Clinical characteristics in patients showing ischemic electrocardiographic changes during adenosine triphosphate loading single-photon emission computed tomography

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Summary
Objectives: Although ischemic electrocardiographic (ECG) changes during dipyridamole or adenosine infusion have been reported as a marker for severe coronary artery disease (CAD), few studies have focused on ST-segment changes with adenosine triphosphate (ATP)-loading myocardial single-photon emission computed tomography (SPECT).
Methods and subjects: Between January 2003 and August 2008, 4650 consecutive patients underwent ATP-loading SPECT. After 1412 patients with left bundle branch block, pacemaker rhythm, or previous coronary revascularization were excluded, 16 out of 3238 patients (0.5%) showed ischemic ST-segment depression during ATP-loading myocardial SPECT. They were aged 67 ± 11 years; 10 were men and 6 women. Of these patients, 8 demonstrated perfusion abnormalities, whereas the remaining 8 showed normal myocardial perfusion imaging. In 6 of the 8 patients with abnormal SPECT, coronary angiography was performed, revealing left main trunk disease in 1 patient, 3-vessel disease in 4, 1-vessel disease with proximal left ascending artery occlusion in 1, and an insignificant lesion in 1. By contrast, no major cardiac event was observed in the 8 patients with normal SPECT during follow-up for an average of 2 years.
Conclusion: The prevalence of ischemic ST-segment changes during ATP loading is very rare. However, this finding should be taken into account since almost half of the patients, particularly those with perfusion abnormalities, may have severe CAD which requires coronary revascularization.

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Introduction

Electrocardiographic (ECG) changes during stress myocardial perfusion imaging (MPI) add diagnostic value to the perfusion images [1,2]. To detect coronary artery disease (CAD), myocardial single-photon emission computed tomography (SPECT) with loading of adenosine triphosphate (ATP) or of any other vasodilator drugs such as adenosine or dipyridamole is useful for those who cannot exercise. Previous studies reported that ischemic ECG changes during dipyridamole or adenosine infusion were a marker for severe CAD such as 3-vessel or left main CAD [3,4]. However, the prevalence and diagnostic significance of ischemic ECG changes induced by adenosine triphosphate is unclear. The present study, therefore, evaluated the clinical importance of ECG changes during ATP-loading MPI.

Methods

Study patients

We retrospectively studied 8186 consecutive patients with suspected or known CAD using stress myocardial SPECT from January 2003 to August 2008 in the Department of Cardiology of Tokyo Medical University. Of these, we identified 4650 patients who underwent ATP-loading myocardial SPECT. Patients who had digitalis, left bundle branch block (LBBB), pacemaker rhythm, atrial fibrillation, frequent extrasystoles, and previous coronary revascularization were excluded.

ATP-loading protocol

After the termination of 18-h anti-anginal medication, using 99mTc-sestamibi/tetrofosmin or 201Tl, ATP-loading myocardial imaging was performed on a 1-day protocol [5]. Patients were also asked not to take a beverage containing caffeine at least 12 h before the ATP stress test. For 99mTc labeled radiotracers, adenosine triphosphate disodium (0.16 mg kg\(^{-1}\) min\(^{-1}\)) was administered intravenously for 6 min [6], and, from the end of the third minute, 99mTc-sestamibi/tetrofosmin was given intravenously, 30 min after which image acquisition was commenced. No exercise was added before the image acquisition. On the same day, the patients were given 99mTc-sestamibi (777 MBq) while at rest, and then, 30 min later, quantitative gated myocardial SPECT images were acquired. The protocols of 201Tl (111 MBq) myocardial SPECT were similar to those of previous methods [7]. Delayed images were acquired 4 h later.

Analysis of ECG

A standard 12-lead ECG was obtained on the same day as the ATP infusion but a few minutes before it. ECG monitoring was taken during ATP infusion and a standard 12-lead ECG was obtained every minute for 8–9 min. The ECGs were interpreted as positive for ischemia in the presence of a >1 mm horizontal or down-sloping ST-segment depression, or a 2 mm or more up-sloping ST-segment depression 80 ms after the J-point, when they were compared with that observed at rest. The ECGs were blindly read by two observers who had no knowledge of the clinical history or the tomography results, any differences being resolved by consensus.

Image acquisition

Data were acquired with a 2- or 3-detector gamma camera (Prism 2000XP or Prism 3000XP, Picker, Cleveland, OH, USA) for 180° or 360° arcs in 20–30 six degree-wide directions, taking 30 s per direction. For both radioisotopes, a low-energy high-resolution parallel multi-hole collimator was used. The maximum matrix size was 64 \(\times\) 64. When the ECG-gated images were made, the R-R interval was divided by the R wave trigger into 8 equal portions, allowing end-diastolic and end-systolic images to be obtained. All patients were in sinus rhythm during the imaging. SPECT images were constructed from the data by a data processor (Odyssey VP, Picker) combined with a Butterworth filter (order 8; cutoff frequency 0.25 cycles/cm for 99mTc-sestamibi/tetrofosmin and 0.2 cycles/cm for 201Tl) and a ramp filter [8].

Image interpretation

According to a method reported elsewhere [9], each SPECT image was divided into 20 segments. The accumulation of radioisotope in the myocardium was visually evaluated by 2 cardiologists using a 5-grade scale: 0 (normal), 1 (slight reduction of uptake), 2 (moderate reduction of uptake), 3 (severe reduction of uptake), or 4 (no radioactive uptake). The totals of the scores for all the segments during exercise and at rest were designated the summed stress score (SSS) and the summed rest score (SRS), respectively. The summed difference score (SDS) was defined as SSS minus SRS. Abnormal results from SPECT were defined as an SSS of \(\geq 4\) and/or SDS of \(\geq 2\) [10]. Disagreements in image interpretation were resolved by consensus.

Coronary angiography

Indications for coronary angiography were decided by the attending physicians on the basis of the clinical risk profiles of patients, the results of noninvasive tests, and the patient’s preference. Multidirectional coronary angiography was performed according to Judkins’ method. The degree of coronary artery stenosis was visually rated using calipers, and stenosis was deemed significant when \(\geq 75\%\) diameter narrowing was reached [11]. For all patients who underwent cardiac catheterization, treatment strategy was discussed in the presence of the primary physicians, nuclear cardiologists, interventional cardiologists, and cardiovascular surgeons.

Patient follow-up

Patient follow-up was performed by physician contact. The follow-up period was defined as the time from the SPECT study until a significant event or the last visit to the institution. Significant events were death, nonfatal myocardial infarction, percutaneous coronary intervention, coronary
Clinical characteristics of patients

From 4650 consecutive patients who underwent ATP-loading myocardial SPECT, 1412 patients who had digitalis, LBBB, pacemaker rhythm, and previous coronary revascularization were excluded. Among the remaining 3238 patients, we identified 16 patients (0.5%) that showed ischemic ST-segment depression during ATP-loading myocardial SPECT. The patients were aged 67 ± 11 years; 10 were men and 6 women. The prevalence of hypertension was 88%, that of diabetes mellitus, 38%, of hyperlipidemia, 44%, and of active smoking, 31%, and a family history of ischemic heart disease was present in 25% (Table 1). There were patients with suspected old myocardial infarctions (13%) and left ventricular hypertrophy (19%) according to the ECG findings. The radiotracer used for MPI was 99mTc-sestamibi in 3 (19%), 99mTc-tetrofosmin in 1 (6%), and 201Tl in 12 (75%).

ECG findings

Sixteen patients (0.5%) were in sinus rhythm and showed ischemic ST-segment depression during ATP-loading myocardial SPECT. In all, there was down-sloping ST depression in 11 (69%), horizontal ST depression in 4 (25%), and up-sloping ST depression in 1 (6%). ST depression occurred 3 ± 1 min after ATP infusion.

Hemodynamic changes and SPECT findings

We separated the study patients into a normal perfusion group and an abnormal perfusion group (SSS = 7 ± 5, SDS = 4 ± 3; n = 8). There was no significance in peak heart rate (94 ± 15 bpm vs. 92 ± 10 bpm; p = NS), peak systolic blood pressure (175 ± 39 mmHg vs. 166 ± 40 mmHg; p = NS), change in heart rate with ATP (10 ± 1 bpm vs. 19 ± 8 bpm; p = NS), and change in systolic blood pressure (17 ± 4 mmHg vs. 19 ± 19 mmHg; p = NS) between the two groups (Table 2).

Clinical courses after SPECT study

Eight of the patients demonstrated perfusion abnormalities, whereas the remaining 8 showed normal myocardial perfusion imaging. In 6 of the 8 patients with abnormal SPECT, coronary angiography was performed, revealing left main trunk (LMT) disease in 1 patient, 3-vessel disease in 3, 1-vessel disease with proximal LAD lesion in 1, and an insignificant lesion in 1 (Table 3). Coronary angiogram was not performed in the remaining 2 patients because of mild severity of perfusion abnormality (Table 3). A typical case that showed ST-segment depression during ATP-loading, and 3-vessel CAD on coronary angiograms is illustrated in Fig. 1.

The 16 patients who had ATP-induced ST depression were followed for a mean of 24 months (Fig. 2). In 5 of 8 patients with normal SPECT, coronary angiography was not performed and no event was observed during a 24-month period. Only one patient with normal SPECT who underwent coronary angiography, had a moderate stenosis in the LAD and percutaneous intervention was performed.

Discussion

In the present study of 3238 patients, ST-segment depression during ATP-loading myocardial SPECT was rarely observed (16 cases, 0.5%). In these 16 patients, myocardial perfusion on SPECT was normal in 8, and abnormal in the other 8. Among the patients with normal perfusion, no severe CAD and no cardiac event was observed for 24 months, except one patient who had 1-vessel CAD (Fig. 2). However, among those with abnormal perfusion, the prevalence of severe and extensive CAD was high.

In previous studies, ST-segment depression in pharmacologic stress myocardial SPECT was also reported. ST-segment depression induced by dipyridamole stress occurred in 8—40% [4,14], and that by adenosine stress in 7.5—20% [15,16]; these incidences were higher than what was seen in ATP stress in the current study, namely 0.5%. Low-level exercise such as walking in place was added after the pharmacologic loading in some of the previous studies, while no exercise was conducted in the current study [14—16]. In our study, furthermore, patients with known CAD who had required coronary revascularization were also excluded. These differences in study protocol and patients may explain, in part, the very low incidence of ATP-induced ST-segment depression.

According to previous studies, ST-segment depression with pharmacologic stress myocardial SPECT implies severe ischemia such as an LMT lesion or multi-vessel CAD [4,14]. It is frequently reported that ST-segment depression during pharmacologic stress is correlated with an amount of reversible defect [4,17]. Adenosine combines with the A2-receptors and increases coronary blood flow 4—5-fold in a normal coronary artery, and it also increases the demand for myocardial oxygen [18]. If coronary flow reserve is preserved, adenosine increases coronary blood flow. If
Table 2  Hemodynamic parameters during ATP loading.

<table>
<thead>
<tr>
<th></th>
<th>Abnormal perfusion (n = 8)</th>
<th>Normal perfusion (n = 8)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>HR at rest (bpm)</td>
<td>81 ± 11</td>
<td>73 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>SBP at rest (mmHg)</td>
<td>157 ± 19</td>
<td>157 ± 34</td>
<td>NS</td>
</tr>
<tr>
<td>HR after ATP loading (bpm)</td>
<td>94 ± 15</td>
<td>92 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>SBP after ATP loading (mmHg)</td>
<td>175 ± 39</td>
<td>166 ± 40</td>
<td>NS</td>
</tr>
<tr>
<td>Change in HR (bpm)</td>
<td>10 ± 1</td>
<td>19 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Change in SBP (mmHg)</td>
<td>17 ± 4</td>
<td>19 ± 19</td>
<td>NS</td>
</tr>
</tbody>
</table>

ATP: adenosine triphosphate; bpm: beats per minute; HR: heart rate; SBP: systolic blood pressure.

Table 3  Profiles of 16 patients showing adenosine triphosphate-induced ST depression.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Leads with ST dep</th>
<th>Max ST dep (mm)</th>
<th>SSS</th>
<th>SDS</th>
<th>Area of perfusion defect</th>
<th>Lesions of coronary arteries by CAG</th>
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<tr>
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<td>CAG: coronary angiography; dep: depression; F: female; HL: high lateral branch; M: male; N/A: not available; PD: posterior descending artery; SDS: summed difference score; SSS: summed stress score.</td>
</tr>
</tbody>
</table>

Normal perfusion

1  61M II, III, aVF V_4—V_6 1 0 0 (7) 90% (1) 50% (7) 50%
2  74M II, III, aVF V_4—V_6 2 0 0 Normal coronary
3  69M II, III, aVF V_4—V_6 1 0 0 N/A
4  61F II, III, aVF V_4—V_6 1 0 0 N/A
5  68M II, III, aVF V_4—V_6 1 3 0 Inferoposterior N/A
6  55M II, III, aVF V_4—V_6 1 0 –1 Inferoposterior N/A
7  72M IaV_L V_5, V_6 1 0 0 N/A
8  80F II, III, aVF V_4—V_6 1 0 0 N/A

Abnormal perfusion

9  62M II, III, aVF V_4—V_6 1 5 0 Inferoposterior (1) 100% (5) 75% (6) 90% (7) 90% (9) 90% (12) 90%
10 57F V_5, V_6 1 16 9 Anteroseptal Lateral (3) 90% (4PD) 90% (7) 99delay (9) 75% (11) 99% delay (HL) 99% (4PD) 90% (7) 75% (9) 90% (11) 75%
11 70F II, III, aVF V_2—V_6 1 11 7 Anterolateral (1) 50% (6) 75% (7) 90% (10) 90% (HL) 90% (11) 75% (12) 50% (13) 90% (14) 90% (15) 75% (7) 99delay (9) 90%
12 84F II, III, aVF V_4—V_6 2 4 4 Anterior (1) 100% (5) 75% (6) 90% (7) 90% (9) 90% (12) 90%
13 83M II, III, aVF V_4—V_6 1 12 6 Anteroseptal (7) 99%delay (9) 90%
14 52M V_5, V_6 1 4 0 Lateral normal coronary
15 46F II, III, aVF V_4—V_6 1 2 2 Anterior N/A
16 70M II, III, aVF V_4—V_6 1 2 2 Inferoposterior N/A
severe stenosis is present, however, coronary flow reserve decreases in the coronaries in order to maintain the flow in the distal portion of an artery [19,20]. The appearance of many collaterals in multi-vessel CAD or in cases of LMT lesion causes the myocardial steal phenomenon due to increased myocardial oxygen demand during stress. As a result, coronary artery pressure in the distal portion decreases, after which ST-segment depression develops [17]. In the present study, 3-vessel CAD with or without an LMT lesion was found in 4 out of 6 patients who had abnormal SPECT and also underwent coronary angiography. Another patient was shown to have a sub-total occlusion of the proximal LAD.
The results of our study are, therefore, consistent with previous studies in that most patients who develop ST-segment depression during pharmacologic stress and who also have abnormal myocardial perfusion on SPECT have severe and extensive CAD.

In contrast to the above observations, severe myocardial ischemia, known as "balanced ischemia," was also reported to occur in patients with ST-segment depression and normal myocardial perfusion on SPECT [20,21]. Some reports, on the contrary, state that ST-depression during pharmacological stress with normal perfusion SPECT implies a good prognosis particularly in women and hypertensive patients [21,22]. According to the previous study, the prevalence of ST-segment depression during adenosine loading in women was higher than that in men [21]. In women, estrogen stimulates the renin-angiotensin system, increases the affinity of α-adrenergic receptors, and the sensitivity of vasoconstriction by catecholamines [23,24]. In the present study, out of 8 patients with normal perfusion on SPECT, 2 were women, in both of whom coronary angiogram was not performed, but they had no cardiac event for 24 months after the study. It is also reported that hypertensive patients frequently have ST-segment depression during myocardial SPECT with adenosine loading [22]. If hypertension is present for decades, coronary blood flow and resistance increase and the coronary flow reserve decreases [25]. These abnormalities in microvasculature may explain ST-segment depression without perfusion abnormality [26]. In the current study, 7 of the 8 patients with normal perfusion on SPECT had hypertension. Although one hypertensive patient had 1-vessel CAD and underwent percutaneous coronary intervention, the remaining 6 hypertensive patients did not have any cardiac event for 24 months. Based on these observations, the nature of ST-segment depression during ATP loading in patients who subsequently showed normal myocardial perfusion on SPECT is mostly considered as benign, not as balanced ischemia masking perfusion abnormality.

The present study had several limitations common to any study relying on retrospective data collection. In particular, not all patients who showed ATP-induced ST-segment depression underwent coronary angiography. The decision was made based on scintigraphic findings since normal myocardial perfusion predicts good prognosis [27,28]. Indeed, 5 patients with normal SPECT who did not undergo coronary angiography had no cardiac events during the follow-up period. Recent perspective on the management of CAD patients underscores the importance of patient outcome, rather than mere coronary anatomy. In this context, the analysis of the present study is considered sufficient for evaluating the clinical significance of ATP-induced ST-segment depression.

**Conclusion**

The prevalence of ischemic ST-segment changes during ATP loading is very rare (16 out of 3238 patients, 0.5%). However, this finding should be taken into account since almost half of them, particularly those with perfusion abnormalities, may have severe CAD which requires coronary revascularization.

**Acknowledgment**

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References


