EFFECTS OF SUBLINGUAL ISOSORBIDE DINITRATE ON LEFT VENTRICULAR PERFORMANCE DURING EXERCISE IN PATIENTS WITH MYOCARDIAL INFARCTION

SUGAO FUKUI, M.D., KUNITOMO SATOH, M.D*, TOSHIHIKO TANAKA, M.D.**
HIROKO INOUE, M.D., YUTAKA HAMANO, M.D., OSAMU KATOH, M.D.
TAKAZO MINAMINO, M.D., KENSHI FUJII, M.D.*** HIDEYUKI SATOH, M.D.***
AND MICHITOSHI INOUE, M.D.***

In order to investigate left ventricular performance during exercise in patients with myocardial infarction and evaluate the effects of sublingual isosorbide dinitrate (ISDN) on left ventricular performance, we performed a symptom-limited multigraded exercise test using a bicycle ergometer in supine position. Thirty-seven patients with myocardial infarction were evaluated in order to clarify the hemodynamic responses to exercise with and without sublingual ISDN.

Patients were subdivided into 3 groups according to the level of pulmonary capillary pressure (PCP) and cardiac index (CI) at peak exercise as follows: Group I (14 patients); $PCP < 18$ mmHg, $CI \geq 5.0$ or $CI < 5.0$ L/min/m², Group II (11 patients); $PCP \geq 18$ mmHg, $CI \geq 5.0$ L/min/m², Group III (12 patients); $PCP \geq 18$ mmHg, $CI < 5.0$ L/min/m². Exercise capacity without ISDN (control study) was correlated with left ventricular performance during exercise. Although left ventricular performance in patients who complained of dyspnea or chest pain at peak exercise was worse than those who complained of leg fatigue, we could not predict hemodynamics during exercise from the level of hemodynamic parameters at rest in each patient. Determinant factors of left ventricular performance during exercise were age, previous history of myocardial infarction, the severity of coronary artery lesion and the extent of left ventricular wall motion abnormality which was estimated by left ventriculogram as an index of infarct size.

After sublingual ISDN (ISDN study), exercise capacity was improved. No patient terminated exercise because of chest pain and only one did because of dyspnea. While no significant differences in heart rate (HR), mean arterial pressure (MAP) cardiac index (CI), stroke volume index (SVI), left ventricular stroke work index (LVSWI) and systemic vascular resistance (SVR) were observed at peak exercise between the control study and ISDN study in

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Division of Cardiology, Sakurabashi Watanabe Hospital, Osaka, *Division of Cardiology, Kanoh General Hospital, Osaka, **Department of Medicine and Geriatrics, Osaka University, Medical School, Osaka, ***First Department of Medicine, Osaka University, Medical School, Osaka, Japan

Mailing address: Sugao Fukui, M.D., Division of Cardiology, Sakurabashi Watanabe Hospital 4-32, 2 Chome, Umeda, Kitaku, Osaka 530, Japan

Groups I and II, PCP was lower in the ISDN study than in the control study. On the other hand, CI and LVSWI in Group III increased and SVR significantly decreased at peak exercise. Effects of ISDN on hemodynamics during exercise was well related to the severity of coronary artery lesion and inversely correlated with the infarct size.

These results indicate that investigation of hemodynamic response to exercise is a useful method for determination of cardiac rehabilitation program in patients with myocardial infarction and ISDN is an effective drug for the improvement of left ventricular performance during exercise.

HEMODYNAMIC responses to exercises is considered to be an effective measure of cardiac rehabilitation. Many studies of hemodynamic responses have been conducted with patients with myocardial infarction upon discharge from the hospital.¹⁻⁴ Furthermore, in order to evaluate the effects of isosorbide dinitrate (ISDN) on left ventricular performance during exercise, many studies have sought to clarify the action of ISDN on hemodynamic responses to exercise in patients with congestive heart failure.⁵⁻⁷ However, there are few reports in the literatures that compare the mechanism of ISDN on left ventricular hemodynamics during exercise with individual hemodynamic responses in patients without congestive heart failure during rest. In this study, we investigate the hemodynamic responses to exercise with and without sublingual ISDN in order to elucidate the factors which affect hemodynamic responses to exercise and to determine the role of ISDN on left ventricular performance during exercise.

MATERIALS AND METHODS

Patients

Thirty-seven patients with myocardial infarction were studied. Thirty-five were male and 2 female. The mean age was 53.3 years, ranging from 29 to 70. Twenty-nine patients had a single episode of infarct and the remaining 8 patients had 2 or more infarcts. All patients were in class I or II according to the classification of the New York Heart Association⁸ and no patient had congestive heart failure at rest. Patients with chronic obstructive pulmonary disease, valvular heart disease and/or atrial fibrillation were excluded from this study. Patients receiving digitalis glycoside or β -adrenegic blocking agents were also excluded.

Exercise Test

The symptom-limited multi-graded exercise test was performed using a bicycle ergometer in

supine position with patients in fasting state. Mean interval between the onset of infarct and exercise test was 45.6 days. The initial work load was set at 150 kpm/min and was increased by 150 kpm/min at 3 minutes intervals. An electrocardiogram was monitored during the exercise test and a 12-lead electrocardiogram was recorded at each stage. The exercise test was terminated when patients complained of chest pain, dyspnea or leg fatigue. Heart rate, blood pressure and electrocardiographic findings were monitored during exercise and hemodynamic parameters were obtained by right heart catheterization. After the control exercise test (control study) when hemodynamic parameters and ECG findings returned to the pre-exercise level, 5 mg of ISDN was administered sublingually. The exercise test was repeated after 5 minutes (ISDN study) and hemodynamics and ECG obtained.

Right Heart Catheterization

A flow-directed catheter was inserted via antecubital or femoral vein, and the right atrial pressure (RAP), pulmonary arterial pressure (PAP) and pulmonary capillary pressure (PCP) were measured. Mixed venous blood was collected through the catheter for determination of oxygen content before and after exercise (at peak exercise). Arterial pressure was measured and arterial blood was obtained by an indwelling catheter in the radial artery. Cardiac output was obtained by the dye-dilution curve method. These hemodynamic measurements were performed before and at peak exercise both with and without ISDN. Hemodynamic variables calculated by hemodynamic parameters were as follows:

Cardiac Index (CI) ($\text{L}/\text{min}/\text{m}^2$) = Cardiac Output (CO)/Body Surface Area (BSA)

Stroke Volume Index (SVI) (ml/m^2) = CI/Heart Rate (HR) $\times 1000$

Left Ventricular Stroke work Index (LVSWI) ($\text{g}\cdot\text{m}/\text{m}^2$) = Mean Arterial Pressure (MAP) – Pul-

monary Capillary Pressure (PCP) $\times$ SVI $\times$ 0.0136

Systemic Vascular Resistance (SVR) (units) = (MAP – Right Atrial Pressure (RAP))/CO

Arterio-venous Oxygen Difference (a-v DO₂) (ml/100 ml) = (aSAT – vSAT) $\times$ Hb $\times$ 1.34, where a-v DO₂ is the arterial mixed-venous oxygen saturation difference, aSAT is the radial arterial oxygen saturation and vSAT is the mixed-venous oxygen saturation obtained from the pulmonary arterial blood, Hb is hemoglobin concentration in g/dl and 1.34 is the factor which indicates the oxygen capacity of 1g of hemoglobin.

Coronary Arteriography and Left ventriculography

In order to investigate the factors affecting the hemodynamic responses to exercise, patients underwent left heart catheterization, coronary arteriography and left ventriculography with Judkins' technique during the time period of the exercise test. Coronary arteriography was performed on 35 mm film at multiple views. Each coronary arteriogram was interpreted by two observers without knowledge of the clinical information and hemodynamic responses to exercise. Seventy-five percent or more of luminal stenosis of the coronary artery was defined as a significant narrowing. Left ventri-

culography was also performed at 60 frames/sec both in 30° right anterior oblique position and 60° left anterior oblique position. Left ventricular wall movement was evaluated as AHA classification.⁹ As an index of infarct size the non-contracting segment (NCS) was measured and it was expressed as the ratio of the segment length of akinesis or dyskinesis to total circumference length of end-diastole left ventriculogram in 30° right anterior oblique position.¹⁰

Statistical Analysis

Student's t-test was used to assess the differences between means of independent observations. The chi-square test was also used to assess the differences in proportions. Differences less than 0.05 level ($p < 0.05$) were considered significant.

RESULTS

Exercise tests were undertaken without any incident in all patients. Patients were subdivided into three groups according to the level of PCP and CI at peak exercise without ISDN (control study) as follows:

Group I (14 patients): PCP < 18 mmHg, CI ≥ 5.0 or CI < 5.0 L/min/m².

Group II (11 patients): PCP ≥ 18 mmHg,

TABLE I EXERCISE CAPACITY, RATE PRESSURE PRODUCT AT PEAK EXERCISE AND THE REASONS FOR TERMINATING EXERCISE BOTH IN CONTROL STUDY AND ISDN STUDY

		Reasons for terminating exercise (No. of patients)			
	Exercise capacity (min)	RPP	LF	D	CP
Control study					
Group I	11.4 ± 0.6	209.1 ± 14.4	12	0	2
Group II	11.6 ± 1.0	237.1 ± 20.8	9	1	1
Group III	8.8 ± 0.8	210.3 ± 14.6	5	3	4
ISDN study					
Group I	12.0 ± 0.6	236.4 ± 18.1	14	0	0
Group II	12.4 ± 0.8	261.4 ± 21.9	11	0	0
Group III	10.4 ± 0.8	221.6 ± 12.4	11	1	0

mean $\pm$ SE; * = $p < 0.05$

Abbreviations: RPP = rate pressure product (10⁻²); LF = leg fatigue; D = dyspnea; CP = chest pain

$CI \geq 5.0 \text{ L/min/m}^2$.

Group III (12 patients): $PCP \geq 18 \text{ mmHg}$,
 $CI < 5.0 \text{ L/min/m}^2$.

Control Study

1) Exercise Capacity, Rate Pressure Product (RPP) at Peak Exercise and the Reasons for Terminating Exercise.

Table I shows the duration of exercise (exercise capacity), rate pressure product (RPP) at peak exercise and the reasons for terminating exercise. The exercise capacity was 11.4 ± 0.6 (SE) min. in Group I and 11.6 ± 1.0 min. in Group II. The exercise capacity of 8.8 ± 0.8 min.

in Group III was significantly shorter than that in Group I or II ($p < 0.05$). No significant difference in RPP was observed among three groups. Twenty-six of 37 patients (70.3%) terminated exercise test because of reported leg fatigue, 4 (10.8%) with dyspnea and the remaining 7 (18.9%) with chest pain. The incidence of dyspnea or chest pain in Group III was higher than those in Groups I and II ($p < 0.05$).

2) Hemodynamics at Rest and Peak Exercise

Table II shows hemodynamic data of patients at rest. No significant differences were found in HR, MAP, RAP, CI and a-v DO_2 among the 3 groups. PCP in Group III was significantly higher

TABLE II HEMODYNAMIC DATA AT REST BOTH IN CONTROL STUDY AND ISDN STUDY
Control study

	HR	MAP	PCP	RAP	CI
Group I	67.1 ± 2.4	89.8 ± 3.6	7.7 ± 0.9	3.4 ± 0.6	3.11 ± 0.86
Group II	74.6 ± 3.4	93.1 ± 3.6	10.0 ± 0.8	4.6 ± 0.8	3.31 ± 0.21
Group III	74.8 ± 3.4	96.6 ± 3.2	14.5 ± 2.1	6.2 ± 2.1	2.59 ± 0.10

	SVI	LVSWI	SVR	a-v DO_2
Group I	46.9 ± 2.3	53.3 ± 2.9	16.6 ± 3.5	3.91 ± 0.22
Group II	44.5 ± 2.4	50.3 ± 3.6	15.5 ± 1.4	4.03 ± 0.19
Group III	35.4 ± 2.0	40.1 ± 3.6	21.8 ± 2.0	3.82 ± 0.52

ISDN study

	HR	MAP	PCP	RAP	CI
Group I	86.1 ± 2.9	85.0 ± 4.4	3.8 ± 0.8	1.7 ± 0.7	2.73 ± 0.20
Group II	92.3 ± 4.5	85.9 ± 3.6	3.6 ± 0.9	1.6 ± 0.6	2.93 ± 0.20
Group III	82.1 ± 4.7	85.4 ± 3.8	6.1 ± 1.3	1.2 ± 0.5	2.54 ± 0.17

	SVI	LVSWI	SVR	a-v DO_2
Group I	31.9 ± 2.7	35.2 ± 3.5	20.0 ± 2.9	4.54 ± 0.26
Group II	32.3 ± 2.9	36.4 ± 3.9	16.5 ± 1.2	4.78 ± 0.30
Group III	30.3 ± 2.5	32.5 ± 3.3	19.6 ± 2.1	4.36 ± 0.50

mean $\pm$ SE; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$

Abbreviations: HR = heart rate (beats/min); MAP = mean arterial pressure (mmHg); PCP = pulmonary capillary pressure (mmHg); RAP = right atrial pressure (mmHg); CI = cardiac index (L/min/m^2); SVI = stroke volume index (ml/m^2); LVSWI = left ventricular stroke work index ($\text{g}\cdot\text{m/m}^2$); SVR = systemic vascular resistance (units), a-v DO_2 = arterio-venous oxygen difference (ml/100ml)

TABLE III HEMODYNAMIC DATA AT PEAK EXERCISE BOTH IN CONTROL STUDY AND ISDN STUDY

Control study

	HR	MAP	PCP	RAP	CI
Group I	121.2 ± 5.7	118.7 ± 5.1	11.1 ± 1.1	4.7 ± 0.9	6.62 ± 0.51
Group II	131.1 ± 7.2	120.5 ± 4.0	25.9 ± 2.1	12.1 ± 2.6	6.34 ± 0.29
Group III	123.8 ± 7.2	114.7 ± 4.9	33.8 ± 1.6	10.8 ± 1.6	3.53 ± 0.23

	SVI	LVSWI	SVR	a-vDO ₂
Group I	56.9 ± 5.7	79.8 ± 5.2	10.9 ± 1.3	9.76 ± 0.65
Group II	49.8 ± 3.2	63.8 ± 4.8	9.7 ± 0.7	10.47 ± 1.18
Group III	29.8 ± 2.6	34.4 ± 4.4	18.8 ± 2.0	10.54 ± 1.62

ISDN study

	HR	MAP	PCP	RAP	CI
Group I	136.1 ± 5.3	112.6 ± 4.8	6.6 ± 1.1	3.2 ± 0.8	6.47 ± 0.40
Group II	144.5 ± 7.2	113.1 ± 6.2	14.2 ± 3.3	7.5 ± 1.2	5.98 ± 0.50
Group III	129.9 ± 5.8	111.9 ± 4.8	21.1 ± 3.0	5.0 ± 1.7	4.61 ± 0.32

	SVI	LVSWI	SVR	a-vDO ₂
Group I	48.7 ± 3.5	67.4 ± 4.5	10.5 ± 1.2	10.01 ± 0.80
Group II	41.9 ± 4.2	55.6 ± 5.2	9.9 ± 1.0	10.51 ± 0.58
Group III	35.8 ± 2.7	46.3 ± 4.7	13.5 ± 1.2	11.00 ± 1.15

mean ± SE; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$

Abbreviations are shown in Table II.

TABLE IV CLINICAL CHARACTERISTICS AND ANGIOGRAPHIC FINDINGS

		Sex		Infarct site			The number of involved coronary vessels				Left ventricular asynergy			
		M	F	A	I	Re	OVD	SVD	DVD	TVD	H	A	D	AN
Group I	49.4 ± 2.6	13	1	5	9	0	2	9	3	0	7	5	0	2
Group II	54.5 ± 3.3	11	0	4	4	3	0	6	4	1	1	4	4	2
Group III	56.7 ± 2.5	11	1	4	3	5	0	3	3	6	2	1	4	5

mean ± SE

Abbreviations: M = male; F = female; A = anterior; I = inferior; Re = reinfarction; OVD = no significant coronary artery lesion; SVD = single vessel disease; DVD = double vessel disease; TVD = triple vessel disease; H = hypokinesis; A = akinesis; D = dyskinesis; AN = aneurysm

than in Group I ($p < 0.01$) and systemic vascular resistance in Group III was also higher than those in Groups I and II ($p < 0.01$, $p < 0.05$). SVI in Group III was smaller than those in Groups I and II ($p < 0.001$, $p < 0.01$). LVSWI in Group III was also significantly smaller than in the other 2 groups (Group I: $p < 0.01$, Group II: $p < 0.05$). However, the hemodynamic response to exercise could not be predicted from the level of hemodynamic parameters of patients at rest.

Table III shows hemodynamic data during peak exercise. While no significant differences were observed in HR and MAP among the 3 groups, PCP and RAP in Groups II and III were significantly higher than those in Group I ($p < 0.001$). CI, SVI and LVSWI in Group III were at a significantly lower level than in Groups I and II ($p < 0.001$). SVR in Group III was higher than those in Groups I and II ($p < 0.001$).

3) Factors Affecting Hemodynamic Responses to Exercise

Table IV shows clinical characteristics and angiographic findings. The mean age in Group I was lower than in Group III ($p < 0.05$). No patients in Group I had multiple episodes of infarct. On the other hand, three of 11 patients (27.3%) in Group II, and 5 of 12 patients (41.7%) in Group III had multiple episodes of infarct.

In determining the relationship of hemodynamic responses to exercise with the severity of coronary artery lesion, we found that 11 of 14 patients in Group I (78.6%) had no significant coronary artery lesion (OVD) or single vessel disease (SVD) and only 3 patients had multiple vessel disease. On the other hand, in Group III only 3 of 12 patients (25.0%) had single vessel disease and the remaining 9 patients (75.0%) had multiple vessel disease. Seven of 14 patients (50.0%) in Group I had hypokinesia at least in one of 7 segments of left ventriculogram according to AHA classification, 5 had akinesia and 2 had aneurysms. Only 2 of 12 patients (16.7%) in Group III had hypokinesia, one akinesia, 4 dyskinesia and 5 aneurysm. Thus, the severity of left ventricular wall motion abnormality was related to hemodynamic responses to exercise.

The mean non-contracting segment (NCS) as an index of infarct size determined by left ventriculogram was 24.1 ± 6.1 (SE) % in Group I (7 patients), $34.1 \pm 4.9\%$ in Group II (10 patients) and $45.1 \pm 7.3\%$ in Group III (10 patients). The NCS in Group III was significantly larger than that in Group I ($p < 0.01$). Furthermore, if the group of 13 patients with single vessel disease

were evaluated separately, the NCS would measure $25.5 \pm 7.1\%$ in Group I (6 patients), $38.2 \pm 8.0\%$ in Group II (5 patients) and $55.1 \pm 17.1\%$ in Group III (3 patients).

ISDN Study

1) Exercise Capacity, Rate Pressure Product at Peak Exercise and the Reasons for Terminating Exercise Test

Table I shows the exercise capacity, rate pressure product at peak exercise and the reasons for terminating exercise in the ISDN study. Exercise capacity was prolonged by sublingual ISDN, but no significant difference was observed in exercise capacity between the control study and the ISDN study in all three patient groups. There were no significant differences between groups in RPP at peak exercise level between the control and ISDN study. While 7 of 37 patients (18.9%) terminated exercise because of the development of anginal pain in the control study, no patient discontinued exercise test due to chest pain in the ISDN study. Similarly, although 4 patients complained of dyspnea at peak exercise in the control study, only one patient terminated exercise because of dyspnea in the ISDN study.

2) Hemodynamics at Rest and Peak Exercise

In Group I, no significant differences were observed in the MAP, RAP, CI and SVR measurements taken at rest between the control and ISDN study. Meanwhile ISDN significantly increased HR ($p < 0.001$) and decreased PCP, SVI and LVSWI ($p < 0.001$). The hemodynamic response to sublingual ISDN was similar both in Groups I and II. However, although there were no significant effects of ISDN on HR, CI, SVI, LVSWI and SVR in Group III, the MAP, PCP and RAP were significantly decreased after sublingual ISDN (MAP: $p < 0.05$, PCP: $p < 0.001$, RAP: $p < 0.001$) (Table II).

While there were no significant differences in HR, MAP, RAP, CI, SVI, LVSWI, and SVR at peak exercise between the control and ISDN study in Group I, PCP in the ISDN study was significantly lower than that in the control study ($p < 0.01$). Patients in Group II had similar hemodynamic responses to exercise in ISDN study and to that in the control study except for the RAP response. Contrary to Groups I and II, the CI and LVSWI at peak exercise in the ISDN study was larger in Group III than in the control study and SVR also significantly decreased during exercise after sublingual ISDN (Table III).

Fig.1. Relationship between pulmonary capillary pressure (PCP) and cardiac index (CI) at peak exercise both in control study and ISDN study. Open circle indicates control study and closed circle does ISDN study.

3) Factors Influencing the Effects of ISDN on Left Ventricular Performance

Figure 1 shows the responses of PCP and CI to exercise before and after sublingual administration of ISDN. In general ISDN lowered PCP and increased CI, but the responses of individual patients were variable. In order to investigate the differences in hemodynamic responses to exercise after sublingual ISDN, we evaluated the responses to PCP and CI in patients of Groups II and III whose PCP at peak exercise were 18 mmHg or more in the control study. PCP at peak exercise in Group II in the control study was 25.9 ± 2.1 (SE) mmHg and 14.2 ± 1.6 in the ISDN study. PCP in Group III was 33.8 ± 1.6 mmHg in the control study and 21.1 ± 3.0 in the ISDN study. The difference in PCP at peak exercise between the control and ISDN study namely, Δ PCP was 11.7 mmHg in Group II and 12.7 mmHg in Group III. Comparing PCP to the severity of coronary artery lesion both in Group II and III, Δ PCP was 6.2 ± 1.4 (SE) mmHg in 20 patients with single vessel disease (SVD), 9.7 ± 2.4 mmHg in 10 patients with double vessel disease (DVD), and 16.3 ± 3.0 mmHg in 7 patients with triple vessel disease (TVD). Δ PCP in TVD was significantly larger than that in SVD ($p < 0.01$). Mean NCS in 8 patients with SVD was 44.5 ± 7.4 (SE)%, $31.6 \pm 6.7\%$ in 5 patients with DVD and $37.0 \pm 8.5\%$ in 7 patients with TVD.

DISCUSSION

This study was performed to investigate left ventricular performance during exercise, to analyze factors affecting left ventricular performance and to evaluate the usefulness of sublingual ISDN in the improvement of hemodynamic response to exercise.

Although all patients were in NYHA class I or II before exercise, the hemodynamic responses to exercise in each patient were variable in both the control study and the ISDN study. This finding indicates that the exercise test is a useful method for evaluation of left ventricular functional reserve and for the selection of drug therapy in patients with myocardial infarction. There were no significant differences in exercise capacity in control study between Groups I and II. On the other hand, exercise capacity in Group III was worse than that in Groups I and II. Thus, it is suggested that exercise capacity is a good index of hemodynamics during exercise. The prevalence of single episode of infarct in Group I was higher than that in Group III. This finding suggested that left ventricular performance during exercise was better in patients with single episode of infarct than that in those with multiple episodes of infarct.

In this study, infarct size determined by left ventriculogram as non-contracting segments (NCS) and the severity of coronary artery lesion

were suggested to be the important determinant factors of left ventricular performance during exercise. These results are in agreement with our previous report and other investigations.²⁻⁴ It is easily understood that the infarct size was one of the determinant factors of left ventricular performance during exercise. If infarct size was large enough, the residual viable myocardium contributing to left ventricular pump function was limited in volume and left ventricular function should have deteriorated during exercise test, despite normal left ventricular function at rest. There are two possibilities of the influence of the severity of coronary artery lesion on left ventricular performance during exercise: First, myocardial ischemia induced by exercise deteriorates myocardial contractility and left ventricular performance declines during exercise with elevated PCP and decreased CI. Secondly, myocardial ischemia reduces left ventricular compliance and exercise-induced myocardial ischemia easily elevates PCP in decreased-compliant heart. In our series, PCP was elevated with decreased CI at the anginal attacks in 3 patients who terminated exercise because of chest pain. Weiner et al. reported that PCP was elevated with either an unchanged or slightly decreased CI at the onset of chest pain in patients with angina pectoris.¹² Williamson et al. serially measured hemodynamics during exercise in patients with coronary heart disease and observed that patients had a normal response of stroke work index before the occurrence of ischemia, but the left ventricular functional curve shifted abruptly to a worse curve when ischemia occurred.¹³ These results indicate that exercise-induced myocardial ischemia deteriorate the left ventricular function, elevates PCP and decreases CI.

Sublingual ISDN did not increase exercise capacity except in patients with angina pectoris following myocardial infarction. After ISDN administration, HR increased and MAP lowered at rest in all patients. PCP and RAP decreased both at rest and peak exercise. The degree of decrease in PCP and RAP was large in Groups II and III with high level of PCP at peak exercise. While ISDN only slightly increased CI and SVI at peak exercise in Groups I and II whose hemodynamic responses to exercise were good in control study, ISDN significantly increased CI and SVI in Group III who had poor response to exercise without ISDN. Thus, the improvement of left ventricular performance after ISDN administration was more remarkable in Group III

whose left ventricular functional reserve was poor. Many studies have been performed concerning the influence of ISDN on left ventricular performance during exercise.⁵⁻⁷ Leier et al. reported that 40 mg of oral ISDN did not increase exercise capacity, but lowered PCP, RAP, systemic arterial pressure, pulmonary venous resistance and SVR in patients with congestive heart failure.¹⁴ Stephens et al. performed submaximal supine exercise on 7 patients with ischemic heart disease who were complicated with left ventricular aneurysm and severe chronic congestive cardiac failure.¹⁵ They reported that left ventricular performance during exercise was improved after 5 mg of sublingual ISDN administration. Other investigators also reported the improvement of left ventricular performance during exercise after sublingual ISDN.^{6,7,16} The interesting result in this study is that infarct size and the severity of coronary artery lesion were important determining factors of hemodynamic response to exercise after sublingual ISDN.

In Groups II and III, we found poor response to ISDN in patients with large infarct and good response in those with small infarct. One of the reasons why response to ISDN is poor in large infarct is explained by the fact that the residual viable myocardium is small in large infarct, and the left ventricular functional reserve is small. Stephens et al. investigated hemodynamic response to exercise before and after 5–10 mg sublingual ISDN in 17 patients with left ventricular aneurysm and congestive cardiac failure, and effects of ISDN on left ventricular performance during exercise.¹⁷ They observed that although ISDN increased mean exercise LVSWI and decreased mean left ventricular filling pressure (LVFP) during exercise, the response to ISDN was poor in patients with ejection fraction of the contractile section (EFCS) obtained by radionuclide ventriculography less than 40% at rest. Although they did not investigate the relation of the severity of coronary artery lesion to left ventricular performance during exercise after sublingual ISDN, left ventricular performance at rest may be considered one of the determinant factors of the hemodynamic response of ISDN to exercise.

In regard to the good response to exercise after sublingual ISDN in patients with TVD in Groups II and III, one of the possibilities may be the improvement of the coronary circulation in ischemic myocardium after sublingual ISDN.

Myocardial ischemia induces the decrease of contractility of myocardium, decreases compliance of left ventricle, elevates PCP, and decreases CI. In TVD, exercise-induced myocardial ischemia was probably more severe than that in SVD or DVD, and the influence of myocardial ischemia on left ventricular performance in TVD was larger than that in SVD or DVD. Another reason for differences in hemodynamic responses to exercise after sublingual ISDN, is that mean NCS as an index of infarct size in SVD was larger than that in TVD, and the amount of viable muscle in SVD was less than in TVD. Thus, the improvement of left ventricular performance during exercise after ISDN in TVD was larger than that in SVD or DVD.

These results strongly suggest that ISDN is a useful drug for improvement of left ventricular performance during exercise, especially in patients with severe coronary artery lesion.

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