Severity of Exercise-induced Ischemia With Chest Pain and Recovery From Ischemia After the Disappearance of Chest Pain

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SUMMARY

The severity of exercise-induced painful ischemia and its recovery after the disappearance of pain are unknown. The aim of this study was to investigate the difference in severity of ischemia at both exercise and postexercise between painful ischemia and painless ischemia.

After injections of technetium-99m tetrofosmin at peak ergometer exercise and thallium-201 at 3 minutes postexercise, dual-isotope single photon emission tomography was performed in 78 patients with angiographically proven ischemic heart disease. The extent of ischemic areas (the number of areas), the depth of ischemia in the ischemic area (the severity score of ischemia) and the extension of ischemia toward long axis of the left ventricle (the number of left ventricular levels with ischemic areas in apical, middle, and basal levels) at both exercise and postexercise were compared on the basis of the presence of pain and a history of diabetes mellitus (DM).

The symptoms improved within 3 minutes postexercise in all painful ischemia patients. Of 59 patients with reversible ischemia, except for 4 painful ischemia patients with DM, the extent and depth of ischemia at postexercise were more severe in 14 painful ischemia patients without DM and 13 painless ischemia patients with DM than 28 painless ischemia patients without DM (extent; 2.9 ± 1.7 areas, 3.5 ± 2.8 areas versus 1.4 ± 1.8 areas, P = 0.005, depth; 3.8 ± 3.1 scores, 5.8 ± 5.4 scores versus 1.9 ± 3.0 scores, P = 0.0084, respectively) despite a comparable severity of ischemia at peak exercise (extent; 5.4 ± 2.6 areas, 6.0 ± 2.4 areas versus 4.3 ± 3.3 areas, depth; 9.3 ± 5.7 scores, 10.7 ± 7.3 scores and 7.5 ± 8.1 scores, all NS). The extension of ischemia toward long-axis of the left ventricle at both peak exercise and postexercise was more severe in the former 2 groups than the latter group (peak exercise; 2.4 ± 0.6 levels, 2.5 ± 0.7 levels versus 1.9 ± 0.8 levels, P = 0.0263, postexercise: 1.8 ± 0.7 levels, 1.5 ± 0.9 levels versus 0.8 ± 0.8 levels, P = 0.0014, respectively).

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The presence of chest pain is related to the extension of ischemia toward long-axis of the left ventricle, and the disappearance of pain was not related to the recovery of ischemia. (Jpn Heart J 2004; 45: 551-560)

**Key words:** SPECT, Exercise testing, Silent ischemia, Diabetes mellitus, Recovery phase after exercise, Coronary artery disease

CHEST pain during exercise predicts the presence of coronary artery disease, similarly to ST segment depression on ECG. However, it is still controversial as to whether the presence of chest pain reflects the severity of ischemia. The difference between painful ischemia and painless ischemia in previous studies has been analyzed not with respect to the various qualities of ischemic burden, but rather the simplified severity of ischemia such as the total extent of ischemic areas in the left ventricle or the severity of ischemia in the ischemic areas. Accordingly, it is not clarified what qualities of ischemia cause the chest pain easily in the clinical setting. On the other hand, the delayed recovery from ischemia after exercise also may be a marker of severe ischemia, and the magnitude of recovery from ischemia may be characterized as the quality of ischemia. A recent study demonstrated that the difference between painful ischemia and painless ischemia was more closely related to the magnitude of recovery from exercise-induced ischemia than the severity of ischemia at peak exercise. However, it has not been clarified whether the ischemia recovers immediately after the disappearance of chest pain, or whether the magnitude of recovery after exercise is different between painful ischemia and painless ischemia. The aim of this study was to investigate the relationship between the presence of chest pain and severity of ischemic burden by analysis of the extent, depth, and magnitude of recovery from ischemia using exercise dual-isotope single photon emission computed tomography (SPECT).

In the present study, patients with diabetes mellitus (DM) were distinguished from patients with painless ischemia because the painless ischemia in patients with DM may be caused by a different mechanism.

**METHODS**

**Patient population:** Exercise SPECT was performed in 78 patients with angiographically proven ischemic heart disease and 10 healthy volunteers. Patients with myocardial infarction diagnosed on the basis of clinical or scintigraphic findings were excluded. Anti-anginal medication was discontinued in all patients at least 48 hours before the radionuclide study. The left ventricular ejection fraction (%) and the regional wall motion (scored from 0 indicating normal to 5 indi-
cating dyskinesis) were measured on left ventriculography. Informed consent was obtained from all patients.

**Exercise testing with dual-isotope SPECT:** Exercise was performed on an upright bicycle ergometer, initially at 50W of workload and then increased stepwise by 25W every 3 minutes. Exercise was terminated by the onset of chest pain, additional ischemic ECG changes (> 2 mm ST-segment depression), or excessive leg fatigue. A 12-lead ECG, heart rate, and blood pressure were monitored at one-minute intervals throughout the study. At the peak of exercise, 7 mCi (259 MBq) of technetium-99m tetrofosmin was injected intravenously, and the patient was asked to continue exercising for an additional minute. Three minutes after termination of exercise, 3 mCi (111 MBq) of thallium-201 was injected intravenously. SPECT images were then obtained after 20 minutes of recovery (initial images with technetium-99m tetrofosmin and thallium-201) and 4 hours after termination of exercise (redistribution images with thallium-201). Cardiac SPECT images were acquired on a dual-detector, rotating, dedicated cardiac camera (Prizm 2000XP, Picker Co., Philadelphia, USA). The 15% main energy window centered at 140 keV and the 24% main energy window centered at 71 keV were set for the technetium-99m images and thallium-201 images, respectively. We used the triple-energy window method to eliminate the counts of scattered photons as reported in both phantom and clinical settings. The reconstructed transaxial slices were then reoriented into vertical long, horizontal long, and short axes.

**Quantitative analysis of SPECT imaging:** Short-axis images of the left ventricle were divided into the apical, middle, and basal slice levels; the last 2 levels were divided into 8 segments in each slice, yielding a total of 17 areas. A myocardial perfusion defect was considered to be present if the percentage uptake of radioactive counts in each area was 2.5 or more standard deviations below the mean normal limit. The normal values were obtained from 10 normal volunteers in this study. The extent of ischemic areas was represented as the number of myocardial areas below this limit. Each perfusion defect area was scored 1-6 by each 10% decrease in tracer uptake of the myocardium. The depth of ischemia in the ischemic areas of each patient was represented as the total scores of perfusion defect areas. The extension of ischemia toward long-axis of left ventricle was represented as the range of left ventricular levels with the ischemic areas (as only 1 level, 2 levels, and all 3 levels of the apical, middle, and basal levels). The severity of ischemia was compared between the painful and painless patients, or the patients with and without DM.

**Statistical analysis:** Comparisons between groups were performed using one-way analysis of variance (ANOVA) for continuous variables and the chi-square
test for categorical variables. A $P$ value of less than 0.05 was considered statistically significant. All data are presented as the mean ± standard deviation.

RESULTS

Patient characteristics: Of 78 patients with coronary artery disease, 59 who exhibited transient ischemia during exercise and resting complete redistribution on 4 hour thallium-201 redistribution images were studied (45 males, 14 females; mean age, 66.7 ± 9.2 years). Of these, 18 patients had typical chest pain during exercise, and the symptoms disappeared within 3 minutes after the termination of exercise without requiring nitrate administration in any of these patients. None had symptoms during the recovery phase alone. Fourteen of the patients with chest pain did not have a history of DM (the non-DM patients with painful ischemia: group A). Forty-one patients did not have chest pain during exercise. Of these, 13 had a history of DM (DM patients with painless ischemia: group B), and 28 patients did not have a history of DM (non-DM patients with painless ischemia: group C). There were no significant differences in the age, gender, history of typical chest pain, or coronary angiographic and left ventriculographic findings among the 3 groups (Table I).

Exercise testing results: The rate pressure product (RPP) at peak exercise in group A was lower than group C and the normal volunteers ($P < 0.05$), but was not different from the RPP in group B (22797 ± 5884 in group A, 25917 ± 6213 in group B, 27301 ± 6529 in group C, and 31067 ± 7241 in normal volunteers). The ratio of RPP at 3 minutes into the recovery to RPP at peak exercise was also lower in group A than group C and the normal volunteers ($P < 0.05$) (0.65 ± 0.14, 0.58 ± 0.16, 0.53 ± 0.17, 0.50 ± 0.13, respectively). The presence of additional

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Group A: painful patients without diabetes mellitus (DM); Group B: painless patients with DM; Group C: painless patients without DM. NS = no significance. All data are expressed as the mean ± 1 standard deviation.
ST-segment depressions (85.7% in 12 of 14 patients in group A, 92.3% in 12 of 13 patients in group B, and 71.4% in 20 of 28 patients in group C), and the magnitude of additional ST depressions (0.20 ± 0.13 mV, 0.17 ± 0.11 mV, 0.14 ± 0.11 mV, respectively) were also similar.

Severity of ischemic burden during exercise and recovery: Exercise-induced perfusion defects on the SPECT images occurred in the anteroseptal areas in 23 patients, lateral areas in 18, inferior areas in 13, and in a combination of areas in 1. The extent of ischemia at peak exercise was slightly larger in group A and group B than that in group C (5.4 ± 2.6 areas, 6.0 ± 2.4 areas versus 4.3 ± 3.3 areas, NS), but the differences were not significant. At 3 minutes postexercise, the extent of ischemia was significantly larger in the same order (2.9 ± 1.7 areas, 3.5 ± 2.8 areas and 1.4 ± 1.8 areas, $P = 0.005$, respectively) (Figure 1). There were no significant differences in the extent of ischemia at both exercise and 3 minutes postexercise between group A and group B. Similar results were obtained with

![Graph showing the total number of ischemic areas (the extent of ischemia) at peak exercise on technetium-99m tetrofosmin images and 3 minutes into recovery on thallium-201 images.](image)

**Figure 1.** Bars show the total number of ischemic areas (the extent of ischemia) at peak exercise on technetium-99m tetrofosmin images and 3 minutes into recovery on thallium-201 images.
respect to the depth of ischemia in the ischemic area (peak exercise; $9.3 \pm 5.7$ scores, $10.7 \pm 7.3$ scores and $7.5 \pm 8.1$ scores, NS, 3 minutes postexercise; $3.8 \pm 3.1$ scores, $5.8 \pm 5.4$ scores and $1.9 \pm 3.0$ scores, $P = 0.0024$, respectively) (Figure 2).

A similar result was obtained in the total number of levels with ischemic areas toward long-axis of left ventricle, and the difference between group A or group B and group C was more significant at both peak exercise and 3 minutes postexercise (exercise; $2.4 \pm 0.7$ levels, $2.5 \pm 0.7$ levels and $1.9 \pm 0.8$ levels, $P = 0.0263$, post-exercise; $1.8 \pm 0.7$ levels, $1.5 \pm 0.9$ levels and $0.8 \pm 0.8$ levels, $P = 0.0014$, respectively) (Figure 3).

Figure 2. Bars show the total defect scores of ischemic areas (the depth of ischemia in the ischemic areas) at peak exercise on technetium-99m tetrofosmin images and 3 minutes into recovery on thallium-201 images.
DISCUSSION

In the present study, there were no significant differences in the extent of ischemic areas and depth of ischemia in the ischemic areas during exercise between painful ischemia and painless ischemia in patients without DM. However, the extent and depth of painful ischemia persisted at 3 minutes postexercise despite the disappearance of cheat pain after exercise compared to the quick recovery of the painless ischemia. It is postulated that exercise-induced painless ischemia is less severe than painful ischemia3,4) because angina is no more than a late manifestation of the ischemic cascade phenomenon. Klein, et al5) demonstrated using thallium-201 SPECT that there was a substantial difference in the depth of ischemia as the magnitude of thallium uptake score in the ischemic area between painless and painful ischemia. On the other hand, Marcassa, et al6) found
that the total extent of ischemic area on exercise technetium-99m sestamibi SPECT was comparable between them, but that the amount of reversible ischemia as measured by the difference in the extent of defects between stress and rest tracer uptake was significantly greater in patients with painful ischemia. The controversy in the difference between them may result from the analysis of the simplified severity of ischemia. Using exercise SPECT, we analyzed the difference between them on the basis of severity of ischemic burden as the extent and depth of ischemia, and the magnitude of recovery from ischemia. We first found that the painful ischemia was characterized by delayed recovery from ischemia despite the quick disappearance of chest pain. Our results indicate that it is important for physical cardiologists to monitor electrocardiography, blood pressure, and the symptoms of ischemia carefully not only during exercise but also postexercise even though the chest pain may have disappeared quickly after exercise.

Second, the painful ischemia was characterized by the extension of ischemia toward long-axis of left ventricle. Although the extension of ischemia in the direction of the long-axis of the left ventricle varies greatly depending on the size and the stenotic coronary artery, the extensive ischemia extends to all levels toward long axis of left ventricle. Therefore, the extension of ischemia toward long-axis of left ventricle indicates the severe ischemia or poor prognosis. We found that the presence of exercise-induced chest pain was more closely related to the extension of ischemic burden toward the long-axis of the left ventricle than the total extent and depth of ischemic burden, although the extension of ischemic burden toward the long-axis of the left ventricle was closely related to the total extent and depth of ischemic burden. This close relation may result from the fact that the sympathetic afferent nerves run parallel to the coronary artery toward the long-axis of the left ventricle.

Third, the severity of ischemia which we measured in the present study was almost comparable between the painful ischemia without DM and the painless ischemia with DM. In a previous study, the episodes of silent myocardial ischemia were more frequent in patients with DM than in patients with non-DM on exercise ECG testing. The mechanism of silent ischemia in patients with DM may be a defective angina warning system or a higher pain threshold, and these mechanisms of silent ischemia in patients with DM may be caused by nerve damage, similar to the patients with prior myocardial infarction, prior coronary bypass surgery, or surgical denervation. Furthermore, the patients with DM had a more severe or different type of vascular involvement, myocardial dysfunction from diffuse myocardial damage due to the metabolic disorder, microangiopathy, or neuropathy of the autonomous nervous system. Therefore, we determined whether patients had a history of DM or myocardial infarction, although the pre-
previous studies which demonstrated a difference between painful ischemia and painless ischemia did not make this distinction.

**Study limitations:** The intrinsic differential uptake of technetium-99m tetrofosmin and thallium-201 were evaluated using dual-isotope SPECT imaging. These values were normalized by the mean normal value in each myocardial area of the left ventricle to compare these different tracer images. In the phantom study in our own laboratory, there was no significant difference in the width of the defect between the thallium-201 image obtained by a single isotope SPECT and that with cross-talk compensation obtained by a simultaneous dual-isotope SPECT as shown in a previous report.

**Conclusions:** Using exercise SPECT, we analyzed the difference between painful ischemia and painless ischemia on the basis of the severity of ischemic burden as the extent and depth of ischemia, and the magnitude of recovery from ischemia. In patients without DM, we found the painful ischemia was characterized by delayed recovery from ischemia despite the disappearance of chest pain compared to the quick recovery of painless ischemia, although the severity of the ischemia was comparable during exercise. The painful ischemia was characterized by the extension of ischemia toward long-axis of the left ventricle compared to the painless ischemia. However, the quality of painless ischemia was not fit for the patients with DM.

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**REFERENCES**