitted to hospitals because of HF (31 in DM group, 23 in non-DM group). Hard cardiac event rates, including AMI and CD, tended to be higher in the DM group than in the non-DM group (2.84% vs. 1.92%, respectively, P=NS). However, total cardiac event rates, including AMI, CD and severe HF requiring hospitalization, were significantly higher in the DM group than in the non-DM group (8.34% vs. 3.76%, respectively; P<0.001).

Annual Event Rates in DM and Non-DM Groups
Annual event rates of AMI, CD and severe HF requiring hospitalization in the DM and non-DM groups are shown in Figure 2. The annual total event rate was significantly higher in the DM group (4.04%/year) than in the non-DM group (1.66%/year, P<0.001). Figure 3 shows the probability of survival without total cardiac events in the DM and non-DM groups. The DM group has a worse prognosis in comparison with the non-DM group. DM, diabetes mellitus.
Figure 4 shows the relationship between the log hazard ratio for predicted total cardiac events and SSS in both groups.

**Predictors of Total Cardiac Events in the DM Group**

Univariate Cox proportional hazard regression analysis was performed for advanced age, sex, history of prior MI, various coronary risk factors, SSS, SDS, poststress EF, resting EDV and HbA1c. It revealed that predictors of total cardiac events were poststress EF (Wald 60.4; P<0.001), resting EDV (Wald 53.8; P<0.001), SSS (Wald 39.6; P<0.001), SDS (Wald 26.1; P<0.001), history of prior MI (Wald 4.32; P<0.05) and HbA1c (Wald 4.30; P<0.05) (Table 2). Multivariate Cox proportional hazard regression analysis showed that poststress EF (Wald 9.85; P<0.01) and SDS (Wald 6.19; P<0.01) were the independent predictors of total cardiac events (Table 3).

**Figure 5** shows both the survival curve without total cardiac events in patients in the DM group with normal scintigraphy, which included normal poststress EF (poststress EF ≥45%) and no ischemia (SDS = 0), and the significantly lower event-free survival in DM patients with abnormal scintigraphy, which included either poststress EF <45% or SDS ≥1 (total cardiac event rate: 7.01% vs. 0.44%/year, abnormal vs. normal, respectively; P<0.0001).

**Discussion**

Cardiac symptoms in DM patients are more often asymptomatic or atypical than in non-DM patients in previous studies.21–24 However, symptoms, cardiac event rates and involvement of myocardial perfusion SPECT parameters in Japanese patients with and without DM have not been well characterized. When compared with previous studies of Western diabetic populations, rates of asymptomatic patients are similar in the Japanese diabetic population (47.5% in Western vs. 46.7% in Japanese).24 According to the classification of CP by Diamond and Forrester, rates of symptomatic patients, including those with non-anginal, atypical and typical CP, are lower in Japanese DM patients than in Western DM patients (40.2% vs. 43.7%, respectively).26,24 Shortness of breath is more frequently present in Japanese than in Westerners (12.9% vs. 8.7%). The frequency of smokers in Japanese and Western populations may account for this dif-

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**Table 2. Predictors of Total Cardiac Events by Univariate Cox Proportional Hazard Regression Analysis in the DM Group**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Wald</th>
<th>P value</th>
<th>95% CI</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.34</td>
<td>0.24</td>
<td>0.98 – 1.05</td>
<td>1.02</td>
</tr>
<tr>
<td>Male</td>
<td>0.25</td>
<td>0.61</td>
<td>0.55 – 2.67</td>
<td>1.22</td>
</tr>
<tr>
<td>Prior MI</td>
<td>4.32</td>
<td>&lt;0.05</td>
<td>1.04 – 3.78</td>
<td>1.98</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.07</td>
<td>0.78</td>
<td>0.55 – 2.19</td>
<td>1.10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.35</td>
<td>0.12</td>
<td>0.84 – 4.03</td>
<td>1.84</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.16</td>
<td>0.68</td>
<td>0.59 – 2.22</td>
<td>1.14</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>1.59</td>
<td>0.20</td>
<td>0.03 – 2.02</td>
<td>0.27</td>
</tr>
<tr>
<td>SSS</td>
<td>39.6</td>
<td>&lt;0.001</td>
<td>1.04 – 1.08</td>
<td>1.06</td>
</tr>
<tr>
<td>SDS</td>
<td>26.1</td>
<td>&lt;0.001</td>
<td>1.06 – 1.15</td>
<td>1.10</td>
</tr>
<tr>
<td>Poststress EF</td>
<td>60.4</td>
<td>&lt;0.001</td>
<td>0.89 – 0.93</td>
<td>0.91</td>
</tr>
<tr>
<td>Resting EDV</td>
<td>53.8</td>
<td>&lt;0.001</td>
<td>1.01 – 1.02</td>
<td>1.01</td>
</tr>
<tr>
<td>HbA1c</td>
<td>4.30</td>
<td>&lt;0.05</td>
<td>1.01 – 1.52</td>
<td>1.24</td>
</tr>
</tbody>
</table>

CI, confidence interval. See Table 1 for other abbreviations.

**Table 3. Predictors of Total Cardiac Events by Multivariate Cox Proportional Hazard Regression Analysis in the DM Group**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Wald</th>
<th>P value</th>
<th>95% CI</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>0.05</td>
<td>0.80</td>
<td>0.40 – 2.03</td>
<td>0.90</td>
</tr>
<tr>
<td>SSS</td>
<td>1.14</td>
<td>0.28</td>
<td>0.98 – 1.04</td>
<td>1.01</td>
</tr>
<tr>
<td>SDS</td>
<td>6.19</td>
<td>&lt;0.05</td>
<td>1.01 – 1.11</td>
<td>1.06</td>
</tr>
<tr>
<td>Poststress EF</td>
<td>9.85</td>
<td>&lt;0.01</td>
<td>0.90 – 0.97</td>
<td>0.94</td>
</tr>
<tr>
<td>Resting EDV</td>
<td>1.00</td>
<td>0.31</td>
<td>0.99 – 1.01</td>
<td>1.00</td>
</tr>
<tr>
<td>HbA1c</td>
<td>1.45</td>
<td>0.22</td>
<td>0.92 – 1.37</td>
<td>1.13</td>
</tr>
</tbody>
</table>

See Tables 1,2 for abbreviations.
In the present study, annual hard cardiac event (AMI and CD) rates were comparable between the DM and non-DM group (1.37% vs. 0.85%, respectively, \( P = NS \)). Zellweger et al documented cardiac event rates in a Western diabetic population, but did not refer to the HbA\(_1c\) values, so although the severity of DM in their population is unclear, when compared with that study, our annual hard cardiac event rates were lower in the Japanese diabetic population (3.10% vs. 1.37%, respectively). \(^{26}\) In the present study the rate of annual total cardiac events (AMI, CD and severe HF requiring hospitalization) was significantly higher in the DM group than in the non-DM group (4.04% vs. 1.66%, respectively, \( P < 0.001 \)).

Figure 2. Hospitalization for congestive HF should be categorized as a soft cardiac event not a hard cardiac event, because it is a nonfatal cardiac event in our definition. According to the UK Prospective Diabetes Study (UKPDS), hyperglycemia is strongly associated with the incidence of HF. \(^{25}\) Thus, it seems to be reasonable to include decompensated HF in the total cardiac events and to perform Cox proportional hazard analysis of this.

We previously described the prognostic value of myocardial perfusion SPECT for predicting nonfatal AMI and CD in a Japanese population. \(^{27}\) The major finding of the present study was the increased risk in the DM group against that in the non-DM group as a function of the SSS (Figure 4). Our results showed that the DM group has an absolutely increased risk for total cardiac events throughout all SSS. This finding also suggests that risk stratification using the SSS provided by myocardial perfusion SPECT is appropriate for diabetic patients. \(^{5}\)

Total cardiac events could be predicted by univariate Cox proportional hazard analysis. History of prior MI, SSS, SDS poststress EF, resting EDV and HbA\(_1c\) value were significant predictors of total cardiac events. It deserves mentioning that our data clearly indicated that the severity of DM, as defined by the HbA\(_1c\) value, is a significant predictor of total cardiac events by univariate analysis in Japanese DM patients, although the relationship between the severity of DM and cardiac event rates has not been reported previously. Conversely, multivariate Cox proportional hazard analysis showed that only poststress EF (Wald 9.85; \( P < 0.01 \)) and SDS (Wald 6.19; \( P < 0.01 \)) were independent predictors for total cardiac events in the DM group and the best predictor was poststress EF. This is in good agreement with a study by Sharir et al, which demonstrated that poststress EF and the extent of stress-induced ischemia were predictors of CD and MI. \(^{26}\) These findings together suggest that the parameters of stress ECG-gated myocardial perfusion SPECT provide the highest prognostic information for DM patients.

In conclusion, ECG-gated myocardial perfusion SPECT added incremental prognostic information regarding predicting future cardiac events in Japanese patients with DM. The present study also demonstrated the importance of a combined assessment of function and perfusion in those with DM.

**Study Limitations**

First, patients undergoing treatment with thiazolidinedines may have the risk of congestive HF. \(^{30}\) Despite the higher incidence of congestive HF in the present DM patients, we do not have enough medication data for this population. Second, we used an 8-frame ECG-gating method for calculating poststress EF by QGS, but this method has been found to underestimate EF by 3.7–4.0% because of undersampling of the time–volume curve. \(^{31}\) The 16-frame gating method would provide more accurate poststress EF and prognostic values in comparison with the 8-frame gating method. Third, the present study is

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**Figure 5.** Kaplan-Meier curves for survival without total cardiac events in patients with normal or abnormal scintigraphy in the diabetes mellitus group. The normal scintigraphy group showed excellent prognosis compared with the abnormal scintigraphy group.
a cross-sectional analysis, so we do not have enough data regarding changes in the HbA1c level during follow-up.

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**References**


