CLINICAL STUDIES

ASSESSMENT OF QUANTITATIVE EXERCISE THALLIUM-201 EMISSION COMPUTED TOMOGRAPHY IN PATIENTS WITH VASOSPASTIC ANGINA — Value of Washout Rate Analysis —

KAZUYUKI SAKATA, M.D., HIROSHI YOSHIDA, M.D., HIROSHI SUGINO, M.D. MASARU IMURO, M.D., YOUICHI MATSUNAGA, M.D., NORIHISA ONO, M.D. SHIGERU MORISHIMA, M.D., TSUNE O HOSHINO, M.D. AND TSUNE O KABURAGI, M.D.

This study was performed to assess the value of washout rate analysis of quantitative exercise thallium-201 emission computed tomography in vasospastic angina patients without significant coronary stenosis. Quantitative analysis of both thallium-201 perfusion and washout rate before and after drug treatment was performed in 48 patients with vasospastic angina and no significant coronary artery stenosis. All of the patients attained more than 90% of their age-predicted heart rate during each exercise test. Before drug treatment, 26 patients exhibited exercise-induced ischemia (perfusion defects on stress polar map), 17 did not exhibit exercise-induced ischemia (normal stress and washout rate polar maps), and the remaining 5 patients showed no perfusion defects, but did show extensive abnormal washout rates. On coronary angiography, multivessel coronary spasm was documented in 12 of the 26 patients with exercise-induced ischemia, in 7 of the 17 patients without exercise-induced ischemia and in 4 patients with an extensive abnormal washout rate and a normal stress polar map. In the 17 patients without exercise-induced ischemia, the mean washout rate was significantly decreased (p<0.05) in association with a significant decrease in the double product (p<0.05) after drug treatment. Of the 26 patients with exercise-induced ischemia, 18 (group 1) showed an increase in the mean washout rate with improved perfusion defect after drug treatment. The remaining 8 patients (group 2) showed a decrease in the mean washout rate with improved perfusion defect after drug treatment, which increased significantly on repeat exercise test performed after additional increased doses of antianginal drugs were administered (p<0.01). The number of patients with multivessel coronary spasm was significantly high in group 2 (p<0.01). Thirteen patients showed an extensive abnormal washout rate before drug treatment, including 8 patients with exercise-induced ischemia and 5 patients with no perfusion defects, who showed an increased mean washout rate after drug treatment (p<0.05). These findings indicate that washout rate analysis aids in the diagnosis in vasospastic angina patients with exercise-induced ischemia. Some patients with exercise-induced ischemia can not be detected by thallium-201 perfusion.

Key words:
Extensive abnormal washout rate
Silent myocardial ischemia
Multivessel coronary spasm
Exercise-induced spasm

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Department of Cardiology, Shizuoka General Hospital.
Mailing address: Dr. Kazuyuki Sakata, Department of Cardiology, Shizuoka General Hospital, 4-27-1 Kitaando, Shizuoka 420, Japan

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EXERCISE-INDUCED ischemia due to vasospasm has been reported in some patients with vasospastic angina\(^1\)--\(^4\). Due to its high diagnostic value, quantitative exercise thallium-201 emission computed tomography is currently in widespread use, both to detect significant coronary stenosis and to evaluate its extent and severity\(^5\)--\(^7\). Several investigators\(^1\)--\(^3\) have used exercise thallium-201 emission computed tomography to demonstrate the characteristics of exercise-induced spasm and the usefulness of Ca-antagonists in suppressing exercise-induced spasm. In these studies, stress polar maps were analyzed quantitatively. However, this type of analysis has limitations associated with its spatial relativity. Therefore, washout rate analysis has been proposed as a new method of scintigraphic interpretation\(^8\)--\(^9\). It is important to perform quantitative analysis of thallium-201 washout in cases of vasospastic angina because simultaneous multivessel coronary spasm has been documented during exercise\(^2\) and antianginal drugs may affect thallium-201 clearance\(^10\). However, scan data concerning washout rate analysis in patients with vasospastic angina are not available.

Therefore, the purpose of this study was to assess the clinical value of quantitative analysis of thallium-201 washout rate before and after drug treatment in patients with vasospastic angina and no significant coronary artery stenosis.

METHODS

Patients

Forty-eight of 72 consecutive patients with vasospastic angina and no significant coronary arterial stenosis (less than 50% diameter narrowing) were included in this study. All of the patients exhibited recent onset of chest pain occurring mainly in the morning. Chest pains were completely relieved after the administration of sublingual nitroglycerin in all cases. Vasospastic angina was confirmed by an acetylcholine provocation test during coronary angiography. None of the patients had prior myocardial infarction, heart failure, chronic lung disease, or other severe complications. Fifteen subjects with atypical chest pain, normal coronaries, and negative acetylcholine tests (10 men and 5 women, mean age 58.6 years) also underwent exercise thallium-201 emission computed tomography to obtain the means and standard deviations of normal values on polar maps. All of the subjects in this study attained more than 90% of their age-predicted maximal heart rate on each exercise test. Informed consent was obtained from all of the subjects.

Acetylcholine Provocation Test

An acetylcholine provocation test was performed as previously described\(^11\). Acetylcholine, 20 to 100 \(\mu g\), was injected separately into the left and right coronary arteries in all patients. Coronary artery spasm induced by acetylcholine was considered to be present if total or subtotal occlusion of the involved artery occurred in association with chest pain and ischemic ST segment changes. Single-vessel coronary spasm and multivessel coronary spasm were defined as acetylcholine-induced spasm occurring in one of three major coronary arteries or their major branches, and in two or more of these coronary territories supplying different major coronary artery territories, respectively. After the acetylcholine provocation test, coronary angiography was performed following the intracoronary injection of 0.3 mg of nitroglycerin. The findings of coronary angiography after injection of nitroglycerin were classified according to the American Heart Association reporting system\(^12\).

Exercise Myocardial Scintigraphy

Patients with vasospastic angina were subjected to a symptom-limited treadmill exercise test within 1 week before cardiac catheterization, and 2 to 3 weeks after cardiac symptoms disappeared with intensive drug
administration. This test employed the Bruce protocol and was performed while patients fasted. The exercise was continued until progressive chest pain or leg fatigue developed. At this point, 111 MBq of thallium-201 chloride was injected through an intravenous cannula that had been previously inserted into a peripheral vein. All of the patients continued to exercise with the same workload for another minute. Electrocardiographic monitoring was performed throughout the exercise. Both blood pressure and heart rate were recorded before exercise, every 3 min during exercise, and when the thallium-201 was injected. Standard 12-lead electrocardiograms were recorded before and immediately after exercise while patients were in a supine position. Criteria for significant ST segment depression were horizontal or downsloping depression of 0.1 mV or more for 0.08 sec after the J point was reached in more than 2 leads, as compared with the resting electrocardiogram. For the first exercise test, which was performed before diagnostic catheterization, all of the patients were routinely instructed to discontinue antianginal drugs, except for sublingual nitroglycerin, for 24 h before the test. For the second exercise test, which was performed 2 to 3 weeks after oral administration of antianginal drugs (nifedipine, 10 mg, or dliltiazem, 30 mg, once every 6 h), all of the patients took antianginal drugs (nifedipine, 10 mg, in 38 patients or dliltiazem, 30 mg, in 10 patients) 2 h before exercise and sublingual 0.3 mg nitroglycerin just before exercise. To account for the circadian variation in exercise capacity in patients with vasospastic angina, all of the exercise tests were performed between 9 AM and 10 AM.

Within 5 min and again 4 h after injection of thallium-201, tomographic images of the heart were obtained by using thallium-201 emission computed tomography and a dedicated computer as described previously.

Quantitative analysis of myocardial perfusion defect and washout rate was also performed as described previously. In brief, a computerized two-dimensional polar maps were generated using a circumferential profile analysis, whereby the pixel count activity from the center to the outer boundary of each short-axis was determined along radians spaced at 6-degree intervals over 360 degrees. Count values at each point in the profile were then normalized to the maximal counts in each profile image. Polar maps were also constructed for washout rate, which was calculated on a pixel-by-pixel basis by subtracting the delay value from the stress value and multiplying by 100/stress value. Individual slices from the cardiac apex to the base were displayed in the polar map as concentric rings from the center to the periphery of the map. The means and standard deviations (SD) of the normal values at each point were determined from the values calculated for the 15 normal subjects.

Mean washout rate was calculated by adding summing the washout rate values of all of the points and dividing by the total number of points on the washout rate map. The extent scores for the size of the perfusion defect and washout rate were determined by calculating the number of points which fell below the corresponding normal lower limits and by expressing this number as a percentage of the total left ventricular points on the extent polar maps. The severity of the perfusion defect was scored by calculating the difference between the normalized maximal counts for each point in the area of the defect and the corresponding normal lower limits. This difference was divided by the total number of left ventricular points. The territories of the 3 major arteries were assigned as described by Depasquale et al.

Definition of Exercise-Induced Ischemia and Abnormal Washout Rate

Abnormal washout rate was defined as the presence of an area 2 SD below the normal values on the washout polar map. The exercise-induced ischemic area in each patient was defined as the area which showed counts 2 SD below the normal values on the stress map. An extensive abnormal washout rate was defined as the presence of abnormal washout rate in all three territories or abnormal washout rate in two or three territories despite the confinement of the perfusion defect to one territory.

Lung thallium-201 Uptake

Lung thallium-201 uptake was measured
TABLE I EXERCISE AND ANGIOGRAPHIC FINDINGS

(continued)

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<th>peak BP (mmHg) D-</th>
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Abbreviations: DM = diabetes mellitus, HT = hypertension, HR = heart rate, BP = blood pressure, DP = double product, ED = exercise duration, CP = chest pain, ECG = ischemic ST changes, D- = without drug treatment, D+ = with drug treatment, MS = multispasm, WR = washout rate, PD = perfusion defect, ES = extent score, SS = severity score. *p<0.05, #p<0.01 as compared to the values before drug treatment. Values are expressed as mean±SD.

as described previously\textsuperscript{13} In the unprocessed anterior projection (number 9 of 32) the initial image, the lung/heart ratio of thallium-201 activity was measured using a region of interest (ROI) method. Separate square ROIs of 5×5 pixels were defined for areas of the left upper lung and left ventricular myocardium. The lung ROI was placed over the most intense lung activity in a region in which the base was five pixels above the anterolateral myocardial wall. The myocardial ROI was placed over the myocardial wall with the greatest count density. The lung/heart ratio was determined as the mean counts/pixel in the lung ROI divided by that in the myocardial ROI.

Statistical Analysis

The results were expressed as the mean±SD. Unpaired t tests were used to compare exercise parameters and mean washout rate, and the extent and severity scores on scintigrams. Paired t tests were used to compare exercise parameters, mean washout rates, and the extent and severity scores on scintigrams taken before and after the drug administration. Proportions in the groups were compared by the chi-square test or by Fisher’s exact test. Significance was defined as a P value of less than 0.05.

RESULTS

As shown in Table I and Fig. 1, the patients with vasospastic angina were divided into 3 groups. Seventeen patients (35%) showed no perfusion defects (no exercise-induced ischemia group). Twenty six patients (54%) showed perfusion defects on the stress polar map (exercise-induced ischemia group). The remaining 5 patients (10%) showed no perfusion defects, but had extensive abnormal washout rates. Extensive abnormal washout rates were also observed in 8 patients with exercise-induced ischemia. Therefore, 13 patients (27%) were included in the extensive abnormal washout rate group.

Exercise Parameters and Angiographic Find-
Fig.1. Polar map representations of extent and severity scores for the thallium-201 perfusion defect and the extent score for the washout rate abnormality before and after drug treatment. All of the polar maps represent a color map on which points falling below the corresponding normal lower limits are shown as a white region for the extent polar maps, and a yellow and green region for the severity polar map. The remaining points fall in a red region. In the left panel, polar maps were obtained from a patient without exercise-induced ischemia. No abnormalities were shown on any of the polar maps obtained before or after drug treatment. In the middle panel, polar maps were obtained from a patient with exercise-induced ischemia. Significant perfusion defects and washout abnormality appeared in the anterior wall. These abnormalities disappeared after drug treatment. In the right panel, polar maps were obtained from patients with multivessel coronary spasm. Polar maps from both the extent and severity scores of the size of the perfusion defect showed no abnormality, while a polar map of the extent score of the washout rate abnormality showed a heterogeneous widespread abnormality (described as extensive washout rate abnormality in the text). This abnormality completely disappeared after drug treatment.

ings (Table I)
Each of the groups showed a significant decrease in peak blood pressure resulting which resulted in a significant decrease in double product on during the exercise test after drug treatment, as compared to those values during the exercise test before drug treatment. There were no significant differences in exercise parameters in each of the exercise tests between patients with and without exercise-induced ischemia.

On coronary angiography, multivessel coronary spasm was documented in 23 patients (12 with exercise-induced ischemia, 7 without exercise-induced ischemia and 4 with extensive abnormal washout and a normal stress polar map). There was no significant difference in the number of patients with multivessel coronary spasm between those with and without exercise-induced ischemia. The number of patients with multivessel coronary spasm and single-vessel coronary spasm was similar in each group.

Effects of Drug Treatment on Washout Rate
In patients without exercise-induced ischemia, the mean washout rate on the second exercise test was significantly less than that on the first exercise test, although there was no abnormal area in the stress polar map on the second exercise test. There was no significant difference in lung thallium-201 uptake ratios between before (0.27±0.04) and after (0.27±0.03) drug treatment.

In patients with exercise-induced ischemia, there were two patterns of a change in the mean washout rate after drug treatment. Eighteen of the 26 patients with exercise-
TABLE II EXERCISE AND ANGIOGRAPHIC FINDINGS IN PATIENTS WITH EXERCISE-INDUCED ISCHEMIA

(continued)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>peak HR (beat/min)</th>
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Abbreviations as in Table I. *p<0.05, #p<0.01 compared to the values before drug treatment.

**Fig.2. Serial changes in the mean washout rate in patients with exercise-induced ischemia. In group 1 (m), the mean washout rate significantly increased after drug treatment (from 37±9 to 45±9). On the other hand, the mean washout rate significantly decreased after drug treatment (from 39±9 to 35±8) in group 2 (l), although increased doses of antianginal drugs (Drug 2) caused the mean washout rate to increase significantly on the third exercise test (to 43±5). Values are the mean±SD.* p<0.05,** p<0.01.**

induced ischemia had showed an increase in the mean washout rate on the second exercise test, as compared to that on the first exercise test (group 1). The remaining 8 patients showed a decrease in mean washout rate after drug treatment (group 2). Angiographic findings and exercise scintigraphic findings of the 2 groups are summarized in Table II. When the exercise parameters between in the 2 groups were compared, the only significant difference was that the duration of exercise in both tests was longer in

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group 2 than group 1. None of the patients in group 1 exhibited chest pain or ischemic ST depression during the exercise test after drug treatment. Two patients in group 2 showed ischemic ST depression during the exercise test after drug treatment. Angiographic findings showed that the number of patients with multivessel coronary spasm in group 1 was significantly higher than that in group 2. In the first exercise test, the extent score for the size of the perfusion defect was significantly lower in group 2 than in group 1, although the severity score of the perfusion defect and the extent score of the washout rate were similar in the two groups. In the second exercise test, both groups had showed a significant decrease in the extent scores of the perfusion defects. In group 1, the severity score of the perfusion defect was also significantly decreased. In accord with the improvement in the perfusion defect, the extent score of the washout rate decreased in group 1. However, the extent score of the washout rate in group 2 significantly increased in the second exercise test. As a result, the extent score of the washout rate in group 2 was significantly higher than that in group 1. Regardless of whether the washout rate abnormality after drug treatment was caused by exercise-induced ischemia, all of the patients in group 2 performed exercise thallium-201 emission computed tomography after receiving increased doses of antianginal drugs (nifedipine 20 mg and isosorbide dinitrate 20 mg). On the third exercise test, each patient showed an improvement in the washout rate (Fig. 2 and 3).

In patients with an extensive abnormal washout rate, the mean washout rate on the second exercise test was significantly greater than that on the first exercise test. Extent and severity scores of the perfusion defect significantly decreased after drug treatment. However, the mean washout rate and the extent score of the washout rate in patients with an extensive abnormal washout rate were significantly lower than those in patients without exercise-induced ischemia even after drug treatment (p<0.01).

DISCUSSION

The present study is the first to address the value of quantitative washout rate analysis of exercise thallium-201 emission computed tomography in vasospastic angina. Due to the high frequency of extensive abnormal washout rate and the effect of anti-
anginal drugs on washout rate, stress polar map analysis underestimated alone can underestimate exercise-induced ischemia due to vasospasm.

**Significance of Washout Rate Analysis**

As pointed out by Bateman et al. part of the reason for scintigraphic underestimation of disease extent lies with the method of scintigraphic interpretation, which is spatially relative. Therefore, washout rate analysis has been recommended as a method of spatially non-relative assessment. In particular, diffuse slow washout from all myocardial regions has been defined as an indicator of extensive coronary artery disease, such as triple-vessel disease or left main coronary artery disease. Since there have been reports of patients with multivessel coronary spasm or left main coronary artery spasm, it is reasonable to perform washout rate analysis in patients with vasospastic angina. The present study included 5 patients with an extensive abnormal washout rate and a normal stress polar map before drug treatment, 4 of whom had multivessel coronary spasm. We did not classify these patients into the exercise-induced spasm group because of the definition we used for exercise-induced ischemia. However, since drug administration improved washout rate abnormality in these patients, these washout rate abnormalities might be primarily the result of exercise-induced ischemia. In addition, 8 of the 26 patients (31%) with exercise-induced ischemia showed a decrease in mean washout rate in the exercise test after drug treatment. The extent scores of perfusion abnormalities on stress polar maps in these patients were improved, as if exercise-induced ischemia were prevented by drug treatment. However, the extent score of the washout rate was significantly aggravated. These patients were still considered to have exhibit exercise-induced ischemia, because 1) 2 showed ischemic ST depression even after drug administration, 2) the severity score of the perfusion defect remained unchanged even after drug treatment, 3) washout abnormality associated with exercise-induced ischemia usually improved after coronary revascularization and 4) all 8 patients showed an improved mean washout rate after receiving increased doses of antianginal drugs. Many of the patients with a decreased mean washout rate after drug treatment had multivessel coronary spasm. It has been reported that simultaneous multivessel coronary spasm is likely to be more extensive and severe. Thus, considerable attention must be given to patients with multivessel spasm when analyzing the results of exercise thallium-201 scintigraphy.

**Possible Mechanism of Decreased Washout Rate after Drug Administration in Patients with Exercise-induced Ischemia**

In the present study, vasospastic angina patients without exercise-induced ischemia had a significantly decreased washout rate after drug treatment. In the exercise test after drug treatment, peak blood pressure and double product were significantly lower than those before drug treatment. Since no data were available regarding the direct effects of isosorbide dinitrate or Ca-antagonists on thallium-201 uptake and clearance, the decrease in washout rate after drug treatment was considered to be due mainly to the effects of the drugs on heart rate and/or blood pressure, which resulted in a change in myocardial metabolism during exercise. We also demonstrated that some patients with exercise-induced ischemia showed a decreased washout rate after drug treatment. The mechanisms of this decreased washout rate after drug treatment remain unclear. Insufficient dilatation of spasm-provoked coronary arteries combined with sufficient dilatation of the other coronary arteries by antianginal drugs might result in a coronary steal phenomenon. In addition, insufficient improvement of the washout rate in the ischemic regions combined with the decreased washout rate in non-ischemic regions in patients without exercise-induced ischemia could result in a phenomenon similar to diffuse slow washout, which showed improved perfusion defects on stress polar maps, as if exercise-induced ischemia were prevented (“pseudonormalization”).

**Mechanisms of Extensive Abnormal Washout in Vasospastic Angina**

In 13 patients with an extensive abnormal washout rate (27% of all of the study patients with vasospastic angina), an abnormal washout rate was observed out of the terri-
tories supplied by the epicardial coronary arteries with acetylcholine-induced spasm. However, washout abnormality did not improve completely in these patients despite intensive drug treatment. Therefore, mechanisms other than exercise-induced ischemia contributing to washout rate abnormality must be considered. Since widespread abnormal washout (diffuse slow washout) in patients with documented coronary artery disease is rare\textsuperscript{9,16} the frequency of this phenomenon in vasospastic angina is rather high. Therefore, it is reasonable to assume that mechanisms other than epicardial coronary artery spasm contribute to this abnormality. Microvascular spasm or impairment of microcirculation might be a mechanism of this phenomenon in vasospastic angina. Since diffuse coronary artery spasms or vasoconstrictions were often observed on coronary angiography in patients with vasospastic angina during the acetylcholine provocation test, it is likely that spasm is provoked in coronary arteries less than 100 \( \mu \)m in diameter, which can not be detected on angiography. Abnormalities in microcirculation have been suggested in patients with angina pectoris and normal coronary arteries\textsuperscript{17,18} In addition, since a high frequency of silent myocardial ischemia due to vasospasm has been reported\textsuperscript{19,20} frequent ischemic insults may cause metabolic or morphologic changes in myocytes, resulting in abnormal thallium-201 clearance. Furthermore, extensive abnormal washout resulting from drug administration in some patients with vasospastic angina was demonstrated in this study.

**Limitations of the Study**

Several physiologic and technical factors influence thallium-201 myocardial washout rate\textsuperscript{19,21} Heart rate and lung uptake in particular have been demonstrated to greatly influence thallium-201 washout.\textsuperscript{21} Considering the effect of Ca-antagonist on heart rate, nifedipine was our first choice to suppress vasospasm, although 10 patients took diltiazem because of side effects from nifedipine, such as flushing, dizziness and leg edema. All of the patients attained 90% of their age-predicted heart rate before and after drug treatment. A sufficient dose of nifedipine or diltiazem alone is known to suppress coronary spasm\textsuperscript{1–3} However, since the recommended high doses of these drugs considerably affected exercise parameters in our preliminary study, we administered only small doses of Ca antagonist and isosorbide dinitrate. These regimens completely abolished cardiac symptoms in the daily lives of all of the subjects. During the exercise tests, all of the patients had adequate heart rate response and exercise capacity. In addition, there was no significant difference in the lung thallium-201 uptake ratio between before and after drug treatment in patients without exercise-induced ischemia. However, lung thallium-201 uptake was not measured in all of the study subjects. Among patients with coronary artery disease, however, those with increased lung thallium-201 uptake had extensive and severe coronary artery disease\textsuperscript{12,22} They often showed lower exercise capacity and a high frequency of ischemic ST depression or chest pain, as compared to patients with normal lung thallium-201 uptake. In the present study, both patients with extensive washout abnormality and patients with a decreased mean washout rate after drug treatment showed good exercise tolerance. Therefore, we believe that there was no significant difference in thallium-201 lung uptake among the study patients.

**CONCLUSION**

More than one half of vasospastic angina patients showed exercise-induced ischemia on quantitative exercise thallium-201 emission computed tomography. However, these patients should be monitored carefully, especially after drug treatment, because some exhibited pseudonormalization of stress polar maps. Washout rate analysis is helpful in identifying these patients. In addition, the high frequency of abnormal washout rate in patients with vasospastic angina is suggestive of microspasm, or impairment of myocyte or microcirculation.

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