

The causes and clinical significance of exercise-induced silent myocardial ischemia evaluated by ischemic range and intensity with exercise Tl-201 myocardial SPECT

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We investigated the causes and long-term prognosis of exercise-induced silent myocardial ischemia (SMI) by means of exercise Tl-201 myocardial SPECT (Ex-SPECT) in 97 patients with effort angina or old myocardial infarction (OMI). These patients were proven to have significant stenosis by coronary angiography. The subjects were divided into three groups based on the presence or absence of Tl-201 redistribution or angina during exercise testing. Group one consisted of 34 patients who had redistribution on Ex-SPECT and angina during exercise testing; the painful myocardial ischemia (PMI) group. The second group consisted of 38 patients who had redistribution on Ex-SPECT, but no angina during exercise testing: the SMI group. The third group consisted of 25 patients who had no redistribution: the RD (—) group.

The ischemic range and intensity were quantified by the defect volume ratio (DVR) and defect severity index (DSI), respectively. Comparison of the DVR and DSI values for the PMI and SMI groups revealed that the DVR and DSI values for the SMI group were lower than those of the PMI group. Also the prognosis of the SMI group tended to be worse than that of the RD (—) group. Thus, we concluded that the SMI and PMI group should receive identical treatment.

Key words: exercise thallium-201 (Tl-201) myocardial SPECT, silent myocardial ischemia, prognosis

INTRODUCTION

CHEST PAIN ASSOCIATED with physical exertion is a common complaint of patients with ischemic heart disease (IHD). Although the exact mechanism of this pain is unknown,¹ it is considered to be a warning sign of myocardial ischemia. However, frequently patients with IHD detected by ST segment depression can experience ischemic episodes without the pain of angina. Such events are termed "silent myocardial ischemia" (SMI).

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Cohn classified SMI into three groups as follows:²

1) Silent myocardial ischemia in persons with totally asymptomatic coronary artery disease; 2) Silent myocardial ischemia in individuals asymptomatic after a myocardial infarction; 3) Silent myocardial ischemia in patients with angina. The frequency, mechanisms, and prognosis of SMI have recently been investigated by many researchers using this classification. SMI has been shown to occupy a large part of the total myocardial ischemic burden. It is very important to clarify the clinical characteristics and long-term prognosis of SMI in considering the management of IHD. In this study, we compared the range and intensity of myocardial ischemia during exercise-induced SMI and painful myocardial ischemia (PMI), and investigated the prognosis of SMI.

SUBJECTS AND METHODS

Our study examined two groups of patients: Those with effort angina ($n=48$) and those having old myocardial infarction (OMI), with or without angina ($n=49$). All patients were proved to have significant stenosis in coronary arteries by coronary angiography and all received medical therapy. We classified the patients with Tl-201 redistribution observed by exercise Tl-201 myocardial SPECT (Ex-SPECT) into two groups. One group consisted of patients who complained of chest pain during exercise testing (painful myocardial ischemia or PMI group). The other group consisted of patients who did not complain of chest pain during exercise testing (SMI group). The patients in whom the redistribution was not observed by Ex-SPECT belonged to the redistribution (RD) (—) group.

Left ventricular and coronary cineangiograms

Left ventricular angiography was performed in the 30° right anterior oblique and 60° left anterior oblique projections. The left ventricular ejection fraction (LVEF) was measured according to Kasser's method. Coronary arteriograms were obtained with the Judkins' technique at least in the 30° right anterior oblique and 60° left anterior oblique. "Significant" coronary artery disease, for the purposes of this study, was defined as a reduction in luminal diameter of 75% or greater.

Exercise protocol

Exercise was performed by graded bicycle ergometer beginning at 50 W with 25 W increments every three min. Exercise testing was stopped if 1) the patient complained of chest pain, leg fatigue, general fatigue, shortness of breath, etc., 2) significant ST segment depression or elevation was observed by ECG monitoring, or 3) the patient's heart rate (HR) reached 85% of the maximal target heart rate.

During testing, Tl-201 (74 MBq) was injected into patients who then exercised for one more minute. Tl-201 SPECT images were taken at 10 min and 4 h after Tl-201 injection. Double product and HR were used as a measure of the circulatory condition. Double product is the product of HR and systolic blood pressure measured by the standard cuff method. Patients were excluded from the study if exercise testing was stopped due to leg fatigue, general fatigue, shortness of breath, etc., and their HRs failed to reach 85% of the maximal target heart rate.

We described the patients' chest pain in terms of quality, location, duration, and radiation of pain, and according to these four characteristics judged whether the chest pain was effort angina.

Ex-SPECT

The instrumentation used in this study included a gamma camera [HITACHI Gamma View D (RC-135T)] and an online mini-computer (HARP). Data collection began from the 45° right anterior oblique view and ended at the 45° left posterior oblique view. Using the slice with the greatest cavity length, the operator selected the apex and the long axis of the left ventricle (LV). Using the long axis, the operator divided the left ventricle into 16 short axial slices. On the short axial slices falling halfway between the apex and the base, the operator then defined the center-point of the LV cavity. The circumferential profile (CP) of each short axial slice was generated from the most basal to the most apical slice for each stress and delayed tomographic study until 4 h after the injection of Tl-201. Each point in these profiles represents the maximum counts (maximum counts in stress study: C stress; maximum counts in delayed study: C delayed) per pixel along a radius extending from the center-point of the LV to the limit of the radius of search. Each radius was spaced at a 6° interval plotted counterclockwise and each short axial slice was divided into 60 segments. The maximum count per pixel along each radius was defined as the count of the segment which was between one radius and the next.

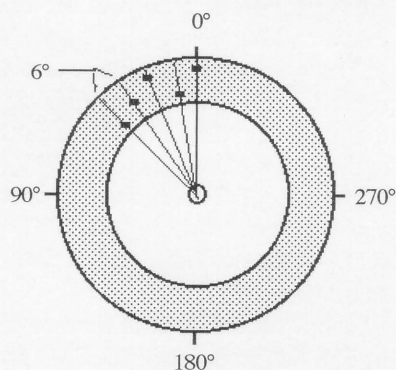
The washout rate (WR) in each segment was calculated as $(C \text{ stress} - C \text{ delayed}) / C \text{ stress} \times 100(\%)$. Normal lower limits of WR were defined in each segment as 2 standard deviations (s.d.) below the mean for the WR which was generated from 8 normal controls. The average of the normal lower limits of WR in the entire left ventricle is $33 \pm 6\%$. The regions where WR fell below the normal lower limits were considered to be ischemic regions.

After the WR for all segments had been extracted, they were expressed in a two-dimensional polar coordinate map (Fig. 1), or so-called Bull's eye map.³ The defect volume ratio (DVR) and defect severity index (DSI) were used as parameters of the range and intensity of myocardial ischemia, respectively. They were calculated with the formula in Fig. 2. DVR and DSI represented the ratio of the quantity of ischemic myocardium to the whole myocardium, and the all defect intensity of ischemia to the whole myocardium respectively. We compared the DVR and DSI values for the PMI and SMI groups.

Follow-up

We investigated the prognosis in the three groups after the performance of Ex-SPECT. Five outcomes were defined as "cardiac events": 1) change to unstable angina; 2) cardiac death; 3) sudden death; 4) non-fatal myocardial infarction; 5) congestive

Circumferential Profile



Bull's Eye Polar Map

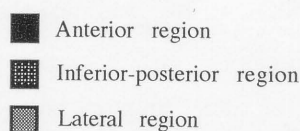
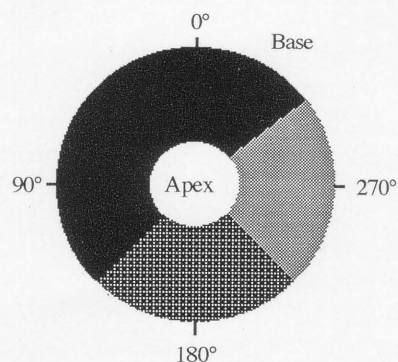
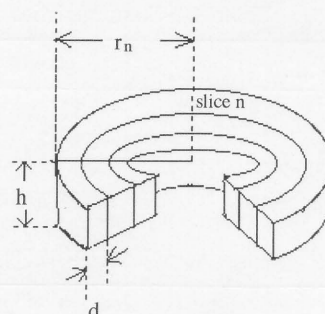
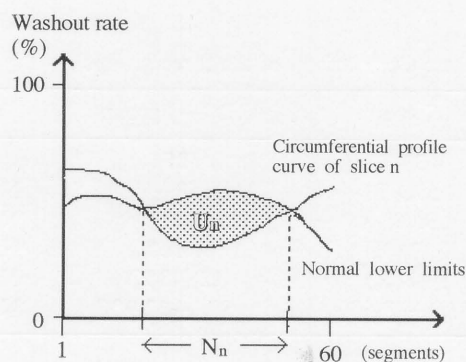


Fig. 1 Construction of Bull's eye map with circumferential profiles.



$$\text{Defect volume ratio (DVR)} = \frac{\sum 2 \pi r_n \cdot N_n / 60}{\pi \cdot 16^2}$$

$$\text{Mean defect severity (MDS)} = \frac{\sum U_n \cdot 2 \pi r_n / 60}{\sum 2 \pi r_n \cdot N_n / 60}$$

$$\text{Defect severity index (DSI)} = \text{DVR} \cdot \text{MDS} \quad \begin{matrix} (r_n = n, n = 1-16) \\ (h = d = 1) \end{matrix}$$

Fig. 2 Formulas for calculating DVR and DSI. DVR and DSI were used as parameters of the range and intensity of myocardial ischemia, respectively. The left ventricle was divided into 16 short axial slices. Each short axial slice was separated into 60 segments. r_n : radius of slice n ; h : height of slice n ; d : depth of slice n ; U_n : sum of difference between circumferential profile values and lower limits in slice n ; N_n : number of segments of which circumferential profile values are below the lower limits.

heart failure. The status of the patients was fully reviewed in sealed letters, out-patient medical records, and/or telephone interviews.

Statistical analysis

Cardiac event rates were assessed by the Kaplan-Meier method with a median follow-up of 2.0 years. Differences among the three groups were studied

with the Chi square test, t test, and generalized Wilcoxon test. Statistical significance referred to a probability (P) value of less than 0.05.

RESULTS

There were no significant differences among the three groups with regard to the clinical characteristics including age, gender, prevalence of diabetes mellitus, prevalence of OMI, and LVEFs (Table 1).

Double products for the three groups in peak exercise (DP_{max}) are shown in Fig. 3. The mean value for the DP_{max} of RD (—) group ($23,736 \pm 5,113$ mmHg·beats/min) was significantly higher than that for the PMI group ($20,451 \pm 5,105$ mmHg·beats/min). However, there was no difference between the SMI and PMI groups in the DP_{max} .

The medications used for each group are shown in Fig. 4. The ratio of patients who were treated with intrinsic sympathomimetic action (ISA) (—) beta-blockers to their whole group was significantly

higher in the PMI group than in the SMI group or in the RD (—) group. There was no difference among the three groups in the usage of nitrates and calcium antagonists.

The number of coronary arteries with significant stenosis is indicated in Fig. 5. The single-vessel disease rates were higher in the SMI group (39%) and in the RD (—) group (44%) than in the PMI group (18%). The number of coronary arteries with significant stenosis in the SMI group and in the RD (—) group had a tendency to be smaller than in the PMI group.

The DVR and DSI of the two groups are indicated in Fig. 6. The DVR of the SMI group (23.1 ± 13.1 %) was significantly lower ($p < 0.05$) than that of the PMI group (42.1 ± 19.1 %). Similarly, the DSI of the SMI group was significantly ($p < 0.05$) lower.

Table 2 shows the results of a prognostic survey in the three groups. The mean follow-up period was 2 years (range 0.1 to 4.8 years). All of the patients in the three groups could be followed up. The cumulative cardiac event rates for the three groups are

Table 1 Characteristics of the patients: Comparison of the three groups

	PMI group	SMI group	RD (—) group	p
Number	34	38	25	
Age	59 ± 7	59 ± 7	58 ± 8	N.S.
Gender (Male/Female)	29/5	30/8	20/5	N.S.
Diabetes mellitus	10 (29%)	13 (34%)	9 (36%)	N.S.
OMI	18 (53%)	18 (47%)	12 (48%)	N.S.
LVEFs	54.7 ± 14.1 %	57.9 ± 13.5 %	58.1 ± 12.9 %	N.S.

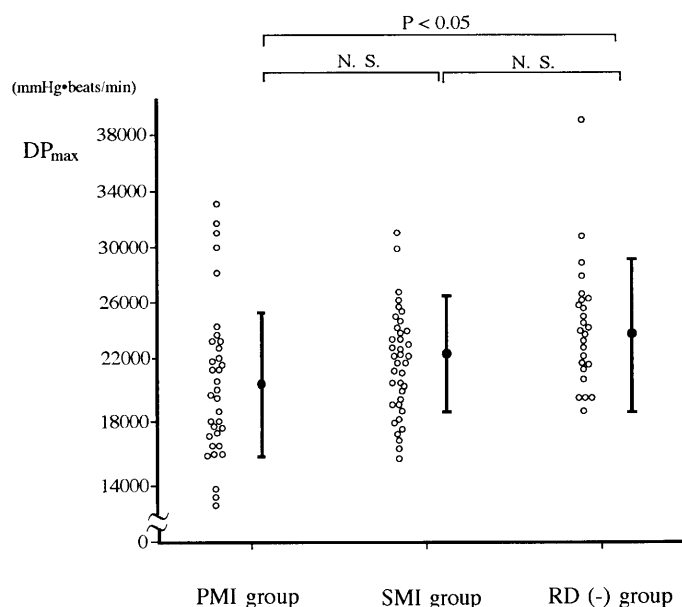


Fig. 3 Comparison of DP_{max} in the three groups. PMI: painful myocardial ischemia; SMI: silent myocardial ischemia; RD (—): redistribution (—).

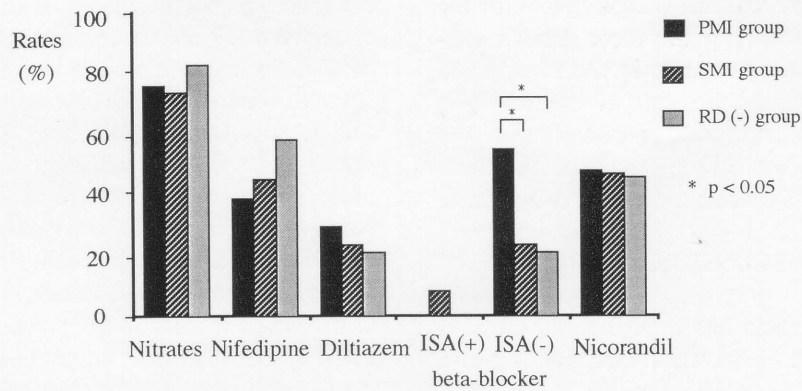


Fig. 4 Medications used for each group: taking medications rates. ISA: intrinsic sympathomimetic action.

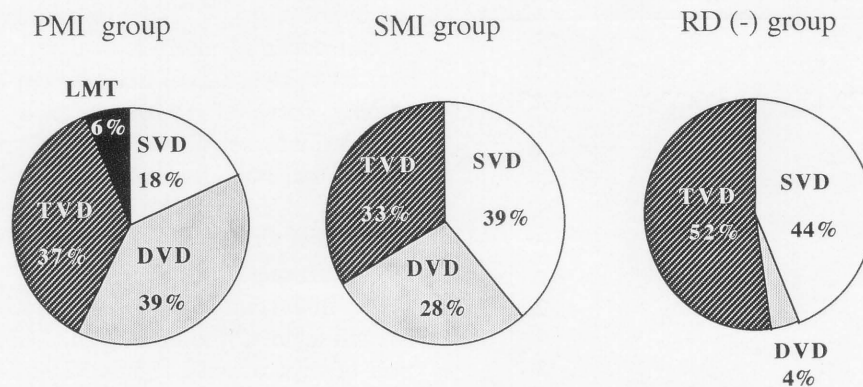


Fig. 5 Number of coronary arteries with significant stenosis in each of three groups. SVD: single-vessel disease; DVD: double-vessel disease; TVD: triple-vessel disease; LMT: lesion of left main trunk.

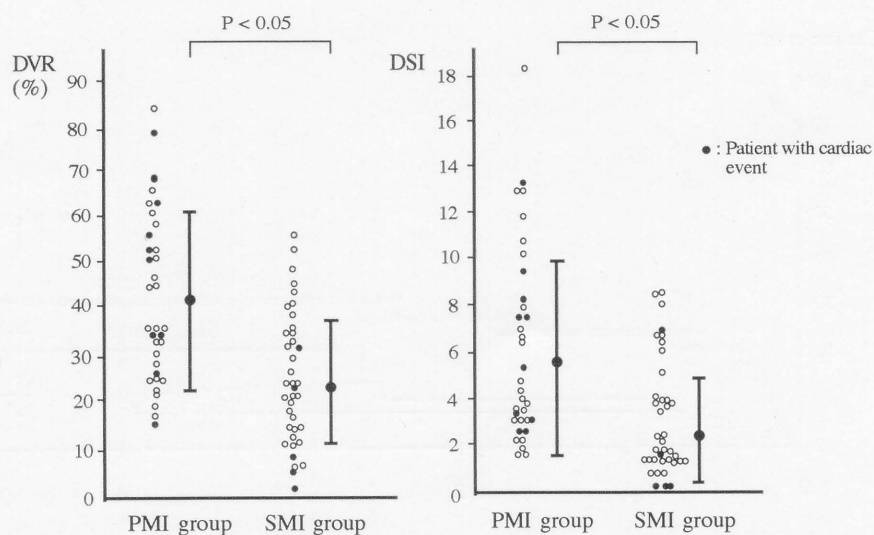


Fig. 6 Comparison of DVR and DSI in the two groups. The DVR of the SMI group ($23.1 \pm 13.1\%$) was significantly lower than that of the PMI group ($42.1 \pm 19.1\%$). Similarly, the DSI of the SMI group was significantly lower.

shown in Fig. 7. A generalized Wilcoxon test for the statistical differences among the three groups confirmed that the cardiac event rate in the PMI group was significantly higher than that of the RD (—) group. The cardiac event rate was higher in the SMI group than in the RD (—) group, but there was no significant difference between the two groups.

DISCUSSION

Recently, much attention has been focused on SMI in patients with IHD. However, the mechanisms and

Table 2 Long-term prognosis of the patients: Comparison of the three groups.

	PMI group	SMI group	RD (—) group
Number	34	38	25
Number of patients with cardiac event	10 (29.4%)	5 (13.2%)	2 (8.0%)
Unstable angina	8	5	0
Medically treated	4	2	0
PTCA or CABG	4	3	0
Non-fatal AMI	1	0	0
CHF	1	0	0
Cardiac death	0	0	2
Fetal AMI	0	0	1
Sudden death	0	0	1
Non-cardiac death	0	0	0

PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass graft; AMI: acute myocardial infarction; CHF: congestive heart failure

prognosis of SMI are not known in detail. Cohn classified SMI into three groups but the mechanisms of SMI in each group are not clear. Rozanski and Berman reported the following three hypotheses on the mechanisms of SMI⁴: 1) SMI represents less severe ischemia, not sufficient to meet pain thresholds; 2) there are important differences in pain perception thresholds or central transmission of painful stimuli among individuals; 3) The pathophysiology may be varied, resulting in different patterns of disturbed myocardial blood flow during SMI and PMI. In view of the range and intensity of myocardial ischemia, we investigated the mechanisms of SMI in effort angina and in OMI by Ex-SPECT.

We must carefully evaluate the region and intensity of myocardial ischemia by Ex-SPECT. If myocardial ischemia is evaluated as only the difference in TI-201 distribution, it is easy to misinterpret a decrease in the distribution of TI-201 in the whole myocardium as can occur in multivessel disease. However, WR evaluates myocardial ischemia by the time-radioactivity curve of TI-201 in each segment of the myocardium, so WR is a useful measure of myocardial ischemia, especially in multivessel disease. Therefore, the range, intensity, and location of myocardial ischemia were quantitatively evaluated by WR in this study.

It is important that the normal lower limit of WR in each segment should be established for the evaluation of myocardial ischemia. In our institution, the mean of the normal lower limits of WR in all segments is $33 \pm 6\%$. Katsuki reported that the mean of the normal lower limits of WR is 33.5% .⁵ The range and intensity of myocardial ischemia of the SMI group were significantly lower than those of the

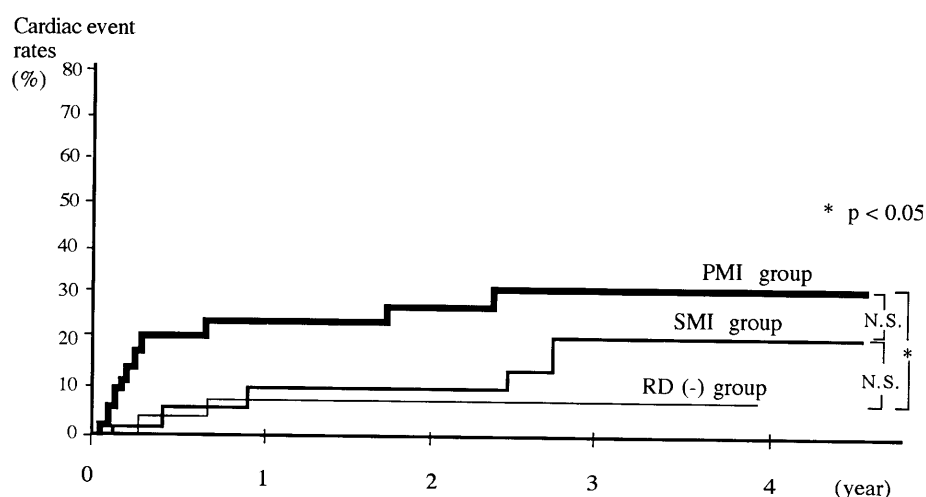


Fig. 7 Kaplan-Meier curves comparing the cumulative cardiac event rates. The cardiac event rate in the PMI group was significantly higher than that of the RD (—) group. The cardiac event rate was higher in the SMI group than in the RD (—) group, but there was no significant difference.

PMI group. This result indicated that myocardial ischemia induced by nearly equal work load was less in the SMI group than in the PMI group and it was considered to support Rozanski and Berman's hypotheses. Imai reported in his study on IHD with Ex-SPECT that the range and intensity of myocardial ischemia were lower in the SMI group than in the PMI group.⁶ However, some patients in the SMI group had comparatively high DVR and DSI. In these patients, the threshold of pain was considered to be high. The threshold of pain might be a function of the sensory nervous system, endogenous opiates and so on.⁷

Recently, it has been shown that concentrations of metaiodobenzylguanidine (MIBG), an analog of norepinephrine, reflect adrenergic neuron integrity and/or function.⁸ In patients with OMI, the uptake of TI-201 and MIBG decreases in the infarct regions, so that in these regions the adrenergic nervous system was considered to be denervated.⁹ The relation between the denervation of the adrenergic nervous system and the threshold of pain is still unclear. Further investigation is required.

For the evaluation of the clinical significance of SMI, it is important to investigate its prognosis. Many studies concerning the prognosis of Cohn's type II and III SMI have been reported. Gottlieb reported that despite intensive medical therapy, patients with 60 minutes or more of silent myocardial ischemia during a 24-hour period had a worse prognosis than those with under 60 minutes of SMI per 24 hours.¹⁰ Fukami reported that cumulative total and cardiac mortality, and the incidence of recurrent myocardial infarction calculated with the actuarial method were higher in the SMI and PMI groups than in the control group.¹¹ In our study on effort angina and OMI, the cardiac event rate for the SMI group was higher than that for the RD (—) group, but lower than that for the PMI group.

Patients with Cohn's type I SMI were difficult to detect because they complain of no chest pain. The frequency of Cohn's type I SMI in adults was considered to be about 5% from several studies.¹² Moreover, Rozanski and Berman reported that an abnormal exercise ECG response in symptom-free individuals indicated an increase in the risk for cardiac events.¹³ The significance of Cohn's type I SMI was very important to public health.

In conclusion, the prognosis for patients with SMI tends to be worse than for patients without SMI, and to be better than for patients with PMI although there was not statistical significance in our study results. The purpose of the treatment of IHD is to control chest pain and to improve quality of life, but it is more important to prevent acute myocardial infarction, cardiac death, and sudden death.

Therefore, we believe that patients with PMI and those with SMI should receive identical treatment.

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