Comparison of Post-Exercise and Post-Vasodilator Stress Myocardial Stunning as Assessed by Electrocardiogram-Gated Single-Photon Emission Computed Tomography

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Background  Exercise gated single-photon emission computed tomography (SPECT) using technetium-99m ($^{99m}$Tc)-sestamibi evaluates both myocardial perfusion during stress and wall motion >30 min after the stress, which has the potential to assess not only exercise-induced myocardial ischemia but also the development of myocardial stunning.

Methods and Results  To evaluate the incidence of post-stress myocardial stunning, as well as comparing the effects of different stress methods on the development of stunning, 179 consecutive patients with known or suspected coronary artery disease (CAD) underwent $^{99m}$Tc-sestamibi SPECT with either exercise (n=135) or adenosine triphosphate disodium (ATP) (n=44). Electrocardiogram-gated SPECT images were acquired >30 min after the stress and again 4 h later, and perfusion and wall motion were evaluated. Post-stress myocardial stunning occurred in 24 patients (13%): 22 after exercise and 2 after ATP stress. The magnitude of the transient wall motion abnormality after exercise was greater in patients with severe ischemia, compared with those with mild-to-moderate ischemia (p<0.0001). By contrast, with ATP stress, the magnitude of the transient wall motion abnormality was similar, regardless of the severity of perfusion abnormality. Furthermore, a significant correlation between summed difference score and transient wall motion abnormality was found after exercise (r=0.68, p<0.0001). With ATP, however, no such correlation was observed (r=0.28, p=NS).

Conclusions  Using $^{99m}$Tc-sestamibi gated SPECT, myocardial stunning is frequently observed after exercise and correlates with the severity of myocardial ischemia, but this does not occur with ATP, which is regarded as a specific marker for severe CAD. (Circ J 2005; 69: 1338–1345)

Key Words:  Adenosine triphosphate disodium (ATP); Coronary artery disease; Electrocardiogram-gated single-photon emission computed tomography (SPECT); Exercise; Myocardial stunning

Although stress-induced wall motion abnormalities usually disappear rapidly once myocardial ischemia is eliminated, there are a few cases in which wall motion abnormalities remain, even >30 min after elimination of the ischemia; myocardial stunning is the apparent mechanism in such cases. The characteristics of technetium-99m ($^{99m}$Tc)-sestamibi, which rarely redistributes, in conjunction with electrocardiogram-gated single-photon emission computed tomography (SPECT) enables assessment of both myocardial ischemia during stress and left ventricular wall motion and function at least 30 min after the stress. Although myocardial stunning has been mainly shown after exercise-induced ischemia, pharmacologic vasodilation, which induces maldistribution of the blood flow in the intramyocardium, is commonly used as the method of inducing stress during myocardial perfusion imaging. Therefore, the aims of the present study were to evaluate the myocardial stunning induced by standard stress tests in clinical practice, and to compare the development of myocardial stunning with either exercise or pharmacologic stress.

Methods

Subjects  The subjects were 179 consecutive patients with known or suspected coronary artery disease (CAD), who underwent exercise or adenosine triphosphate disodium (ATP) stress myocardial perfusion imaging. Patients with a history of coronary angioplasty or bypass graft surgery were considered to have known CAD, whereas those with a clinical risk profile, symptoms or electrocardiographic abnormalities were considered as having suspected CAD. Patients with a history of prior myocardial infarction were excluded. In total, there were 112 men and 67 women, with a mean age of 66±9 years, and 77 of them underwent coronary angiography because of clinical symptoms, electrocardiographic abnormalities or scintigraphic findings. Of those with known CAD, 50 patients had a history of coronary revascularization (coronary angioplasty in 39 patients, coronary artery bypass grafting in 11). Written informed consents were given by all participants.

Stress $^{99m}$Tc-Sestamibi SPECT  Stress myocardial SPECT with $^{99m}$Tc-sestamibi was performed using a 1-day exercise–rest protocol. Exercise...
99mTc-sestamibi myocardial perfusion imaging was carried out in 135 patients and comprised symptom-limited multi-stage exercise while seated on a bicycle ergometer at an initial workload of 25 W or 50 W, with increments of 25 W every 3 min. If a submaximal heart rate was attained, or if the patient developed typical chest pain, ST-segment elevation or depression ≥0.1 mV, lower limb fatigue or severe arrhythmia, 259 MBq of 99mTc-sestamibi was administered intravenously. Exercise was then resumed for 1 min at the previous level. At 30 min after the last session of exercise, electrocardiogram-gated myocardial SPECT image acquisition began. The remaining 44 patients, who did not have sufficient exercise capacity, underwent pharmacological stress SPECT at least 15 h after the cessation of cardioactive medication. ATP (0.16 mg·kg⁻¹·min⁻¹) was administered intravenously for 6 min and 3 min later, 259 MBq of 99mTc-sestamibi was given intravenously. Imaging began a further 30 min later. In both the stress SPECT procedures, 777 MBq of 99mTc-sestamibi was given intravenously to all the patients 4 h later while they were resting and 30 min later electrocardiogram-gated myocardial SPECT was performed.

**Acquisition Protocol of SPECT**

Data were acquired with a 3-detector gamma camera (Prism 3000XP, Picker, Cleveland, OH, USA) over a 360-degree arc (in 20 six-degree-wide directions, with 30 s/direction). A low-energy, high-resolution, parallel multi-hole collimator was used, with a maximum matrix size of 64×64. When taking the electrocardiogram-gated images, the R-R interval was divided by the R-wave trigger into 8 equal portions. End-diastolic and end-systolic images were thus obtained. All the patients were in sinus rhythm during the imaging. SPECT images were reconstructed from the data using a data Odyssey VP processor (Picker) combined with a Butterworth filter (order 8; cutoff frequency 0.25) and a ramp filter.14

**Visual Analysis of SPECT**

According to a method reported elsewhere, each SPECT image was divided into 20 segments, with segments 1–3, 7–9, 13–14 and 19–20 corresponding to the areas perfused by the left anterior descending coronary artery, segments 4, 10 and 15–16 corresponding to the areas perfused by the right coronary artery, and segments 5–6, 11–12 and 17–18 corresponding to the areas perfused by the left circumflex coronary artery. The accumulation of radioisotope in the myocardium was visually evaluated by 2 cardiologists, without knowledge of patient information, using a 5-point scoring system: 0 (normal), 1 (slight reduction of uptake), 2 (moderate reduction of uptake), 3 (severe reduction of uptake) or 4 (absent of radioactive uptake) (Fig 1). The total of the scores for all of the segments, during exercise and at rest, was designated as the summed stress score and the summed rest score, respectively. The sum of the differences between the summed stress score and summed rest score was defined as the summed difference score to assess the overall extent and severity of stress-induced myocardial ischemia. A summed difference score <2 was defined as no ischemia; 2–7 mild to moderate, and >7 as severe ischemia. Disagreements in image interpretation were resolved by consensus.

**Quantitative Analysis of Gated SPECT**

Each reconstructed short-axis gated SPECT image was processed by a quantitative gated SPECT program developed by Germano (Cedars-Sinai Medical Center, Los Angeles, CA, USA), to calculate the left ventricular end-diastolic volume, left ventricular end-systolic volume and left ventricular ejection fraction. In addition, changes in left ventricular volumes with stress were calculated as left ventricular end-diastolic volume after stress minus left ventricular end-diastolic volume at rest, or left ventricular end-systolic volume after stress minus left ventricular end-systolic volume at rest.

**Wall Motion Analysis by Gated SPECT**

The simultaneously obtained, 3-dimensional electrocardiogram-gated images of the left ventricular myocardium (the end-diastolic peripheral image of the left ventricular tunica intima overlapped the end-systolic image), were displayed in 2 directions. One approximately corresponded to right anterior oblique 30-degree left ventriculography, the other to left anterior oblique 60-degree imaging. For the images thus obtained, the periphery of the left ventricular tunica intima was divided into 7 areas according to the American Heart Association classification of left ventriculograms. Five areas (anterobasal, anterior, apical, inferior and inferobasal) were derived from the right anterior oblique view, and 2 areas (lateral and posterior) from the left anterior oblique view (Fig 2). The regional wall motion of each area was visually rated by 2 cardiologists, who

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**Fig 1.** Assignment of myocardial segments for scoring of single-photon emission computed tomography images. The accumulation of radioisotope in the myocardium was evaluated using a 5-grade scale (see text).

**Fig 2.** Assignment of left ventricular regional wall motion for scoring of quantitative gated single-photon emission computed tomography images. A 4-point scoring system graded the wall motion of each segment (see text). LAO, left anterior oblique; RAO, right anterior oblique.
were unaware of patient information, with a 4-point scoring system: 0 (normal), 1 (mild hypokinesis), 2 (moderate to severe hypokinesis), 3 (akinesis or dyskinesis). The global wall motion score was calculated by totaling the regional wall motion scores for all 7 areas. The change in global wall motion score with stress, defined as a wall motion difference score, was obtained by subtracting the wall motion score at rest from the score after stress. We defined a definite stress-induced wall motion change if there was a difference in the wall motion difference score ≥3 was documented after the stress. When this definite stress-induced wall motion change was observed >30 min after the stress, the development of myocardial stunning was considered to have occurred.5,6

**Coronary Angiography**

Multidirectional coronary angiography was performed according to the Judkin’s method in 77 patients, based on clinical symptoms, electrocardiographic abnormalities and SPECT findings. The degree of coronary artery stenosis was measured using a caliper, according to the American Heart Association criteria.22 Significant stenosis was deemed to be present when there was >50% narrowing of the actual diameter.

**Statistical Analysis**

Results are generally presented as mean value±SD or percentage. Student’s unpaired t-test or Mann-Whitney U-test was used to compare the means of continuous variables, and contingency tables were analyzed using a chi-square test. Analysis of variance (ANOVA) was performed for comparisons among 3 groups or more, followed by Bonferroni’s post hoc test. Spearman’s correlation coefficient was used to estimate the correlation between summed difference score and wall motion difference score, or changes in cardiac volumes. A p-value <0.05 was considered statistically significant. Analyses were performed using the SPSS-PC+ computer program (version 11.0, SPSS Inc, Chicago, ILL, USA).

**Results**

**Comparison of Patient Characteristics in the Exercise and ATP Stress SPECT Groups (Table 1)**

There were more elderly and female patients in the ATP group than in the exercise group. Height and body weight were also significantly lower in the ATP group. However, the prevalence of coronary risk factors, history of coronary angioplasty or coronary artery bypass grafting, and baseline electrocardiogram were similar in the 2 groups.
Among the 135 patients who underwent exercise stress testing, chest pain was reported in 6 cases (4%), and significant ST-segment depression was observed in 57 cases (42%) (Table 2). However, ST-segment depression was not observed in any of the 44 patients undergoing ATP stress. No significant differences between the 2 groups were noted regarding the incidence and severity of reversible perfusion abnormalities, based either on visual or semi-quantitative analyses. Reversible perfusion abnormalities were observed in 21 of the 57 patients (37%) in the exercise group in which ST-segment depression was confirmed (Table 2). Of the 179 patients, 77 underwent coronary angiography; summed stress and summed difference scores were greater in patients who underwent coronary angiography than in those who did not (8.2±5.4 vs 3.7±4.0; p<0.0001, 5.2±3.2 vs 1.4±2.2; p<0.0001, respectively). In these 77 patients, the extent of stress-induced myocardial ischemia and CAD were similar between the exercise and ATP groups (Table 3). In addition, the incidence of >90% stenosis in 1-vessel CAD was similar (11/17 vs 3/5; p=NS).

**Stress-Induced Myocardial Stunning**

At least 30min after stress, prolonged left ventricular wall motion abnormalities that were regarded as myocardial stunning were observed in 22 patients (16%) in the exercise group, and 2 patients (5%) in the ATP group (Table 2). Among the 22 patients in the exercise group who presented myocardial stunning, 10 (45%) had ST-segment depression during exercise stress with a mean maximum ST-segment depression of 0.29±0.08 mV.

In the exercise group, myocardial stunning was observed in 13 of 53 patients with mild-to-moderate ischemia (25%), and in all 9 of those with severe ischemia (100%). However, myocardial stunning was found in only 2 of 7 patients with severe ischemia (29%) in the ATP group. Among all of the 24 patients in whom myocardial stunning was observed, the area of the perfusion abnormalities was supplied by the left anterior descending coronary artery in 17 patients (71%), by the right coronary artery in 5 patients (21%), and by the left circumflex coronary artery in 2 patients (8%). In all of the 24 patients, these perfusion results coincided with the area in which wall motion abnormalities occurred in the gated SPECT analyses. A strong association was found between the severity of perfusion abnormalities and wall motion difference score in the exercise group, whereas no significant association was observed in the ATP group (Table 3). Furthermore, a significant correlation was found between summed difference score and wall motion difference score (r=0.68, p<0.0001), whereas no significant linear correlation was observed in the ATP group (r=0.28, p=NS).

### Table 3 Scintigraphic and Angiographic Findings in 77 Patients Who Underwent Coronary Angiography

<table>
<thead>
<tr>
<th></th>
<th>Exercise stress (n=61)</th>
<th>ATP stress (n=16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scintigraphic findings</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Summed stress score</td>
<td>7.9±5.1</td>
<td>9.8±6.6</td>
<td>NS</td>
</tr>
<tr>
<td>Summed difference score</td>
<td>3.4±3.8</td>
<td>4.7±4.9</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Angiographic findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insignificant lesion</td>
<td>28 (46%)</td>
<td>9 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>17 (28%)</td>
<td>5 (31%)</td>
<td>NS</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>11 (18%)</td>
<td>1 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>5 (8%)</td>
<td>1 (6%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ATP, adenosine triphosphate disodium.

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**Fig 3.** Wall motion difference score in relation to the severity of reversible perfusion abnormalities in patients undergoing (A) exercise and (B) pharmacologic (adenosine triphosphate disodium) stress myocardial single-photon emission computed tomography.
Correlation between the wall motion difference score and summed difference score in (A) exercise and (B) pharmacologic (adenosine triphosphate disodium) stress myocardial single-photon emission computed tomography.

Fig 4.

Table 4 Comparison of Left Ventricular Function Between Exercise and ATP Stress SPECT

<table>
<thead>
<tr>
<th></th>
<th>Exercise stress (n=135)</th>
<th>ATP stress (n=44)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>82±23</td>
<td>68±24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>31±15</td>
<td>24±14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>63±8</td>
<td>67±9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Post stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>82±25</td>
<td>72±28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>33±16</td>
<td>29±17</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61±9</td>
<td>63±9</td>
<td>NS</td>
</tr>
</tbody>
</table>

ATP, adenosine triphosphate disodium; SPECT, single-photon emission computed tomography; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.

Relationship between changes in left ventricular volumes as assessed by gated single-photon emission computed tomography and summed difference scores. Correlation between the summed difference score and changes in (A) left ventricular end-diastolic volume (LVEDV) and (B) left ventricular end-systolic volume (LVESV) in the exercise stress group. Correlation between the summed difference score and changes in (C) LVEDV and (D) LVESV in the adenosine triphosphate disodium stress group.

Fig 5.

Circulation Journal  Vol.69, November 2005
Coronary Anatomy in Relation to Myocardial Stunning

Coronary angiography was performed in 19 of the 24 patients who developed myocardial stunning: 3-vessel CAD was found in 5 patients, 2-vessel CAD in 5, and 1-vessel CAD in 9; coronary artery narrowing was ≥90% in all of the 9 patients with 1-vessel CAD. In the 2 patients with ATP-induced myocardial stunning, 1-vessel disease with 90% narrowing and 99% narrowing, respectively, was observed. Coronary angiography was also performed in 58 of 155 patients who did not develop myocardial stunning: 3-vessel CAD was found in 1 patient, 2-vessel CAD in 6, and 1-vessel CAD in 13; the remaining 38 patients had insignificant lesions. The incidence of multivessel CAD was higher in patients who developed myocardial stunning than in those who did not (10/19 vs 7/58; p<0.0001). Among the patients with 1-vessel CAD, the incidence of coronary artery narrowing of ≥90% was higher in patients who developed myocardial stunning than in those who did not (9/9 vs 6/13; p=0.006).

Left Ventricular Function at Rest and Post Stress (Table 4)

In the comparison of the indexes of cardiac function at rest, left ventricular end-diastolic volume and end-systolic volume were larger and left ventricular ejection fraction was lower in the exercise group than in the ATP group. Comparing the same indexes during stress, left ventricular end-diastolic volume was significantly larger in the exercise group than in the ATP group, and left ventricular end-systolic volume and ejection fraction were similar. Regarding the change in left ventricular volume resulting from exercise stress, both end-diastolic and end-systolic volumes correlated significantly with the summed difference score (Fig 5). In the ATP group, however, only the end-systolic volume had a weak correlation with summed difference score (Fig 5). Although the changes in left ventricular ejection fraction correlated significantly with the summed difference score in the exercise group, no linear correlation was observed in the ATP group (Fig 6).

Discussion

Although the primary purpose of 99mTc-sestamibi SPECT is to evaluate myocardial perfusion at the time of injection of the radioisotope during stress, image acquisition is generally carried out at least 30 min after, in order to improve image quality. Applying this principle, we evaluated myocardial perfusion defects during stress and left ventricular wall motion abnormalities that persisted for 30 min or more after stress in the form of myocardial stunning. Of 179 consecutive patients with known or suspected CAD, 24 (13%) were found to have myocardial stunning that persisted after stress and of these 24 patients, 19 (79%) underwent coronary angiography, which revealed that approximately half of them had multivessel CAD, although 1-vessel diseases with high-grade coronary narrowing of ≥90% was found in the remaining half. In contrast, the prevalence of multivessel CAD or 1-vessel CAD with high-grade coronary narrowing was significantly lower in patients who did not develop myocardial stunning. It is therefore apparent that post-stress myocardial stunning can be used as a highly specific marker of extensive or severe CAD. Transient ischemic dilatation of the left ventricle and increased thallium uptake by the lungs are both well-known indexes for severe CAD but are usually seen in patients with multivessel CAD. From our results, it is noteworthy that post-stress myocardial stunning appears even in patients with 1-vessel CAD, if there is high-grade coronary narrowing.

In this study, 135 patients underwent exercise stress testing and the remaining 44 underwent pharmacologic stress using ATP. Although statistical differences existed between the exercise and ATP stress groups in terms of patient characteristics, these differences were similar to those reported in previous studies. Nevertheless, the extent of CAD was considered similar in the 2 groups because the coronary risk factors, baseline electrocardiogram and myocardial perfusion abnormalities assessed by SPECT were similar. Indeed, in the 77 patients who underwent coronary angiography, the extent and severity of CAD were similar in the 2 groups and for this reason, a comparison between the 2 groups as to post-stress myocardial stunning seemed appropriate.

The incidence of post-stress myocardial stunning was 16% in the exercise stress group, but only 5% in the ATP stress group. The majority of patients with post-stress stunning were confirmed as those with severe myocardial ischemia based on SPECT findings. Post-stress myocardial stunning was found in only 29% of the patients with ATP-induced severe perfusion abnormalities, whereas myocardial stunning was found in all of the patients with exercise-
induced severe perfusion abnormalities. These results concur with reports that pharmacologic stress using coronary vasodilators results predominantly in maldistribution of the intramyocardial blood flow with the rare occurrence of myocardial ischemia through blood steal phenomenon, whereas myocardial stunning developed in ≥10% of patients who underwent standard exercise stress testing, after the elimination of exercise-induced real ischemia. Hence, true myocardial ischemia and stunning are seldom induced by pharmacologic stress using vasodilator drugs such as ATP. This conclusion is supported by the fact that the summed difference score, an index of transient myocardial perfusion defects, significantly correlated with the wall motion difference score, an index of transient wall motion abnormalities, only in cases of exercise stress, and not in those of pharmacologic stress.

In the present study, we also used electrocardiogram-gated SPECT to examine the degree to which global cardiac function was affected by post-stress myocardial stunning. In the exercise group, left ventricular end-diastolic and end-systolic volumes resulting from myocardial stunning were both larger, as well as there being more severe myocardial ischemia during stress. Conversely, left ventricular ejection fraction decreased. In contrast, in the ATP stress group there was no significant correlation between the severity of myocardial perfusion abnormalities and left ventricular end-diastolic volume or ejection fraction, except for a weak correlation with left ventricular end-systolic volume. However, the aforementioned correlations between these global cardiac functions and myocardial perfusion abnormalities were weaker than the correlations between transient wall motion and myocardial perfusion abnormalities. Thus, the evaluation of left ventricular wall motion used by us in our study of the detection of post-stress myocardial stunning by electrocardiogram-gated SPECT, is more sensitive than assessment of global cardiac function, and should be used to detect extensive and severe CAD.

Study Limitations

The present study has several limitations that are common with any study relying on retrospective data collection. Most importantly, the presence of selection bias for each stress method, which is common in stress myocardial perfusion imaging in clinical practice, resulted in several differences in the patient characteristics of the exercise and ATP stress groups. However, the extent and severity of stress-induced myocardial ischemia on SPECT, as well as the extent and severity of CAD as assessed by coronary angiography, were similar in the 2 groups. Although these findings imply that the 2 groups were compatible with regard to CAD, our preliminary results that the development of myocardial stunning is more frequent after exercise than after ATP stress need confirmation through prospective studies with well-matched patient populations.

References


