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HEMODYNAMIC EFFECTS OF MOLSIDOMINE ON WEIGHT SUSTAINING ISOMETRIC EXERCISE IN PATIENTS WITH ISCHEMIC HEART DISEASE

BY

Takashi TSUJIBAYASHI, Akihiro NIWA, Koichi TANIGUCHI, and Jugoro TAKEUCHI*1

ABSTRACT

Hemodynamic effects of 2 mg of sublingual molsidomine were evaluated in 11 patients with ischemic heart disease using a weight-sustaining isometric exercise (WSIE) that we developed. Left ventricular end diastolic pressure (LVEDP), mean pulmonary pressure, mean systemic arterial pressure (mAP), cardiac index and stroke work index increased significantly during WSIE before and after molsidomine. Although WSIE resulted in a similar rise of mAP before and after molsidomine, the increment value of LVEDP during WSIE was significantly lower after molsidomine. The recovery time to the resting state of all parameters was shorter and the left ventricular function curves showed a leftward deviation with molsidomine.

In conclusion, the results suggest that molsidomine will produce a preload reduction and improve the left ventricular function during WSIE in patients with ischemic heart disease.

Key words: molsidomine, isometric exercise.

INTRODUCTION

Molsidomine (N-ethoxycarbonyl-3-molpholinosydononimine), a new vasodilating agent, has antianginal effects similar to those of nitroglycerin, and the duration of its effects appear to be longer[1, 2]. Although previous studies [3, 4, 5] suggest that molsidomine produces both a preload and afterload reduction at rest, little information on the cardiac response to molsidomine during and after exercise is available [6, 7].

Though isometric exercise rarely provokes angina[8], it increases the heart rate and blood pressure, the resulting increase in cardiac work often inducing left ventricular dysfunction[9].

In this study, we examined the hemodynamic effects of molsidomine in the patients with ischemic heart disease during and after weight-sustaining isometric exercise.

MATERIAL AND METHOD

Patients: Eleven patients (9 males and 2 females) with a mean age of 52 (44 to 62) years were studied, including 6 with previous myocardial infarction and 5 with angina pectoris. They were all class II by the New York Heart Association classification. All drugs were discontinued at least 24 hours before the study.

Protocol: This study was performed during the routine cardiac catheterization. The pulmonary arterial pressure and the left ventricular pressure were determined using a Cournand catheter and pig tail catheter, respectively. The systemic arterial pressure was examined

*1 辻林 隆, 丹羽明博, 谷口興一, 武内重五郎: 2nd Department of Internal Medicine (Chief: Prof. T. TAKEUCHI), Faculty of Medicine, Tokyo Medical and Dental University (Tokyo Ika Shika Daigaku).
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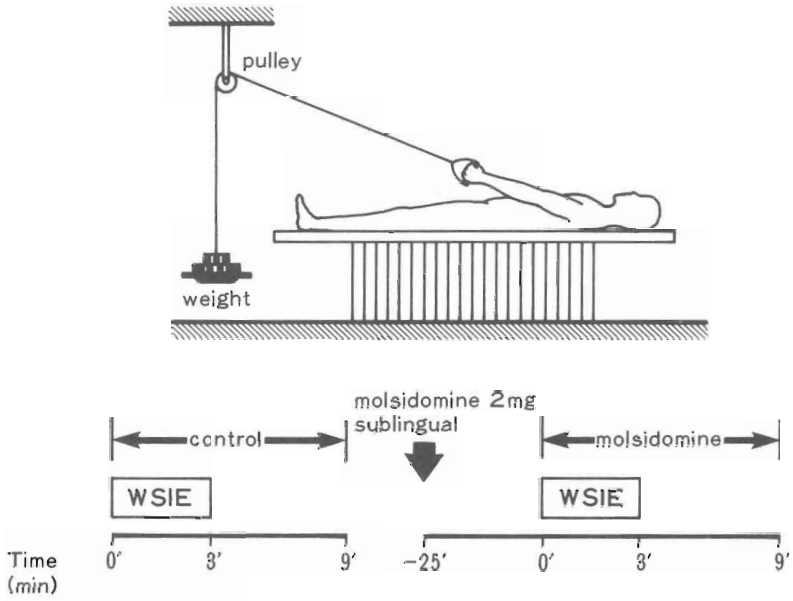

Fig. 1. Method.
The patient sustained a weight hung through a pulley, corresponding to 50 percent of his maximum voluntary contraction, for three minutes. The exercise was performed before (control) and 25 minutes following medication of molsidomine (2 mg).

by means of direct puncture of the femoral artery. Cardiac output was measured by the cuvette dye dilution method.

Hemodynamic parameters were determined at rest and during the weight-sustaining isometric exercise (WSIE) that we developed. This new method consisted of the following: The patient sustained a weight hung through a pulley, corresponding to 50 percent of his maximum voluntary contraction, for three minutes in the supine position. Hemodynamic parameters were measured at rest, during and after WSIE before medication. After all parameters recovered to the resting values, molsidomine (2 mg) was administrated sublingually and then the measurements were performed in the same manner for 25 minutes following the medication (Fig. 1).

The derived hemodynamic variables were calculated as follows: cardiac index (CI)=cardiac output/body surface area; stroke volume index (SVI)=CI/heart rate; stroke work index (SWI)=SVI×(mAP−mRA)×0.0136, where mAP is the mean systemic arterial pressure and mRA the mean right atrial pressure; total systemic resistance (TSR)=mAP/CO×80, where CO is the cardiac output; total pulmonary resistance (TPR)=mPA/CO×80, where mPA is the mean pulmonary arterial pressure; rate pressure product (RPP)=heart rate×systolic systemic arterial pressure.

Statistics: Statistical analysis was performed using the t test for paired data. Data are presented as the mean±standard deviation.

Results

Hemodynamics during WSIE: The summary of hemodynamic change induced by WSIE is presented in Table 1. Heart rate, mPA, mAP, left ventricular systolic pressure, left ventricular end di-

Table 1. Hemodynamic Effects of Molsidomine During Isometric Exercise

	Exercise before molsidomine		Exercise after molsidomine		(c)=(b)−(a)	(c')=(b')−(a')
	Rest(a)	Exercise(b)	Rest(a')	Exercise(b')		
HR(beats/min)	70.5±11.2	80.5±13.3**	72.4±11.7	85.1±13.0**	10.0±9.1	12.7±7.1
mAP(mmHg)	101±10.9	124±13.6**	95.5±13.1	119±16.6**	23.0±13.4	23.1±11.4
LVs(mmHg)	149±21.7	180±23.9**	140±28.1	174±30.7**	31.6±17.7	34.6±17.7
mPA(mmHg)	14.1±2.7	18.8±4.0**	12.2±3.7	15.3±4.7**	4.7±3.3	3.1±2.4
LVEDP(mmHg)	10.6±3.7	16.6±6.1**	8.5±4.2	11.4±5.6**	6.0±4.5	2.9±2.7#
CI(l/min/m²)	2.08±0.29	2.38±0.31*	1.96±0.20*	2.47±0.58**	0.35±0.32	0.52±0.42
RPP(mmHg/min)	10600 ±2160	14800 ±3290**	10200 ±2740	14900 ±3590**	4200 ±2980	4700 ±2300
SWI(gm·m/m²)	38.9±7.31	46.7±8.68**	34.0±6.40	46.6±13.5**	8.31±5.97	12.6±9.1
TSR(dynes·sec/cm⁵)	2420±338	2580±311	2400±344	2450±406	126±280	49.6±41.3
TPR(dynes·sec/cm⁵)	341±92	394±94*	298±92	304±83	51.0±68.8	6.6±48

Vaues are represented as mean±SD.
Abbreviations: HR=heart rate, mAP=mean systemic arterial pressure, LVs=left ventricular systolic pressure, mPA=mean pulmonary arterial pressure, LVEDP=left ventricular end diastolic pressure, CI=cardiac index, RPP=rate pressure product, SWI=stroke work index, TSR=total systemic resistance, TPR=total pulmonary resistance, *=$p<0.05$ (a) vs (b) or (a·) vs (b·), **=$p<0.01$ (a) vs (b) or (a·) vs (b·), #=$p<0.05$ (c) vs (c·).

Table 2. Recovery Time to Resting State (min)

	Exercise before molsidomine (min)	Exercise after molsidomine (min)	p value
HR	2.5±2.4	1.7±1.2	NS
mPA	2.8±1.9	1.6±0.7	NS
mAP	2.9±2.3	1.6±0.9	$p<0.05$
LVs	3.6±2.9	2.3±2.1	NS
LVEDP	3.7±2.6	1.3±0.5	$p<0.01$
RPP	3.7±2.5	2.4±1.7	$p<0.05$

Values are mean±standard deviation (min).

astolic pressure (LVEDP), CI, SWI and RPP increased significantly during WSIE both before and after molsidomine. TSR did not change by WSIE, and TPR increased only before molsidomine. Increment value of LVEDP (ΔLVEDP) with WSIE was greater before (6.0±4.5 mmHg) than after molsidomine (2.9±2.7 mmHg).

Recovery time to the resting state (Table 2): For all parameters, recovery time was shorter after medication. The recovery time of mPA, LVEDP and RPP, in particular, was significantly shorter with molsidomine ($p<0.05-0.01$).

Left ventricular function curves (Fig. 2): The relationship between LVEDP and CI or SWI were determined. After molsidomine, LVEDP decreased during exercise, CI remained unchanged and SWI decreased at rest. The slopes in Fig. 2 were steeper and deviated to the left after the administration of molsidomine.

Discussion

Our results indicate that WSIE produced a significant increase in mAP, LVEDP, CI and SWI before and after molsidomine. Although the increment value of mAP (ΔmAP) during WSIE was similar before and after molsidomine, that of LVEDP (ΔVEDP) was significantly smaller after molsidomine. Assuming that mAP is the index of afterload and LVEDP is that of preload, these findings suggest that molsidomine induces the preload reduction without influencing the afterload during the isometric exercise.

Molsidomine has been reported to re-

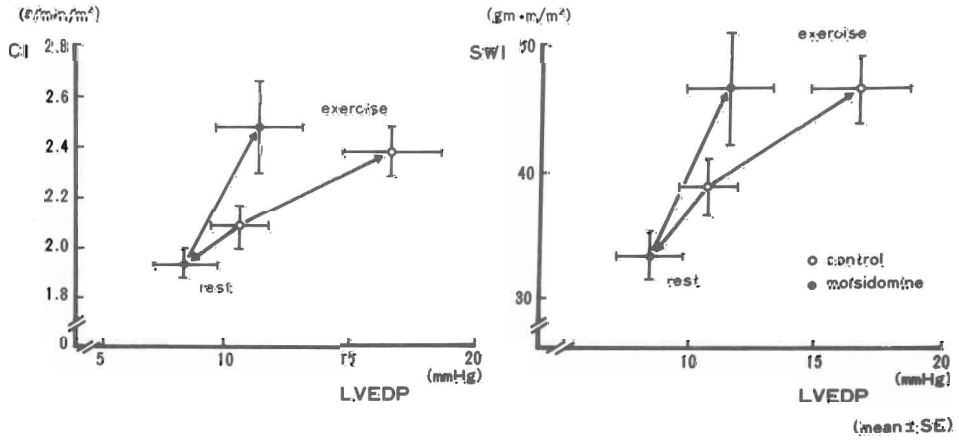

Fig. 2. Left Ventricular Function curves.
The relationship between left ventricular end diastolic pressure (LVEDP) and cardiac index (CI) or stroke work index (SWI) were determined. The slopes were steeper and deviated to the left after administration of molsidomine.

lieve angina and increase the angina threshold in patients with chronic ischemic heart disease [10, 11]. The effects of molsidomine are similar to those of nitroglycerin and the duration of it appears to be longer. Concerning its hemodynamic effects, some investigators reported that molsidomine caused both the preload and afterload reduction [12, 13] while the other authors found only a preload reduction without influencing the afterload [14]. These hemodynamic differences among the previous studies are probably due to the cardiac functional state of the subjects and/or the environmental conditions (e.g. resting or exercise).

Benefits of WSIE are as follows: (1) The test is simple; patients just do sustaining of weight. (2) A constant load can be obtained. (3) The test is performed safely. (4) The Valsalva effect can be easily avoided [15, 16]. Hemodynamic effects of isometric exercise have been reported to chiefly affect the afterload increment, with little influence on the preload [17]. In the patients with left ventricular dysfunction, the increase of LVEDP was greater and the left ventricular contractile function was impaired during the isometric exercise[18]. Some authors reported that the reproducibility of the exercise test was generally good[19, 20] that the adaptation or the training effect of WSIE may be neglected.

As for the relationship between LVEDP and CI, molsidomine shifted the left ventricular function curve to the left during the exercise as shown in fig. 2. Similar results were obtained in the relationship between LVEDP and SWI. Therefore, molsidomine will improve the cardiac function during the isometric exercise.

The recovery time of all parameters to the resting values became shorter with molsidomine. It is expected that molsidomine will produce favorable hemodynamic effects even during the post-exercise course.

In conclusion, our results indicate that molsidomine will produce a preload reduction and improve the ventricular function during WSIE in the patients with ischemic heart disease.

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