Normal myocardial perfusion scan portends a benign prognosis independent from the pretest probability of coronary artery disease. Sub-analysis of the J-ACCESS study

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Summary

\textbf{Background and purpose:} We assessed the usefulness of gated stress/rest 99mTc-tetrofosmin myocardial perfusion single photon emission computed tomography (SPECT) to predict ischemic cardiac events in Japanese patients with various estimated pretest probabilities of coronary artery disease (CAD).

\textbf{Methods and results:} Of the 4031 consecutively registered patients for a J-ACCESS (Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT) study, 1904 patients without prior cardiac events were selected. Gated stress/rest myocardial perfusion SPECT was performed and segmental perfusion scores and quantitative gated SPECT results were derived. The pretest probability for having CAD was estimated using the American College of Cardiology/American Heart Association/American College of Physicians—American Society of Internal Medicine guideline data for the management of patients with chronic stable angina, which includes age, gender, and type of chest discomfort. The patients were followed up for three years. During the three-year follow-up period, 96 developed ischemic cardiac events: 17 cardiac deaths, 8 nonfatal myocardial infarction, and 71 clinically driven

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Introduction

In the evaluation of patients with suspected coronary artery disease (CAD), the role of noninvasive imaging has increased exponentially over the past decade. The usefulness of stress/rest myocardial perfusion single photon emission computed tomography (SPECT) for the prediction of ischemic cardiac events has been widely accepted [1–4]. Noninvasive evaluation of symptomatic patients to further stratify risk beyond traditional risk factor scoring has primarily relied on stress myocardial perfusion imaging. But most of the data are of Western origin and existing data on the prognostic value of SPECT findings in the Japanese population are still scarce. The J-ACCESS (Japanese Assessment of Cardiac Events and Survival Study) investigation is a multicenter study to establish a Japanese database of patients with known or suspected ischemic heart disease by gated myocardial perfusion SPECT, and it has been demonstrated that large myocardial perfusion defects and decreased cardiac function could be predictors of cardiac events [5].

However, the estimated pretest probability of having significant CAD in a study population should be taken into account in the evaluation of the diagnostic accuracy of myocardial perfusion SPECT to detect or rule out the presence of CAD. Based on the database from the J-ACCESS investigation, the present study was designed to assess the usefulness of gated stress/rest myocardial SPECT findings to provide independent prognostic information for the prediction of ischemic cardiac events in patients with various pretest probabilities of CAD.

Subjects and methods

Study population

The design, entry criteria, and protocol of the J-ACCESS study have been published previously [6]. Briefly, the entry criteria include: age 20 years or more, and scheduled to undergo stress/rest electrocardiogram (ECG)-gated SPECT due to suspected or extant ischemic heart disease. Patients with the onset of myocardial infarction or unstable angina pectoris within three months, valvular heart disease, idiopathic cardiomyopathy, severe arrhythmia, or heart failure with class III or higher New York Heart Association (NYHA) classification, or severe liver or renal disorders were excluded. Among 4031 patients registered for the J-ACCESS study, patients with prior cardiac events, myocardial infarction or previous history of angina requiring percutaneous coronary intervention (PCI), as well as coronary artery bypass grafting (CABG), were excluded. A total of 1904 patients without prior cardiac events were selected for this analysis.

The pretest probability for having CAD was estimated using the American College of Cardiology/American Heart Association/American College of Physicians—American Society of Internal Medicine (ACC/AHA/ACP—ASIM) guideline data for the management of patients with chronic stable angina, which includes age, gender, and type of chest discomfort [7]. Typical angina was defined as having 3 characteristics: (1) substernal discomfort; (2) precipitated by physical exertion or emotions; and (3) relieved with rest or nitroglycerin. Atypical angina pectoris was defined as having 2 of 3 of the definition characteristics. Nonanginal chest pain was characterized as having 1 or none of the definition characteristics. Patients were categorized into a low probability (<0.15), intermediate probability (0.15–0.85), or high probability (>0.85) of having CAD. The institutional review board at each of the involved hospitals approved the protocol of the J-ACCESS study, and all patients gave written informed consent before entering the study.

SPECT imaging and stress ECG

Stress/rest 99mTc-tetrofosmin SPECT was performed depending on the preference of each
institution. The exercise protocol or the pharmaceu-
tical method to induce stress was not specially
regulated. The imaging conditions and image pro-
cessing procedures were surveyed separately [8].
The SPECT images were divided into 20 segments,
and visual perfusion scores for 99mTc-tetrofosmin
uptake in individual segments were scored in five
stages as follows: 0, normal; 1, mildly reduced; 2,
moderately reduced; 3, severely reduced; and 4,
no uptake. All images were scored at the partic-
ipating hospitals by hospital staff well-trained in
interpretation and quantification of typical SPECT
images. The summed stress score (SSS) and summed
rest score (SRS) were obtained by adding the scores
of the 20 segments of the respective images. The
summed difference score (SDS) was defined as the
difference between SSS and SRS [9]. The SPECT
images were considered normal when summed
scores were 0—3 and abnormal myocardial perfu-
sion defects was defined as summed scores >3.
Quantitative gated SPECT was performed at rest
and the parameters of ejection fraction (%), end-
diastolic volume (EDV, mL), and end-systolic volume
(ESV, mL) were calculated at each institution using
the same QGS software (Cedars Sinai Medical Cen-
ter, Los Angeles, CA, USA) [10]. The agreement
of summed scores among participating hospitals
and inter-institution reproducibility of gated SPECT
quantification was good [11].
A 12-lead ECG was recorded during the stress test
and significant ST-segment depression was defined
as a >1 mm of horizontal or downsloping depres-
sion occurring at 80 ms after the end of the QRS
complex.

Follow-up data
All patients underwent stress/rest myocardial per-
fusion SPECT using 99mTc-tetrofosmin. Age, gender,
subjective symptoms, history of present illness, the
image data, and examinations other than SPECT
were surveyed. The patients were followed up for
three years thereafter. The outcome cardiac events
recorded were cardiac death, nonfatal myocardial
infarction, and clinically driven revascularization
(surgery or angioplasty). Because referral to coro-
nary revascularization in the first 60 days after
nuclear testing tends to be based on the myocardial
perfusion scan results, late (>60 days after SPECT)
revascularization was chosen as a cardiac event. All
information on cardiac events was based on inves-
tigator report forms.

Statistics
Continuous variables are expressed as aver-
ages ± SD. We applied the unpaired t-test to
compare results from patients with and without
cardiac events, and the chi-square test was used
for categorical data.

The association of selected variables with out-
come was assessed with the Cox proportional
hazard model using univariate and stepwise mul-
tivariate procedures. The variables considered

| Table 1  | Baseline characteristics of patients with and without cardiac events. SSS indicates summed stress score; SRS, summed rest score; SDS, summed difference score; LVEF, left ventricular ejection fraction; EDV, end-diastolic volume; and ESV, end-systolic volume. Data are presented as number (%) or mean value ± SD. p-Values for comparison between cardiac-event and event-free groups. NS means not significant. |
|----------|---------------------------------------|-----------------|-----------------|
|          | Cardiac event                        | Event-free       | p-Value         |
|          | 96                                    | 1808             |                 |
| Age      | 66.8 ± 9.4                           | 64.2 ± 10.8      | 0.0240          |
| Gender (male%) | 68(71)                       | 934(52)          | 0.0004          |
| Body Mass Index | 22.1 ± 3.4                     | 23.4 ± 3.2       | <0.0001         |
| Multiple risk factors (≥2) | 51(53)                          | 587(32)          | <0.0001         |
| Diabetes mellitus | 49(49)                           | 398(22)          | <0.0001         |
| Hypertension | 56(58)                           | 904(50)          | NS              |
| Hyperlipidemia | 43(45)                           | 832(46)          | NS              |
| Typical angina | 29(30)                           | 201(11)          | <0.0001         |
| Positive ECG response | 35(36)                           | 329(18)          | <0.0001         |
| SSS      | 9.9 ± 9.5                            | 4.4 ± 6.5        | <0.0001         |
| SRS      | 5.3 ± 7.0                            | 3.3 ± 5.6        | 0.0050          |
| SDS      | 4.5 ± 6.1                            | 1.2 ± 3.5        | <0.0001         |
| LVEF at rest (%) | 58.2 ± 14.3                       | 65.9 ± 11.9      | <0.0001         |
| EDV at rest (mL) | 94.6 ± 37.0                      | 77.4 ± 29.8      | <0.0001         |
| ESV at rest (mL) | 43.3 ± 32.4                       | 28.3 ± 21.8      | <0.0001         |
included age, gender, presence of typical angina, number of coronary risk factors (hypertension, diabetes mellitus, and hyperlipidemia), stress ECG response, segmental perfusion scores, and QGS parameters. A significance of \( p < 0.05 \) was required for a variable to be included into the multivariate model. Hazard ratios with the corresponding 95% confidence intervals were estimated. Survival rates were estimated with Kaplan–Meier curves and compared by the log-rank test.

A \( p \)-value < 0.05 was considered statistically significant.

All statistical calculations were performed with the Statistical Analysis System 9.1.3 (SAS Institute, Cary, NC, USA) computer program.

### Results

#### Patients’ characteristics and clinical outcome

During the three-year follow-up period, 96 ischemic cardiac events (17 cardiac deaths, 8 nonfatal myocardial infarctions, and 71 clinically driven revascularizations) were reported and used in the analysis.

Table 1 details the baseline characteristics of study patients stratified by clinical outcome.

Patients with cardiac events were older and exhibited a higher prevalence of multiple risk factors, typical angina, and positive ECG response. The SSS, SRS, and SDS were significantly higher in patients with cardiac events. Of the QGS values, LVEF was lower, and EDV and ESV were larger in the cardiac event group.

### Outcome prediction

Cox univariate prognostic indicators are exhibited in Table 2. High age, male gender, multiple risk factors, typical angina, positive ECG response, segmental perfusion scores (SSS, SRS, and SDS), and the QGS parameters (LVEF, EDV, and ESV) were predictors of ischemic cardiac events. When Cox multivariate regression analysis was applied to these variables, SSS was the most powerful independent predictor of cardiac events, followed by typical angina, multiple risk factors, SRS, gender, and LVEF (Table 3). In the present study, the hard events rate (cardiac death and nonfatal myocardial infarction) was only 0.4%/year. We included late revascularization as cardiac events. But the prognostic power of SSS was the same when only the hard events were chosen as cardiac events (Wald chi-squared = 29.41, hazard ratio 1.039, CI 1.013–1.108).

### Table 2 Univariate prognostic predictors of cardiac events.

<table>
<thead>
<tr>
<th></th>
<th>Wald chi-squared</th>
<th>HR</th>
<th>95% CI</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≧75)</td>
<td>5.76</td>
<td>1.023</td>
<td>1.004–1.043</td>
<td>0.0164</td>
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<tr>
<td>Gender (male)</td>
<td>12.77</td>
<td>2.069</td>
<td>1.389–3.083</td>
<td>0.0004</td>
</tr>
<tr>
<td>Multiple risk factors (≧2)</td>
<td>14.81</td>
<td>2.063</td>
<td>1.427–2.983</td>
<td>0.0001</td>
</tr>
<tr>
<td>Typical angina</td>
<td>34.02</td>
<td>3.308</td>
<td>2.213–4.945</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Positive ECG response</td>
<td>12.03</td>
<td>2.014</td>
<td>1.356–2.992</td>
<td>0.0005</td>
</tr>
<tr>
<td>SSS</td>
<td>62.31</td>
<td>1.066</td>
<td>1.049–1.083</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SRS</td>
<td>17.84</td>
<td>1.046</td>
<td>1.024–1.068</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SDS</td>
<td>58.42</td>
<td>1.111</td>
<td>1.081–1.141</td>
<td>&lt;0.0001</td>
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<tr>
<td>LVEF at rest</td>
<td>20.78</td>
<td>0.970</td>
<td>0.958–0.983</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDV at rest</td>
<td>10.62</td>
<td>1.008</td>
<td>1.003–1.013</td>
<td>0.0011</td>
</tr>
<tr>
<td>ESV at rest</td>
<td>14.46</td>
<td>1.010</td>
<td>1.005–1.015</td>
<td>0.0001</td>
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</tbody>
</table>

### Table 3 Multivariate prognostic predictors of cardiac events.

<table>
<thead>
<tr>
<th></th>
<th>Wald chi-squared</th>
<th>HR</th>
<th>95% CI</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>4.18</td>
<td>1.548</td>
<td>1.018–2.354</td>
<td>0.041</td>
</tr>
<tr>
<td>Multiple risk factors (≧2)</td>
<td>9.23</td>
<td>1.784</td>
<td>1.228–2.590</td>
<td>0.0024</td>
</tr>
<tr>
<td>Typical angina</td>
<td>13.87</td>
<td>2.303</td>
<td>1.485–3.574</td>
<td>0.0002</td>
</tr>
<tr>
<td>SSS</td>
<td>23.18</td>
<td>1.077</td>
<td>1.045–1.110</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SRS</td>
<td>6.03</td>
<td>0.955</td>
<td>0.920–0.991</td>
<td>0.014</td>
</tr>
<tr>
<td>LVEF at rest</td>
<td>4.09</td>
<td>0.984</td>
<td>0.968–0.999</td>
<td>0.0431</td>
</tr>
</tbody>
</table>
Risk stratification using perfusion SPECT in coronary artery disease

Figure 1
Cardiac event rate and pretest probability of CAD. $p < 0.01$ for intermediate probability subgroup vs low probability subgroup, high probability subgroup vs low probability and intermediate probability subgroups, respectively.

Relationship between the cardiac event rate and the pretest probability of CAD

Fig. 1 depicts the relationship between the ischemic cardiac event rate and the pretest probability of CAD. The analysis comprised 532 (28%) patients with low, 1160 (61%) patients with intermediate, and 212 (11%) patients with high pretest probability of CAD. Compared to the event rate in patients with the low probability for CAD (event rate = 6.7%), the event rate increased in patients with intermediate (event rate = 11.1% $p < 0.001$ versus low probability group) to high probability of CAD (event rate = 19.3% $p < 0.001$ versus low and intermediate probability groups).

Cardiac event rate and SSS

Kaplan–Meier survival analysis revealed that the cardiac event rate was significantly higher in patients with abnormal scan (SSS > 3) than in those with normal scan (SSS $\leq 3$) (Fig. 2). Fig. 3 shows the cardiac event-free survival curves by SSS (SSS $\leq 3$ versus SSS > 3) subgroups stratified by the pretest probability of CAD (low, intermediate, high). In the low probability of CAD group, the cardiac event rates were similarly low in patients with SSS $\leq 3$ and those with SSS > 3 (Fig. 3A). In the intermedi-
Figure 4 Cardiac event-free curves according to the pretest probability of CAD in patients with normal perfusion scan (SSS \(\leq 3\)). The cardiac event rate was similarly low independent from the pretest probability of CAD.

![Cardiac event-free curves](image)

Discussion

The major findings of this study are that (1) stress/rest 99mTc-tetrofosmin myocardial SPECT imaging provides an independent and the best prognostic information, especially in patients with intermediate to high pretest probability of CAD, and (2) normal myocardial perfusion scan results are associated with a benign prognosis independent from the pretest probability of CAD.

Segmental perfusion scores, especially SSS, were related to a significant increase in the risk for ischemic cardiac events. The nature of the 99mTc-tetrofosmin abnormality that is prognostically important may depend on patient selection and clinical end point. If most events are cardiac death, the total perfusion abnormality (fixed and reversible) may be the most important predictor [12]. But if most endpoints are ischemic cardiac events, reversible perfusion abnormality of tetrofosmin may be the most important predictor. In this study, the outcome events recorded were mainly ischemic cardiac events including nonfatal myocardial infarction, and late coronary revascularization. Reversible perfusion defects can be a sign of jeopardized myocardium that is at risk for future ischemic events. Therefore, it is proper that SSS, which reflects both fixed and reversible perfusion abnormalities, is chosen as the best predictor. The predictive power of SRS and SDS was less than that of SSS. It is because the participants selected were without prior cardiac events, which included ischemic events, and SRS was almost zero. Therefore, the predictive power of SRS was weak. SDS was defined as difference between SSS and SRS and the predictive value of SDS was included in that of SSS, and thus the predictive power of SDS was weak compared with that of SSS.

The extent of perfusion abnormality was the best prognostic predictor of ischemic cardiac events. Patients with a large perfusion abnormality, SSS > 3, had a higher event rate than those with normal perfusion scan (SSS \(\leq 3\)). These results are concordant with the multiple clinical studies showing that the major prognostic variables on stress perfusion images predictive of future cardiac events are a large defect size (>20% or >15% of the left ventricle), defects in >1 coronary vascular supply region, and defect reversibility reflective of inducible ischemia in multiple myocardial scan segments [13—15]. Furthermore, in the present study, patients with intermediate to high probability of CAD could be further stratified by SSS into subgroups with low and high event rates. These observations suggest that myocardial perfusion SPECT may be as accurate in patients with either intermediate to high pretest probability of CAD.

Importantly, this is the first study showing that normal myocardial perfusion scan (SSS \(\leq 3\)) is associated with good prognosis independent from the pretest probability of CAD in the Japanese population. One of the most valuable features of stress/rest myocardial perfusion imaging is its good negative predictive value. Patients with normal scan at peak stress have a <1%/year combined mortality and nonfatal infarction rate [16—18]. The prognostic value of 99mTc perfusion imaging is comparable to that reported with 201Tl imaging. Normal stress 99mTc-sestamibi or 99mTc-tetrofosmin images were associated with an average annual hard event rate of 0.6—0.9% [19—21]. Berman et al. demonstrated that the cardiac event rate for patients with normal scans was low for all levels of pretest likelihood of CAD after the acquisition of exercise ECG stress test results [22]. These observations may have important implications for the clinical use of SPECT imaging. That is, a noninvasive strategy for the assessment of patients with suspected CAD may be safe and effective, thus avoiding unnecessary invasive cardiac catheterization.
In the present study, among QGS parameters, LVEF at rest was associated with ischemic cardiac events, but its predictive value was weak compared with SSS. Post-stress LVEF and volume measured by quantitative gated SPECT have been shown to be a highly predictive marker of cardiac events [23,24]. But QGS parameters in the current study were determined at rest, not at peak stress, and the possibility of CAD cannot be excluded by normal left ventricular function at rest [25]. Therefore, it is natural that the predictive power of SSS was superior to that of QGS parameters at rest.

Study limitations

In this study, we used the ACC/AHA/ACP—ASIM guideline data, which incorporate age, gender, and clinical presentation of chest pain, to estimate the pretest probability of having CAD. Despite this limitation, the incidence of ischemic cardiac events correlated well with the estimated pretest probability of CAD. Thus, although the ACC/AHA/ACP—ASIM guideline data are of Western origin, their data on pretest probability of CAD may be applicable to the Japanese population.

Clinical implications

Our results demonstrate that stress/rest myocardial perfusion SPECT imaging provides independent prognostic information on future ischemic cardiac events in patients with an intermediate to high pretest probability of CAD. The salient result from this trial is that a normal scan result (SSS ≤ 3) is associated with a benign prognosis and is independent from the pretest probability of CAD.

Recently, multi-slice computed tomography (MSCT) has been proposed as an alternative imaging modality for evaluation of patients with suspected CAD [26,27]. It is important to recognize, however, that myocardial perfusion imaging and MSCT provide complementary but different information on CAD. The MSCT identifies atherosclerosis rather than ischemia and atherosclerosis is not synonymous with ischemia. Therefore, long-term outcomes for patients may be determined by utilizing myocardial perfusion SPECT even when MSCT data are also available. The establishment of the predictive accuracy of myocardial SPECT imaging in a sufficiently large cohort of patients provides substantial supportive evidence for its use in daily clinical decision making.

Conclusions

SPECT 99mTc-tetrofosmin imaging results provide independent prognostic information for the prediction of ischemic cardiac events and SSS can further risk-stratify patients with intermediate to high estimated pretest probability of CAD. The salient result is that a normal scan portends a benign prognosis independent from the pretest probability of CAD.

Acknowledgments

We thank the many physicians and technologists at all of the participating hospitals in the J-ACCESS study for their cooperation. A list of participating institutions and physicians appears elsewhere [5].

References


