Prognostic Value of Stress Myocardial Perfusion Imaging in Patients With Mildly Impaired Systolic Left Ventricular Function or Left Ventricular Asynergy Without Chest Pain but With Suspected Coronary Artery Disease

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Background  The prognostic value of myocardial perfusion imaging (MPI) was investigated in patients with mildly impaired left ventricular (LV) function who had no chest pain but were suspected to have coronary artery disease (CAD).

Methods and Results  Consecutive patients (n=72, mean age = 67) who had no chest pain but with mildly impaired systolic LV function (mean LV ejection fraction = 52%) or LV asynergy and suspected to have CAD were followed up for 4.9 years after stress MPI. The follow-up time was censored at the occurrence of cardiac death, hospitalization for congestive heart failure (CHF), acute coronary syndromes (ACS), or revascularization. Images were scored using a 20-segment model and a 0–4 scale, and then the summed stress, rest, and difference scores (SDS) were calculated. During follow-up, there were 2 cases of cardiac death, 8 of hospitalization for CHF, 4 of ACS and 2 of revascularization. Cox regression demonstrated that SDS ≥4 was an excellent predictor of cardiac events in all patients (hazard ratio = 4.2, p=0.01), and especially in diabetic patients (hazard ratio = 28.4, p=0.01).

Conclusion  Stress MPI is useful for predicting cardiac events and may be performed in patients without chest pain if they have mildly impaired systolic LV function or LV asynergy. (Circ J 2006; 70: 762–767)

Key Words:  Cardiac events; Diabetes mellitus; Risk stratification; Silent myocardial ischemia; Systolic left ventricular dysfunction

Left ventricular (LV) global systolic function and volumes have been well documented as important predictors of prognosis in patients with coronary artery disease (CAD). In patients with chronic CAD, the LV ejection fraction (EF) measured at rest by either left ventriculography or radionuclide ventriculography is predictive of long-term prognosis. Specifically, as LVEF declines, mortality increases. In these patients, a resting EF <35% is associated with an annual mortality rate >3%. There is another report that a resting LVEF <40% is associated with an increase in the annual mortality rate >10% per year. However, it can be difficult to predict prognosis only by LVEF in patients with mildly impaired LV function (LVEF ≥40%) because to our knowledge there is no evidence of the importance of LVEF in patients with mildly impaired LV function. Which is the best predictor in patients with mildly impaired LV function? The ACC/AHA guidelines recommend the use of treadmill exercise testing or stress myocardial perfusion imaging (MPI) in patients with chest pain and an intermediate likelihood of CAD. Currently, there is no evidence to recommend the use of MPI in those patients without chest pain but who have mildly impaired LV function on echocardiography.

There are some reports on the predictive value of stress MPI in Japanese patients with symptoms including chest pain and normal systolic LV function, but none that stress MPI is useful for risk stratification in patients without angina but with mildly impaired LV function. The purpose of the present study was to prospectively investigate the prognostic value of stress MPI in such patients.

Methods

Study Population
We sorted the objective patients prospectively. We performed cardiac echocardiography based upon the symptoms of shortness of breath, palpitation or abnormal resting elec...

Table 1  Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>No chest pain</td>
<td>Known moderate or severe valvular heart disease</td>
</tr>
<tr>
<td>No history of CAD</td>
<td>Early coronary revascularization (within 6 months of the SPECT study)</td>
</tr>
<tr>
<td>40% ≤ LVEF &lt;50% or LVEF ≥50% with LV asynergy by cardiac echo study</td>
<td>CAD, coronary artery disease; LVEF, left ventricular ejection fraction; LV, left ventricular; SPECT, single-photon emission computed tomography.</td>
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</table>

(Circ J 2006; 70: 762–767)
trocardiogram (ECG) with no chest pain (typical, atypical, noncardiac) and no history of CAD. We performed stress myocardial perfusion single-photon emission computed tomography (SPECT) within 1 month of the echo study if it showed mildly impaired systolic LV function (40% ≤ LVEF < 50%) or LVEF ≥ 50% with LV asynergy. Inclusion and exclusion criteria are shown in Table 1. We identified 82 consecutive patients who had undergone stress thallium-201 (201TI, Daiichi Radioisotope, Tokyo, Japan) SPECT between June 1997 and June 2003. Patients with known moderate or severe valvular heart disease were not included.

Exercise Stress Myocardial Perfusion Protocol
Symptom-limited Bruce protocol exercise treadmill testing was performed. At near maximal exercise, 201TI (111 MBq) was injected, and exercise continued at maximal workload for 1 min. Patients were monitored for 3 min after stopping exercise. Exercise treadmill testing was considered positive for ischemic heart disease when ≥1 mm horizontal or down-sloping ST-segment depression occurred at 80 ms after the J point, or ≥2 mm upsloping ST-segment depression occurred at 80 ms after the J point. The stress cardiac scintigraphic imaging with 201TI was started 5 min after the end of exercise. Redistribution images were acquired 3 h later.

Pharmacologic Stress Myocardial Perfusion Protocol
Patients who could not exercise underwent pharmacologic stress testing with intravenous adenosine triphosphate (ATP, Adetphos, Kowa, Tokyo, Japan) infusion. ATP is a precursor of endogenous adenosine, with a very short half-life (<10 s). The effect of ATP is dependent mostly on its degradation to adenosine. ATP has been used in pharmacologic stress testing to detect CAD, with an accuracy similar to that of dipyridamole or adenosine. ATP stress testing is safe and useful in predicting the prognosis of patients with known or suspected CAD. ATP stress testing is performed using a constant infusion pump to infuse ATP at a rate of 0.16 mg·kg⁻¹·min⁻¹ for 6 min. 201TI 111 MBq was injected at 5 min after the ATP infusion. Electrocardiographic and hemodynamic monitoring was performed, and symptoms attributable to the ATP infusion were recorded.

Image Acquisition
MPI was performed with a triple-head rotating gamma camera (MULTISPECT-3, Siemens Medical Systems, Chicago, IL, USA) equipped with a cardiofocal collimator. Thirty projections were obtained in 4-degree steps for 20 s of imaging time each in a 360-degree orbit. All projections were stored in a 64×64 matrix. A 20% symmetric energy window centered on the 70 keV peak for 201TI were used. Tomographic reconstruction was performed by means of a standard filtered back-projection technique with a Butterworth filter cutoff of 0.1. Neither attenuation correction nor scatter correction was applied. Tomograms reoriented in the short-axis and horizontal and vertical long-axes were obtained.

Image Interpretation
A semiquantitative visual interpretation was performed using short and vertical long-axis myocardial tomograms that were divided into 20 segments for each study (Fig 1). These segments were assigned to 6 evenly spaced regions in the apical, midventricular, and basal slices of the short-axis views and 2 apical segments on the midventricular long-axis slice. Each segment was scored by consensus of 2 experienced observers using a 5-point scoring system (0=normal, 1=equivocal reduction in radioisotope uptake, 2=moderate reduction in radioisotope uptake, 3=severe reduction in radioisotope uptake, and 4=absence of detectable tracer uptake in a segment). Using the described 20-segment system and the 5-point scoring system, 3 nuclear variables were defined: the summed stress score (SSS), the summed rest score (SRS) and the summed difference score (SDS), which is the difference between the SSS and the SRS. We classified the above scores into normal (<4) and abnormal (≥4).

Echocardiography Study
The volume of a cube is based on a single LV measurement of the mid-cavity diameter derived from the M-mode data obtained from the parasternal long-axis view (Teichholz method). The quantitative determination of LVEF can be calculated using LV end-diastolic and end-systolic volume estimates. Global and regional LV systolic function can both be assessed accurately by experienced readers.

Patient Follow-up
During the mean follow-up period of 4.9 years (maximum: 8.5 years), the patients or their relatives (in the case of patient death) were contacted. In 5 cases informed consent for coronary angiography or percutaneous coronary intervention was not given by patients who showed a SPECT abnormality. The study endpoints were defined as cardiac death, development of acute coronary syndrome (ACS) or congestive heart failure (CHF) requiring hospitalization, or clinical need for late myocardial revascularization (<6 months). ACS was defined as unstable angina or nonfatal myocardial infarction. Unstable angina was defined as typical precordial chest pain of class IIB or IIIB in the Braunwald classification. Myocardial infarction was documented by a consistent history accompanied by elevation of cardiac enzymes and/or new Q wave on the ECG. The first cardiac event was used in the statistical analysis. When ACS, CHF and cardiac death occurred during the same admission, the event was recorded as cardiac death only.

The committee on Clinical Research of Toho University Ohashi Medical Center approved the protocol for prospec-
Eighty-two patients who were satisfied with inclusion criteria and did not have moderate or severe valvular heart disease underwent stress myocardial perfusion imaging.

72 patients

Finally, 72 patients were analyzed for this study.

Fig 2. Patients’ flow charts. Eighty-two patients who were satisfied with inclusion criteria and did not have moderate or severe valvular heart disease underwent stress myocardial perfusion imaging. Seven patients who underwent early coronary revascularization (within 6 months of the single-photon emission computed tomography study) were excluded and 3 patients were lost to follow-up, leaving a total of 72 patients for analysis.

Table 2 Patient Characteristics (n=72)

| Age (years) | 67±13 |
| Gender (M/F) | 47/25 |
| Symptoms |
| Asymptomatic | 34 (47%) |
| Shortness of breath | 35 (49%) |
| Palpitations | 3 (4%) |
| Abnormal rest ECG | 56 (78%) |
| Cardiac echo study |
| Mean LVEF (%) | 52±10 (range: 40–70) |
| 40% ≤ LVEF<50% | 32 (44%) |
| 50% ≤ LVEF<70% with LV asynergy | 40 (56%) |
| Risk factors |
| Diabetes mellitus | 28 (39%) |
| Hypertension | 50 (69%) |
| Hyperlipidemia | 27 (38%) |
| Hemodialysis | 21 (29%) |

ECG, electrocardiogram. Others abbreviations see in Table 1. Data, excluding age and LVEF, show patient numbers (%).

Table 3 Incidence of Cardiac Events

| Overall (n=72) | DM (n=28) | nonDM (n=44) |
| All cardiac events | 16 (22%) | 9 (32%) | 7 (16%) |
| Cardiac death | 2 (3%) | 2 (7%) | 0 (0%) |
| CHF | 8 (11%) | 2 (7%) | 6 (14%) |
| ACS | 4 (6%) | 3 (11%) | 1 (2%) |
| CABG | 2 (3%) | 2 (7%) | 0 (0%) |

DM, diabetes mellitus; CHF, congestive heart failure; ACS, acute coronary syndrome; CABG, coronary artery bypass graft.

Fig 3. Event-free survival in all patients. There was a significant difference in cardiac events between patients with summed difference score (SDS) ≥4 and SDS <4. Similar results were revealed for patients with summed stress score (SSS) ≥4 and SSS <4, or summed rest score (SRS) ≥4 and SRS <4.
tive study. Informed consent was given by all patients.

**Statistical Analysis**

Statistical analysis was performed with commercially available software for Windows systems (SPSS Advanced Models 11.0, SPSS Inc, Chicago, IL, USA). Continuous variables are reported as the mean ± SD. A value of p<0.05 was considered statistically significant. Comparisons between the 2 groups were performed using a one-way analysis of variance for continuous variables, the Bonferrri/Dunn test was used as post-hoc analysis when there was a difference between groups. The Fisher exact test was used for categorical variables when the number of observations was less than 5. Kaplan-Meier curves were generated to assess cardiac event-free survival and were compared using the log-rank test. Mann-Whitney nonparametric analysis was performed when there was no cardiac event in any group. Cox regression analysis was performed to determine predictors of cardiac events.

**Results**

**Patient Characteristics**

Seven patients who underwent early coronary revascularization (within 6 months of the SPECT study) were excluded and 3 patients were lost to follow-up. Therefore, 72 patients were analyzed statistically (Fig 2, Table 2). Of them 34 were asymptomatic (47%), 35 had shortness of breath (49%) and 3 had palpitations (4%). The mean LVEF was 52% with a range of 40–70%; 32 patients (44%) had a LVEF between 40% and 50%, and 40 (56%) had LVEF between 50% and 70% with LV asynergy.

**Physiologic and Pharmacologic Stress Testing**

Exercise treadmill testing was carried out for 24 of 72 patients (33%) and positive results occurred in 10 patients (42%). There was no significant difference in survival between patients with a positive result and those with negative result on exercise treadmill tests (p=0.3). SPECT abnormality was seen in 5 patients (50%) who had a positive result on exercise treadmill testing.

Pharmacologic stress testing was carried out for 48 patients (67%) and 2 showed ST depression on ECG. A SPECT abnormality was seen in 23 patients (48%). There was no significant difference in the occurrence of abnormal SPECT images between the patients undergoing treadmill exercise or ATP pharmacologic stress testing (p=0.2).

**Cardiac Events**

Cardiac events occurred in 16 of the 72 patients (22%): 2

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDS ≥4</td>
<td>4.2</td>
<td>1.4–12.4</td>
<td>0.01</td>
</tr>
<tr>
<td>SSS ≥4</td>
<td>3.9</td>
<td>1.3–11.6</td>
<td>0.01</td>
</tr>
<tr>
<td>SRS ≥4</td>
<td>2.4</td>
<td>0.9–6.4</td>
<td>0.09</td>
</tr>
<tr>
<td>LVEF ≤50%</td>
<td>1.1</td>
<td>0.4–3.0</td>
<td>0.8</td>
</tr>
<tr>
<td>DM</td>
<td>3.0</td>
<td>1.1–8.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

CI, confidence interval; SDS, summed difference score; SSS, summed stress score; SRS, summed rest score. Other abbreviations see in Tables 1, 3.

between 50% and 70% with LV asynergy.

**Fig 4.** Event-free survival in diabetic patients. There was a significant difference in cardiac events between diabetic patients with summed difference score (SDS) ≥4 and SDS <4, or summed rest score (SRS) ≥4 and SRS <4. SSS, summed stress score.
cardiac deaths (3%), 8 cases of CHF (11%), 4 of ACS (6%) and 2 of coronary artery bypass grafting (3%) (Table 3). One of the 4 ACS patient and one of the 8 CHF patient showed ST depression on ECG during pharmacologic stress.

Kaplan-Meier curves showed a significant difference in cardiac events between patients with SDS ≥4 and SDS <4 (p=0.0004), SSS ≥4 and SSS <4 (p=0.003), SRS ≥4 and SRS <4 (p=0.04) (Fig 3). There was no significant difference in the occurrence of cardiac events between patients undergoing treadmill exercise and those undergoing ATP pharmacologic stress testing (p=0.8).

**Cox Regression Analysis**

As shown in Table 4, Cox regression analysis after adjusting for age and gender showed that SDS ≥4, SSS ≥4 and diabetes mellitus (DM) were important predictors of cardiac events. An LVEF <50% was not a significant predictor of cardiac events.

**Patients With DM**

We performed a subanalysis of patients with DM, which was defined as a fasting glucose concentration ≥126 mg/dl (6.9 mmol/L) or a random (or “casual”) plasma glucose concentration ≥200 mg/dl (11.1 mmol/L). As shown in Fig 4, Kaplan-Meier curves showed a significant difference in cardiac events between diabetic patients with SDS ≥4 and SDS <4 (p=0.0008), SSS ≥4 and SSS <4 (p=0.01). Diabetic patients with SSS <4 did not have any cardiac events. Therefore, cardiac event-free survival of patients with SSS ≥4 was compared with that of patients with SSS <4 using Mann-Whitney non-parametric analysis at the follow-up time of 5.5 years. Cox regression analysis after adjustment for age and gender showed that SDS ≥4 and SRS ≥4 were important predictors of cardiac events in diabetic patients (Table 5). An LVEF <50% was not a significant predictor of cardiac events in these patients.

**Discussion**

We evaluated the prognostic value of stress MPI in patients who did not have chest pain but had echocardiographic evidence of mildly impaired systolic LV function or LV asynergy. In these patients, perfusion defect reversibility was a better predictor of cardiac events. Stress MPI may be useful for predicting cardiac events and should be performed in patients with mildly impaired systolic LV function or LV asynergy even if they do not have chest pain. Furthermore, in patients with DM, perfusion defect reversibility was much better predictor of cardiac events (hazard ratio: 28.4). Diabetic patients often have silent myocardial ischemia, with an incidence of 10–20% compared with nondiabetic patients. Stress MPI is more useful in diabetic patients without chest pain and with mildly impaired systolic LV function or LV asynergy.

Stress MPI is a relatively expensive examination compared with exercise ECG testing. In Japan, the cost of MPI is approximately US$800, whereas the cost of exercise treadmill testing is approximately US $60. However, it is important to determine whether we can detect the presence of CAD with only exercise treadmill testing in patients with mildly impaired LV function. In this study, exercise treadmill testing was performed in 24 of 72 patients (33%) and positive results occurred in 10 patients (42%). Generally, the sensitivity and specificity of exercise treadmill testing are 68% and 77%, respectively but in the present they were 60% and 63%, respectively. There was no significant difference in cardiac events between patients with positive and negative results for exercise treadmill tests (p=0.3). The Duke treadmill score is widely used to determine prognosis following exercise treadmill testing and on that basis 11 of the present patients were in the low risk group and 2 were in the high risk group.

Echocardiography was performed in patients with no symptoms based on the presence of an abnormal rest ECG (n=56) or because of routine screening in patients with a normal rest ECG (n=16). We also assessed LV function by echocardiography in patients with shortness of breath. If they had LV asynergy, stress MPI was performed. Why was LVEF not a predictor of CAD in this study population? Local asynergy of the LV was observed in 40 patients and impaired systolic LV function (LVEF <50%) without local LV asynergy was observed in 32 patients. We consider there are 2 possible reasons for this finding. First, LV asynergy was observed in approximately 50% of the patients in this study, therefore LVEF determined by M-mode echocardiography would not be a predictor for cardiac events. Second, systolic LV function was mildly impaired and the study population did not include patients with severely impaired systolic LV function.

The value of normal stress 201TI perfusion SPECT images in patients with suspected or known CAD is well established. In our study 21 of 72 patients had normal perfusion images and did not have any cardiac events. Normal MPI may promise a good prognosis, even in patients without chest pain but with mildly impaired systolic LV function or LV asynergy. In conclusion, we demonstrated that a SDS ≥4 is a better predictor of cardiac events in patients who do not have chest pain but have mildly impaired systolic LV function or LV asynergy, and especially in diabetic patients. Stress MPI may be useful for predicting cardiac events and should be performed in these patients.

**Acknowledgments**

We thank Kazuhiro Hamasaki and Takeharu Ando for their excellent technical assistance.

**References**

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**Table 5 Cox Regression Analysis in Diabetic Patients Adjusted for Age and Gender**

<table>
<thead>
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<th>95%CI</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>SDS ≥4</td>
<td>28.4</td>
<td>2.2–363.2</td>
<td>0.01</td>
</tr>
<tr>
<td>SRS ≥4</td>
<td>11.3</td>
<td>1.7–75.6</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF &lt;50%</td>
<td>0.8</td>
<td>0.2–3.6</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Abbreviations see in Tables 1, 4.


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