THE EFFECT OF MOLSIDOMINE ON INTRAMYOCARDIAL PRESSURE AND REGIONAL MYOCARDIAL BLOOD FLOW IN THE CANINE ISCHEMIC MYOCARDIUM

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Molsidomine was administered intraduodenally to anesthetized dogs which were instrumented for measurements of aortic and left ventricular (LV) pressures, coronary perfusion pressure, intramyocardial pressure in the subendocardium, and subendocardial and subepicardial myocardial blood flow in the ischemic and non-ischemic regions. The dogs were divided into two groups: group M ($n = 9$) was administered molsidomine (0.2 mg/kg), group S ($n = 10$), saline only. Maximum LV systolic pressure decline was 20% in group M and 3% in group S ($p < 0.05$). Maximum LV end-diastolic pressure decline was 63% and 35% in groups M and S, respectively ($p < 0.05$). There was no difference between mean aortic pressure and coronary perfusion pressure between the two groups.

The subepicardial blood flow in the ischemic region was decreased (-23% in group M vs 5% in group S; $p < 0.05$), but subendocardial blood flow in the ischemic region increased only slightly in group M. The ratio of subendocardial to subepicardial blood flow increased at 15 and 30 min after administration of molsidomine in the ischemic area (67% in group M vs -10% in group S; $p < 0.05$), but did not show any change in the non-ischemic region.

Intramyocardial pressure at systole did not show any change but it decreased at end-diastole, (-32% in group M vs -7% in group S; $p < 0.05$). Thus molsidomine redistributed the myocardial blood flow from the subepicardium to the subendocardium and from the non-ischemic to the ischemic region. This redistribution was associated with a reduction in both LV end-diastolic pressure and intramyocardial pressure at end-diastole.

ANIMAL studies have shown that the hemodynamic effects of molsidomine are similar to those of nitroglycerin, but last appreciably longer!¹⁻³ Nitroglycerin has been reported to dilate the capacitance vessels, thereby decreasing

the preload to the left ventricle. However, few studies have been performed on the effect of molsidomine on myocardial blood flow.⁴⁻⁶ The most important factor affecting flows in different layers is probably the intramyocardial pressure. This pressure is not homogenous across the myocardial wall at both systole and at diastole.⁷⁻⁹ Analysis of this relationship between myocardial blood flow and intramyocardial pressure may help clarify the mechanism

Key Words:

Intramyocardial pressure
Regional myocardial blood flow
Molsidomine
Myocardial ischemia

(Received September 13, 1984; accepted January 8, 1985)

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Fig.1. Diagram of an experimental preparation showing the position of the catheter-tipped manometer to measure the intramyocardial pressure (IMP) and of the platinum electrode to record an H₂ clearance curve.

"EPI" and "ENDO" indicate the sub-epicardium and the subendocardium, respectively. "LAD" indicates the left descending coronary artery. "LA" and "LVP" indicate the left atrium and the left ventricular pressure, respectively.

of the antianginal action of molsidomine. In addition pharmacokinetic studies have been performed following intraduodenal administration in the dog.

METHOD

Nineteen mongrel dogs were anesthetized with sodium pentobarbital, 30 mg/kg. Left thoracotomy was performed in the fifth intercostal space. Left ventricular (LV) and aortic pressures were measured using an 8F Dacron catheter and P-23Db Statham strain gauge transducers and the gain matched to the hydraulic pressure tracing; zero pressure was set at mid-chest level. Coronary perfusion pressure was measured through a polyethylene tube placed into the distal coronary artery. Aortic and coronary per-

fusion pressure transducers were calibrated and measured simultaneously throughout the experiment using a single hydraulic system. To measure intramyocardial pressure a Millar-microtipped manometer embedded in a 16 gauge needle was inserted into the center of the myocardium supplied by the left anterior descending coronary artery as shown in Fig. 1. The catheter-tipped manometer was 1.0 x 1.6 x 2.0 mm in size. The transducer was inserted up to 20 mm in length into the myocardium at an angle of 30 degrees to the epicardial surface to place it in the subendocardium. The transducer remained firmly implanted in the beating ventricle throughout the study, which continued for approximately 3 hours. We did not observe any spontaneous extrusion of the tip. The sensor had a base line drift of 9.3 ± 1.4 mmHg during 3 hours, a phenomenon particularly pronounced during the later hours of the experiment.

The thermal stability, frequency response and phase lag of the sensor were almost the same as reported previously.⁷ At the conclusion of each experiment the location of the sensor was ascertained to be about 9 mm within the wall in the subendocardium. The thickness of the myocardium in the region of the insertion of the transducer was found at autopsy to range between 11 and 12 mm.

The myocardial blood flow was measured using the hydrogen washout method, described elsewhere in detail.¹⁰ In brief, four platinum wires 0.1 mm in diameter, were embedded in the myocardium, one 3–4 mm within the wall in the subepicardium, and the other 9 mm within the wall in the subendocardium of the central ischemic region as well as one in the non-ischemic region. Ten per cent of the hydrogen gas was inhaled through the side hole of the intratracheal tube for approximately 60 seconds to saturate the tissue with the gas. The hydrogen washout curve was plotted on semilogarithmic paper to obtain the half time (T_{1/2}) of the initial monoexponential part of the curve. If the curve displayed non-exponential characteristics in its initial region, the data were excluded. The regional myocardial blood flow (RMBF) was calculated as follows:

$$\text{RMBF} = \frac{0.693 \times 60 \times 100}{T_{1/2} (\text{sec})} \text{ ml/min/100g}$$

The left anterior descending coronary artery, 1–2 cm from the orifice of the coronary artery was isolated by blunt dissection to place the

TABLE I HEMODYNAMIC PARAMETERS FOLLOWING MOLSIDOMINE ADMINISTRATION

		Control	15 min.	30 min.	60 min.	90 min.	120 min.	150 min.	180 min.
HR (bpm)	M	140 ± 28 (9)	145 ± 23 (9)	145 ± 24 (9)	143 ± 20 (9)	138 ± 16 (9)	136 ± 16 (9)	146 ± 20 (5)	147 ± 29 (4)
	S	137 ± 18 (9)	144 ± 23 (9)	139 ± 19 (9)	136 ± 18 (9)	134 ± 21 (9)	125 ± 17 (8)	128 ± 18 (6)	119 ± 12 (4)
mAoP (mmHg)	M	119 ± 17 (9)	116 ± 15 (9)	115 ± 18 (9)	110 ± 24 (9)	105 ± 24 (9)	110 ± 24 (8)	116 ± 28 (5)	122 ± 22 (4)
	S	127 ± 12 (9)	129 ± 13 (9)	133 ± 11 (9)	132 ± 10 (9)	131 ± 13 (9)	129 ± 9 (8)	130 ± 11 (5)	125 ± 13 (4)
PP (mmHg)	M	52 ± 9 (4)	45 ± 14 (4)	44 ± 22 (4)	40 ± 18 (4)	46 ± 20 (4)	47 ± 11 (4)	47 ± 0 (1)	43 ± 0 (1)
	S	62 ± 16 (4)	60 ± 19 (4)	64 ± 16 (4)	52 ± 19 (4)	55 ± 21 (4)	55 ± 31 (3)	58 ± 34 (3)	63 ± 19 (3)
LVSP (mmHg)	M	136 ± 22 (9)	127 ± 16 (9)	124 ± 17 (9)	120 ± 23 (9)	114 ± 22 (9)	119 ± 24 (9)	127 ± 31 (5)	130 ± 26 (4)
	S	143 ± 13 (10)	148 ± 13 (9)	148 ± 14 (10)	146 ± 10 (10)	146 ± 15 (10)	140 ± 12 (9)	141 ± 14 (7)	134 ± 16 (4)
LVEDP (mmHg)	M	19 ± 6 (9)	11 ± 4 (9)	9 ± 4 (9)	7 ± 4 (9)	7 ± 4 (9)	7 ± 4 (9)	10 ± 5 (5)	12 ± 8 (4)
	S	21 ± 5 (10)	19 ± 6 (9)	17 ± 5 (10)	14 ± 4 (10)	12 ± 4 (10)	10 ± 4 (9)	5 ± 3 (7)	8 ± 4 (4)
IMSP (mmHg)	M	95 ± 27 (9)	93 ± 15 (9)	94 ± 11 (9)	92 ± 16 (9)	94 ± 23 (9)	102 ± 19 (9)	107 ± 17 (5)	105 ± 17 (4)
	S	115 ± 25 (9)	120 ± 31 (9)	121 ± 23 (9)	119 ± 19 (9)	123 ± 20 (9)	126 ± 16 (8)	137 ± 21 (5)	124 ± 16 (4)
IMEDP (mmHg)	M	20 ± 12 (9)	16 ± 11 (9)	13 ± 8 (9)	14 ± 6 (9)	14 ± 6 (9)	14 ± 7 (8)	17 ± 11 (5)	16 ± 16 (4)
	S	23 ± 7 (9)	24 ± 10 (9)	23 ± 8 (9)	22 ± 8 (9)	22 ± 8 (9)	24 ± 6 (8)	24 ± 9 (5)	22 ± 7 (4)

Abbreviations: Numbers in parentheses indicate the number of experiments; HR = Heart rate; M = Group M; S = Group S; mAoP = Mean aortic pressure; PP = Coronary perfusion pressure; LVSP = Left ventricular systolic pressure; LVEDP = Left ventricular end-diastolic pressure; IMSP = Intramyocardial systolic pressure; IMEDP = Intramyocardial enddiastolic pressure; bpm = beats per min.

constrictor around the vessel. The constrictor consisted of a plastic syringe and a screw, which made gradual occlusion possible. The gradual constriction was performed to obtain a coronary perfusion pressure of about 70 mmHg, below which RMBF in the subendocardium was decreased. Thereafter dextran (15 ml/kg) was infused intravenously to elevate LV enddiastolic pressure. After recording baseline measurements, the dogs were divided into two groups, one receiving normal saline (group S, n = 10), and the other, molsidomine (group M, n = 9). Molsidomine, dissolved in saline, was administered intraduodenally. Hemodynamics and

RMBF were measured at 15, 30, and then every 30 min for the next 2.5 hours. In seven dogs administered molsidomine, the plasma levels were measured at 15, 30 and then every 30 min for the next 2.5 hours.

The assay was performed by means of high-performance liquid chromatography, which can measure molsidomine and its metabolite, SIN-1C simultaneously.¹¹ Statistical analysis was undertaken using two-way analysis of variance and unpaired t-test. For the comparison between groups M and S percent changes to the control value were used.

A p value of < 0.01 was taken as the level of

Fig. 2. Percent changes from the control in mean aortic pressure (m AoP) and coronary perfusion pressure (PP).

An open circle indicates group M and closed one, group S. * indicates a statistical significance of $p < 0.05$ between the control and the data following molsidomine administration.

Numbers in parentheses indicate the number of experiments performed.

significance in the analysis of variance, and a p value of < 0.05 was taken as the level of significance in the unpaired t -test. All values were expressed as the mean $\pm$ the standard deviation.

RESULTS

Hemodynamics

The hemodynamic data are presented in Table I. There was no difference in heart rate between groups M and S throughout the experiment.

Mean aortic pressure in control was 119 ± 17 mmHg in group M and 127 ± 12 mmHg in group S. The percent change from the control value increased by $4.5 \pm 4.5\%$ within 30 min, after saline administration and decreased by $3.6 \pm 1.3\%$ at the same time after molsidomine administration (Fig. 2).

However there was no significant difference in mean aortic pressure between groups M and S throughout the experiment. There was no significant difference in coronary perfusion pressure between groups M and S throughout the experiment, although it tended to decrease in group M. LV systolic pressure began to decrease

Fig. 3. Percent changes from the control in left ventricular systolic pressure (LVSP) and left ventricular enddiastolic pressure (LVEDP).

An open circle indicates group M and closed one, group S. * and # indicate a statistical significance of $p < 0.05$ between the control and the data, and between groups M and S, respectively.

** and ## indicate a statistical significance of $p < 0.01$ between the control and the data, and between groups M and S, respectively.

Numbers in parentheses indicate the number of experiments performed.

from 15 min after the administration and maximally decreased by $16.6 \pm 18.5\%$ in group M, increasing by $1.6 \pm 8.5\%$ in group S 90 min after the administration (Fig. 3).

There was a significant difference in LV systolic pressure between groups M and S at 60 and 90 min after the administration.

LV enddiastolic pressure was decreased significantly at 15 min being maximally decreased by $63 \pm 20\%$ in group M and $35 \pm 18\%$ in group S at 60 min after the administration (Fig. 3).

Intramyocardial Pressure

The systolic intramyocardial pressure did not change significantly throughout the experiment (Fig. 4). The end-diastolic intramyocardial pressure decreased by 20% at 15 min and 32% in group M at 30 min after the administration in contrast to a slight increase of $7 \pm 3\%$ in group S

TABLE II REGIONAL MYOCARDIAL BLOOD FLOW (ml/min/100 g) IN THE ISCHEMIC REGION

		Control	15 min.	30 min.	60 min.	90 min.	120 min.	150 min.	180 min.
END	M	30 ± 18 (9)	33 ± 14 (9)	37 ± 15 (9)	37 ± 16 (9)	46 ± 24 (8)	51 ± 28 (8)	61 ± 30 (4)	54 ± 37 (4)
	S	33 ± 23 (8)	33 ± 21 (8)	37 ± 27 (8)	40 ± 33 (8)	37 ± 30 (8)	41 ± 28 (7)	52 ± 22 (4)	49 ± 19 (4)
EPI	M	98 ± 53 (9)	84 ± 59 (9)	82 ± 52 (9)	76 ± 48 (9)	74 ± 44 (9)	78 ± 44 (9)	80 ± 41 (5)	94 ± 52 (3)
	S	59 ± 36 (8)	66 ± 37 (8)	69 ± 43 (8)	65 ± 33 (8)	60 ± 31 (8)	65 ± 30 (7)	59 ± 12 (4)	49 ± 11 (4)
END/EPI	M	0.32 ± 0.15 (9)	0.49 ± 0.26 (9)	0.54 ± 0.25 (9)	0.63 ± 0.32 (9)	0.62 ± 0.24 (8)	0.70 ± 0.31 (8)	0.71 ± 0.40 (4)	0.88 ± 0.51 (3)
	S	0.62 ± 0.28 (8)	0.54 ± 0.21 (8)	0.56 ± 0.21 (8)	0.60 ± 0.27 (8)	0.62 ± 0.37 (8)	0.63 ± 0.37 (7)	0.85 ± 0.22 (4)	0.98 ± 0.26 (4)

Abbreviations: END = Subendocardial blood flow; EPI = Subepicardial blood flow; END/EPI = The ratio of subendocardial to subepicardial blood flow.

(Fig. 4).

There was a significant difference between groups M and S at 15 and 30 min intervals.

Regional Myocardial Blood Flow (RMBF)

RMBFs in the ischemic region are shown in Table II. There were no significant differences in RMBF in the subendocardium and the subepicardium between groups M and S, though subendocardial RMBF in group M tended to increase gradually following administration of the agent (Fig. 5). In contrast, subepicardial RMBF in group M tended to decrease with a maximal value of $23 \pm 27\%$ instead of the slight increase of $10 \pm 59\%$ in group S 60 min following administration. There was a significant difference in subepicardial RMBF between groups M and S at 60 min only.

A significant difference was observed in the ratio of subendocardial to subepicardial RMBF between groups M and S at control (F value = 3.58), suggesting a difference in the severity of myocardial ischemia between the two groups. The marked improvement with molsidomine was clearly evident since the severity of ischemia became more pronounced. The percent increase in the ratio was noted following administration in group M and reached $96 \pm 83\%$ 60 min after the administration, compared with $-4 \pm 40\%$ in group S (Fig. 6). There was a statistically significant difference in the percent change at 15 and 30 min following administration between groups M and S. RMBFs in the non-ischemic region are

Fig. 4. Percent changes from the control in systolic intramyocardial pressure (IMSP) and enddiastolic intramyocardial pressure (IMEDP).

An open circle indicates group M and closed one, group S. * indicates a statistical significance of $p < 0.05$ between the control and the data. Numbers in parentheses indicate the number of experiments performed.

shown in Table III.

In the non-ischemic region subendocardial RMBF in group M decreased to a level slightly greater than that of subepicardial blood flow

Fig.5. Percent changes from the control in regional myocardial blood flow (RMBF) in the ischemic area. RMBF (END) indicates the subendocardial blood flow, and RMBF (EPI), the subepicardial blood flow.

An open circle indicates group M and closed one, group S. * and # indicate a statistical significance of $p < 0.05$ between the control and the data, and between groups M and S, respectively.

Numbers in parentheses indicate the number of experiments.

Fig.6. Percent changes from the control in the ratio of subendocardial (END) to subepicardial (EPI) blood flow.

An open circle indicates group M and closed one, group S. * and # indicate a statistical significance of $p < 0.05$ between the control and the data, and between groups M and S, respectively. ** indicates a statistical significance of $p < 0.01$ between the control and the data.

Numbers in parentheses indicate the number of experiments undertaken.

after the administration. RMBF in group S slightly decreased throughout the experiment (Fig. 7).

In the non-ischemic region the ratio of subendocardial to subepicardial RMBF tended to decrease throughout the experiment in group M and, in contrast, tended to increase in group S (Fig. 6). However the differences were not significant.

Plasma Levels of Molsidomine

We administered molsidomine intraduodenally in 7 dogs to measure plasma levels. Fifteen min after administration of molsidomine, plasma molsidomine levels ranged from 9 to 160 ng/ml with a mean of 70 ± 20 ng/ml. Plasma concentrations of SIN-1C were also at maximal levels (4 to 46 ng/ml) 15 min after the administration, generally declining in parallel with the plasma

concentration of molsidomine levels (Table IV).

The distribution and elimination half-lives for molsidomine were 0.08 hour and 1.05 hours, respectively. A significant difference in hemodynamics between groups M and S was noted, starting from 15 min to 90 min after the administration, thereby indicating that the effective plasma levels of molsidomine are over 20 ± 5 ng/ml.

DISCUSSION

Hemodynamics

The present study is consistent with previously reported data stating that molsidomine causes a marked reduction in LV preload and improves systolic emptying through a direct action on the veins and, to a lesser extent, dilatation of systemic arteriolar beds^{3,12-14}

TABLE III REGIONAL MYOCARDIAL BLOOD FLOW (ml/min/100 g) IN THE NON-ISCHEMIC REGION

		Control	15 min.	30 min.	60 min.	90 min.	120 min.	150 min.	180 min.
END	M	118 ± 40 (8)	111 ± 52 (8)	101 ± 44 (8)	84 ± 38 (8)	78 ± 33 (7)	68 ± 30 (8)	60 ± 32 (4)	58 ± 37 (3)
	S	87 ± 29 (6)	88 ± 31 (6)	81 ± 25 (6)	73 ± 25 (6)	67 ± 24 (6)	56 ± 23 (5)	60 ± 13 (3)	52 ± 13 (3)
EPI	M	103 ± 39 (8)	99 ± 44 (8)	89 ± 40 (8)	80 ± 32 (8)	79 ± 42 (7)	71 ± 35 (8)	68 ± 46 (4)	65 ± 35 (3)
	S	91 ± 40 (6)	98 ± 38 (5)	100 ± 36 (5)	76 ± 39 (5)	68 ± 24 (5)	48 ± 18 (4)	64 ± 31 (3)	56 ± 25 (3)
END/EPI	M	1.20 ± 34 (8)	1.14 ± 39 (8)	1.16 ± 23 (8)	1.08 ± 33 (8)	1.06 ± 30 (7)	0.99 ± 32 (8)	0.97 ± 32 (4)	0.94 ± 47 (3)
	S	1.05 ± 33 (6)	1.02 ± 28 (5)	0.92 ± 26 (5)	1.21 ± 45 (5)	1.16 ± 30 (5)	1.34 ± 20 (4)	1.07 ± 43 (3)	1.01 ± 30 (3)

Abbreviations: END = Subendocardial blood flow; EPI = Subepicardial blood flow; END/EPI = The ratio of subendocardial to subepicardial blood flow.

Therefore, molsidomine resembles nitroglycerin in its mode of action.¹³ Although nitrates are absorbed rapidly after sublingual administration their effects are transient, lasting only thirty minutes. The net effects of molsidomine, on the other hand, last longer. These differences are probably related to the mode of molsidomine metabolism.¹⁵ Molsidomine is absorbed very rapidly after intraduodenal administration since the effect of hypotensive action appears only 15 min after administration. In addition, the plasma level of molsidomine was highest 15 min after administration. Intramyocardial pressure at systole did not reflect a change in LV systolic pressure in the present study. The reason may be that the intramyocardial pressure peculiar to this study indicates the pressure in the subendocardium subject to ischemia.

The intramyocardial pressure during ischemia is slightly lower than the LV cavity pressure.¹⁶ Therefore, the intramyocardial pressure becomes less sensitive to alterations in LV cavity pressure. A diastolic intramyocardial pressure in the subendocardium was reported to be higher than the LV end-diastolic pressure and was influenced by acute ischemia.¹⁶

According to Burton,¹⁷ the small arterioles are most vulnerable to closure because their intravascular pressures are relatively low. Since the intramyocardial pressure shows the highest value in the subendocardium, coronary perfusion may be least in that area of the myocardium at systole. In fact no flow could have occurred in the

Fig. 7. Percent changes from the control in regional myocardial blood flow (RMBF) in the non-ischemic area. RMBF (END) indicates the subendocardial blood flow, and RMBF (EPI), the subepicardial blood flow.

An open circle indicates group M and closed one, group S. * and * indicate a statistical significance of $p < 0.05$ between the control and the data, and between groups M and S, respectively. ** and ** indicate a statistical significance of $p < 0.01$ between the control and the data, and between groups M and S, respectively.

Numbers in parentheses indicate the number of experiments performed.

TABLE IV PLASMA LEVELS OF MOLSIDOMINE

	15 min.	30 min.	60 min.	90 min.	120 min.	150 min.	180 min.
<i>Molsidomine (ng/ml)</i>	70 ± 20	44 ± 11	31 ± 7	20 ± 5	14 ± 4	12 ± 4	9 ± 3
<i>SIN-1C (ng/ml)</i>	22 ± 6	21 ± 5	19 ± 3	14 ± 2	11 ± 1	11 ± 2	8 ± 2

subendocardium in systole since all the vessels were squeezed and closed by intramyocardial pressure.

The fact that there was a lower pressure gradient between coronary perfusion pressure and intramyocardial pressure in the subendocardium than in the subepicardium during diastole may explain the preferential flow to the subendocardium during that period⁸. The intramyocardial pressure in the subendocardium during diastole does not decrease after acute ischemia notwithstanding the increase in LV enddiastolic pressure during ischemia¹⁶. Sabbah et al.¹⁶ concluded that ischemia had a greater effect on the intramyocardial pressure in the subepicardium during diastole than in the subendocardium. In the present study the decrease in the intramyocardial pressure after molsidomine administration may have a favorable effect on subendocardial RMBF in the ischemic myocardium.

Myocardial Blood Flow

There are confusing data available on the effect of nitroglycerin on RMBF distal to a flow-limiting coronary stenosis which is analogous to an animal model of coronary artery disease in man.

In acute experiments Weintraub et al.¹⁸ reported that nitroglycerin reduced subendocardial and subepicardial blood flow in both the ischemic and non-ischemic zone and that reduction in subendocardial blood flow of the ischemic region was most probably due to the reduction in perfusion pressure, and not to decreased oxygen demand. These findings are in conflict with ours in that subendocardial blood flow in the ischemic region tends to increase and that the ratio of subendocardial to subepicardial blood flow was found to increase significantly, although coronary perfusion pressure tends to decrease.

This discrepancy may be explained by the absence of a decrease in enddiastolic pressure by nitroglycerin in their study. Scholtholt et al.⁵ showed that molsidomine improved the ratio of

subendocardial to subepicardial RMBF in the infarcted area and the border zone of infarction. They accounted for the effects of the compound by suggesting a stronger influence on the extravascular factors of coronary vascular resistance due to a decrease in end-diastolic pressure. The increase in the ratio of subendocardial to subepicardial blood flow is not due to an active dilation of coronary circulation but rather to a passive dilation secondary to the decrease in the end-diastolic pressure and the intramyocardial pressure in the subendocardium. This redistribution of myocardial blood flow took place from the normal to the ischemic region as well as from the subepicardium to the subendocardium. We previously reported that gradual reduction in coronary perfusion pressure decreased subendocardial blood flow to a greater extent than it did subepicardial blood flow¹⁹. Molsidomine probably counteracts the diminution of subendocardial blood flow caused by coronary stenosis. It was reported that nitroglycerin preferentially increased in subendocardial blood flow in the ischemic region²⁰, although Scholtholt et al.⁵ could not show any increase in the ratio of subendocardial to subepicardial blood flow following nitroglycerin injection. Rudolph et al.⁴ showed an increase in RMBF following an intravenous administration of molsidomine in man.

Gross and Gharaideh⁶ also demonstrated that molsidomine increased the ratio of subendocardial to subepicardial blood flow in the ischemic region and decreased both RMBFs in the non-ischemic region. They concluded that the increase in the ratio was due to the decrease in myocardial oxygen consumption induced by molsidomine. In conclusion, the mechanism of the anti-ischemic effect of molsidomine may be due to a decrease in LV end-diastolic and intramyocardial pressures in the subendocardium, which cause a redistribution of RMBF from the normal to the ischemic region and from the subepicardial to the subendocardial region. In addition molsidomine can be easily absorbed intraduodenally and its effects are more enduring.

Acknowledgements

We thank Mr. Fukio Nakagawa and Hiroshi Okuno for their technical help, and Takeda Pharmaceutical Company for providing molsidomine and measuring its blood concentration.

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