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Abstract

Effects of propranolol on ischemic segmental function were studied in anesthetized open-chest dogs. Two segment-length gauges were used for measuring the regional myocardial function: one was sutured on to the left ventricular surface perfused by the anterior descending coronary artery (ischemic zone) and the other was on to that perfused by the circumflex coronary artery (normal zone). A bolus of propranolol (0.5 mg/kg) was injected into the right femoral vein. Five min later, the left anterior descending coronary artery (LAD) was completely occluded for one mine and thereafter released. Then a second coronary occlusion for 20 min was performed; an interval of 20 min was allowed between two occlusions. Propranolol, in the ischemic segment, apparently decreased the extent of paradoxical lengthening in the late systole following one min LAD occlusion, and facilitated improvement of segmental function after release of the occlusion. Moreover, the extent of abnormal stretching induced by 20 min occlusion during early systole, was also reduced by propranolol pretreatment. In contrast, compensatory increase in shortening by the normal segment was disturbed by propranolol. These results suggest that propranolol might exert a favourable influence on the segmental myocardial function during either transient or maintained myocardial ischemia.

KEYWORDS: propranolol, regional myocardial function, ischemia

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EFFECT OF PROPRANOLOL ON REGIONAL MYOCARDIAL FUNCTION IN ANESTHETIZED OPEN-CHEST DOGS WITH MYOCARDIAL ISCHEMIA

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Abstract. Effects of propranolol on ischemic segmental function were studied in anesthetized open-chest dogs. Two segment-length gauges were used for measuring the regional myocardial function: one was sutured on to the left ventricular surface perfused by the anterior descending coronary artery (ischemic zone) and the other was on to that perfused by the circumflex coronary artery (normal zone). A bolus of propranolol (0.5 mg/kg) was injected into the right femoral vein. Five min later, the left anterior descending coronary artery (LAD) was completely occluded for one min and thereafter released. Then a second coronary occlusion for 20 min was performed; an interval of 20 min was allowed between two occlusions. Propranolol, in the ischemic segment, apparently decreased the extent of paradoxical lengthening in the late systole following one min LAD occlusion, and facilitated improvement of segmental function after release of the occlusion. Moreover, the extent of abnormal stretching induced by 20 min occlusion during early systole, was also reduced by propranolol pretreatment. In contrast, compensatory increase in shortening by the normal segment was disturbed by propranolol. These results suggest that propranolol might exert a favourable influence on the segmental myocardial function during either transient or maintained myocardial ischemia.

Key words: propranolol, regional myocardial function, ischemia

In the past few years much attention has been directed towards various methods of therapeutic intervention which slow or prevent the development of myocardial necrosis following an acute coronary artery occlusion (1, 2). Propranolol has been suggested as a possible means of reducing acute ischemic injury and thus potentially protecting myocardial tissue (3). An important cause of impaired cardiac function in ischemic heart disease, however, is mechanical dysfunction of different regions of the ventricle in addition to myocardial tissue loss (4, 5). The effect of propranolol on regional contractile function of

the ischemic and normal zones following coronary occlusion has not been evaluated sufficiently. The purpose of this study therefore was to determine the effect of propranolol on both ischemic and normal zonal contractile performance.

METHODS

Experiments were performed in 14 mongrel dogs weighing 10–20 kg under anesthesia with intravenous sodium pentobarbital (25–30 mg/kg). Seven dogs were used for propranolol pretreatment and the remainder for control. The animals were respirated with room air through an endotracheal tube connected to an intermittent positive pressure pump. A polyethylene tube was inserted into the right femoral vein for intravenous injection. A stiff bore catheter (#8 French) was introduced into the ascending aorta by way of the right femoral artery for monitoring central aortic pressure. Pressure was measured with Nihonkoden model MP-24T strain gauge placed at the midchest level. The heart was exposed through a left thoracotomy in the fifth intercostal space and supported with a pericardial cradle. The left anterior descending coronary artery (LAD) was isolated and a loose ligature was placed around the vessel. The ends of the ligature were threaded through a short plastic tube for occluding the vessel. An electromagnetic flow transducer was positioned around the aorta as near its root as possible for measuring aortic blood flow. Two strain gauges (Nihonkoden model RP-5) were used for measuring the segment-length; one was placed with deep sutures on the left ventricular wall perfused by the LAD (ischemic area), perpendicular to the interventricular septum, and the other was sutured on to the left ventricular surface (supplied by the left circumflex coronary artery [normal area]) in parallel with the gauge in the ischemic area (Fig. 1, left). A segment-length of approximately 1.0 cm of myocardium was delineated by the points of attachment of the gauge.

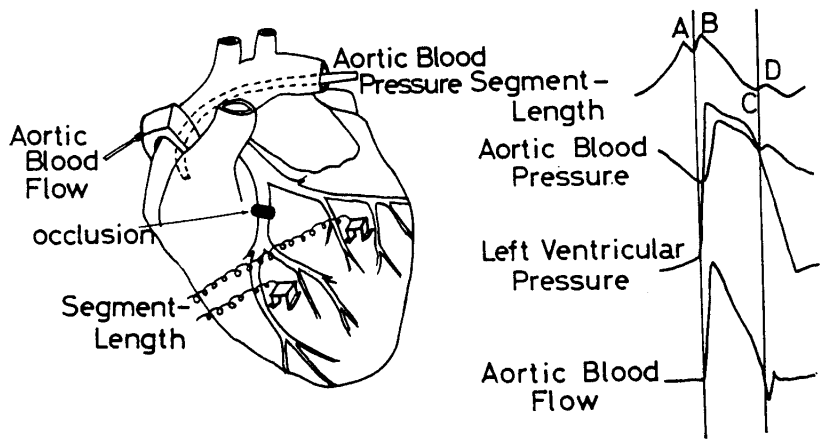

Fig. 1. Schematic illustration of instrumentation and the points analyzed in the segment-length curve.

After instrumentation was completed, seven dogs were given a bolus of 0.5 mg/kg of propranolol intravenously via the tube placed in the right femoral vein. Five min after the injection of propranolol, the LAD was completely occluded for one min and then released. Twenty min later a second occlusion of the LAD was performed for 20 min.

As a control, the same procedures except for pretreatment with propranolol were carried out on another seven dogs.

Hemodynamic variables and segment-length curves were recorded with a lead II electrocardiogram using a multichannel direct visual oscillograph (Yokogawa-Denki, model 2901) at paper speed of 100 mm per second.

Though strict attention was paid to applying the gauge in the same position on each heart and to delineate the same myocardial length between the points of attachment of the gauge, the actual attachment of the gauge was not completely the same in individual animals. Therefore, the dimension of each point in the segment-length curve was expressed as millimeters from point A prior to the LAD occlusion.

The unpaired Student's t-test was used for comparison of the data between the groups, and the paired Student's t-test was used for comparison within the group.

RESULTS

The segment-length curve was named at four points and analyzed according to Tawara (6) as illustrated in Fig. 1 (right). Point A and point B were coincident with the end of diastole and early phase of left ventricular ejection, respectively. Point C appeared at the phase of reducing ejection and point D synchronized at the end of ejection.

TABLE 1. HEMODYNAMIC DATA BEFORE OCCLUSION OF THE LAD

		Heart rate (beat/min)	LVET (sec.)	SV (ml)	Systolic BP (mmHg)	Diastolic BP (mmHg)
A. Before the LAD occlusion for one minute.						
Pretreated with propranolol	M	125	0.17	15.0	122[a]	90
	SD	20.8	0.08	0.80	8.6	9.0
Control	M	150	0.18	15.5	142	94
	SD	22.5	0.03	0.62	8.0	8.7
B. Before the LAD occlusion for 20 minute.						
Pretreated with propranolol	M	150	0.17	15.1	120[a]	89
	SD	18.6	0.02	0.84	8.0	6.2
Control	M	146	0.18	15.3	138	92
	SD	24.6	0.04	0.73	6.5	8.6

LVET=left ventricular ejection time; SV=stroke volume; BP=blood pressure.
M=mean, SD=standard deviation of mean.
a Significant difference from control ($P<0.01$).

Effects of propranolol (Table 1). Intravenous injection of propranolol significantly slowed the heart rate ($P<0.01$) and decreased the systolic blood pressure ($P<0.01$). A significant difference from the control group, however, was only seen in the systolic blood pressure prior to occlusion of the LAD.

In segment-length, point A was slightly but significantly ($P<0.01$) streched in association with a marginal decrease in the dimensions of points B, C and D.

Effects of LAD occlusion. One min occlusion of the LAD caused a slight elongation of point A in the propranolol group the same as in the control group. Paradoxical systolic lengthening in ischemic myocardial segment was produced by LAD occlusion at points B, C and D. Points B and C in propranolol group lengthened the same as those in control group. However, lesser reduction in the dimension of point D occurred in the propranolol group at 10, 20 and 40 seconds after the occlusion ($P<0.05$, $P<0.05$, $P<0.01$, respectively) as represented in Table 2 and Fig. 2.

TABLE 2. SEGMENT-LENGTH (MM) BEFORE, DURING AND AFTER ONE MIN OCCLUSION OF THE LAD

		Pretreated with propranolol				Control			
		Point A	Point B	Point C	Point D	Point A	Point B	Point C	Point D
Before occlusion	M	0	−0.13	2.90	2.60	0	−0.20	3.21	2.56
	SD	—	0.46	0.25	0.28	—	0.28	0.37	0.28
After the occlusion									
10 sec	M	0	−0.10	2.43	0,83[a]	−0.20	−0.40	2.80	0.33
	SD	0.08	0.29	0.52	0.41	0.12	0.32	0.22	0.26
20 sec	M	−0.10	−0.50	1.97	0.17[a]	−0.26	−0.62	2.16	−0.41
	SD	0.08	0.36	0.43	0.56	0.08	0.34	0.43	0.18
40 sec	M	−0.17	−1.70	−0.20	−1.57[b]	−0.31	−1.85	−0.38	−2.58
	SD	0.09	0.62	0.68	0.53	0.14	0.49	0.36	0.16
After release of the occlusion									
Release (0 sec)	M	−0.37	−2.86	−1.50	−2.43	−0.63	−3.23	−1.59	−2.81
	SD	0.12	0.33	0.76	0.83	0.18	0.52	0.40	0.18
10 sec	M	−0.20	−0.90[b]	1.16[b]	1.10[b]	−0.62	−3.23	0.20	−0.61
	SD	0.08	0.50	0.41	0.36	0.18	0.50	0.39	0.20
20 sec	M	−0.10	−0.87[c]	1.80[b]	1.63[a]	−0.55	−1.78	1.02	1.20
	SD	0.08	0.53	0.24	0.21	0.20	0.41	0.38	0.21
40 sec	M	−0.10	−0.57	2.33[a]	2.03	−0.24	−0.63	2.56	2.04
	SD	0.08	0.36	0.20	0.24	0.16	0.45	0.31	0.20
60 sec	M	−0.10	−0.03	2.77	2.38	−0.20	−0.22	2.88	2.25
	SD	0.08	0.50	0.36	0.37	0.18	0.37	0.40	0.26

M=mean, SD=standard deviation.

Significant difference from the control, *a* $P<0.05$, *b* $P<0.001$, *c* $P<0.01$.

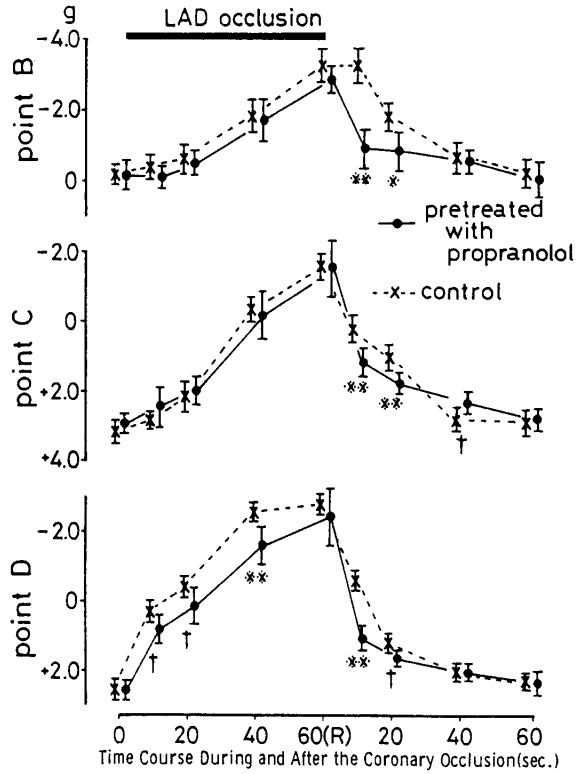

Fig. 2. Dimensional changes in points of the segment-length curve in the ischemic zone during and after brief coronary occlusion.
Significant difference between the two groups: **P<0.001, *P<0.01, +P<0.05.

Throughout this period, the segment-length in the normal area showed only little change. A significant decrease in stroke volume ($P<0.001$), left ventricular ejection time ($P<0.001$) and systolic blood pressure ($P<0.01$) was seen during one min of LAD occlusion in both canine groups. The percent decrease in the propranolol group, however, was slightly less than the control group in the left ventricular ejection time (LVET) and systolic blood pressure, and significantly so in stroke volume ($P<0.05$) (Table 3).

Reflow in the LAD caused a more rapid improvement in stroke volume and systolic blood pressure. Stroke volume in the propranolol group returned to the preocclusion level within 10 sec and rather increased during the following 10 sec, while in the control group longer than 20 sec was required for restoration (Fig. 3). The release of LAD occlusion improved abnormal contraction for a

short time in points B, C and D. Recovery appeared more rapidly in the propranolol group than in the control; a significant difference in the dimension between groups was seen for points B, C and D at 10 and 20 sec following the release of the coronary artery occlusion.

TABLE 3. PERCENT CHANGES OF HEMODYNAMIC MEASUREMENTS DURING AND AFTER ONE MIN LAD OCCLUSION (%)

		Pretreated with propranolol				Control			
		LVET	SV	sBP	dBP	LVET	SV	sBP	dBP
Time after LAD occlusion.									
10 sec	M	88.0	88.6	95.2	94.5	84.5	85.8	96.4	87.6
	SD	3.7	3.3	7.0	10.0	3.7	5.7	3.3	6.5
20 sec	M	86.0	90.1[a]	95.3	96.4	84.1	84.1	94.0	90.0
	SD	2.6	4.1	5.9	9.2	6.2	5.7	2.8	6.3
40 sec	M	94.2	91.2[a]	91.4	93.7	89.5	83.2	91.0	90.5
	SD	6.2	5.3	6.2	7.6	8.9	6.5	3.8	6.7
Time after release of the LAD occlusion.									
Release (0 sec)	M	97.4	94.0[a]	93.2	94.0	95.0	85.7	93.0	90.1
	SD	5.3	5.5	2.4	6.4	6.4	8.4	4.5	7.6
10 sec	M	100.0	101.0[a]	98.6[a]	94.3	96.1	92.1	93.3	92.4
	SD	4.3	3.8	2.9	6.4	3.3	6.3	4.7	6.7
20 sec	M	100.2	105.0[b]	99.0	97.9	98.1	94.3	95.8	95.9
	SD	3.3	4.4	1.9	4.8	2.3	6.9	4.7	8.0
40 sec	M	99.8	101.0	100.2	101.6	99.1	101.6	99.2	96.9
	SD	1.4	2.0	5.1	9.5	3.3	5.2	4.5	8.2
60 sec	M	102.0	103.0	99.1	101.2	98.9	101.7	99.5	98.2
	SD	2.2	2.3	5.7	9.5	3.0	3.5	3.7	7.5

LVET=left ventricular ejection time; SV=stroke volume; sBP=systolic blood pressure; dBP=diastolic blood pressure. M=mean, SD=standard deviation.
Significant difference from control, *a* $P<0.05$, *b* $P<0.01$.
Data represented a percentage of hemodynamic measurement to each preocclusion value.

In the ischemic area prolonged occlusion of the LAD for 20 min markedly lengthened points B, C and D during the initial five min. The changes in segment-length did not differ substantially between two groups. The extent of early systolic (point B) bulging was smaller in the propranolol group than in the control at 10 and 20 min after occlusion ($P<0.05$), because point B in the control group gradually lengthened during the 20 min following occlusion, whereas in the propranolol group no further elongation was observed. Point D reached maximal lengthening during the first five min in both canine groups; no significant

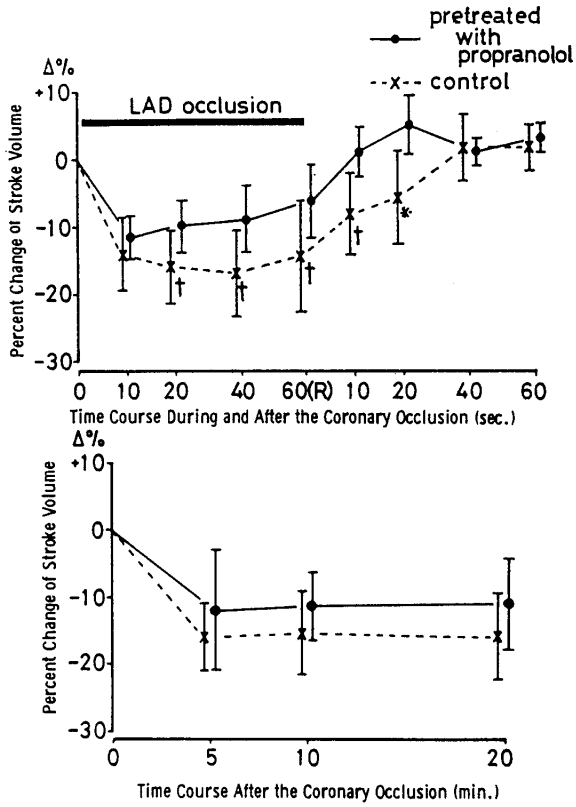

Fig. 3. Percent changes of stroke volume during and after release of brief coronary occulusion (top), and that during coronary occlusion maintained for 20 min (bottom).
Significant difference between the two groups: *P<0.01, +P<0.05.

TABLE 4. SEGMENT-LENGTH (MM) BEFORE AND AFTER OCCLUSION FOR 20 MIN

		Pretreated with propranolol				Control			
		Point A	Point B	Point C	Point D	Point A	Point B	Point C	Point D
Before occlusion	M	0	0.31	2.78	2.90	0	−0.12	2.43	2.96
	SD	—	0.23	0.51	0.38	—	0.45	0.62	0.44
5 min after occlusion	M	−0.39	−2.47	−1.86	−0.98	−0.30	−3.87	−1.83	−1.64
	SD	0.27	0.96	0.41	0.70	0.20	1.26	0.48	0.40
10 min after occlusion	M	−0.60	−2.75[a]	−2.01[a]	−1.28[a]	−0.45	−4.51	−2.63	−1.91
	SD	0.20	1.28	0.30	0.51	0.23	1.25	0,46	0.59
20 min after occlusion	M	−0.64	−2.90[a]	−1.96[a]	−1.30	−0.53	−4.80	−2.61	−1.92
	SD	0.38	1.29	0.44	0.49	0.21	1.23	0.52	0.69

M=mean, SD=standard deviation.
Significant difference from the control, *a* P<0.05.

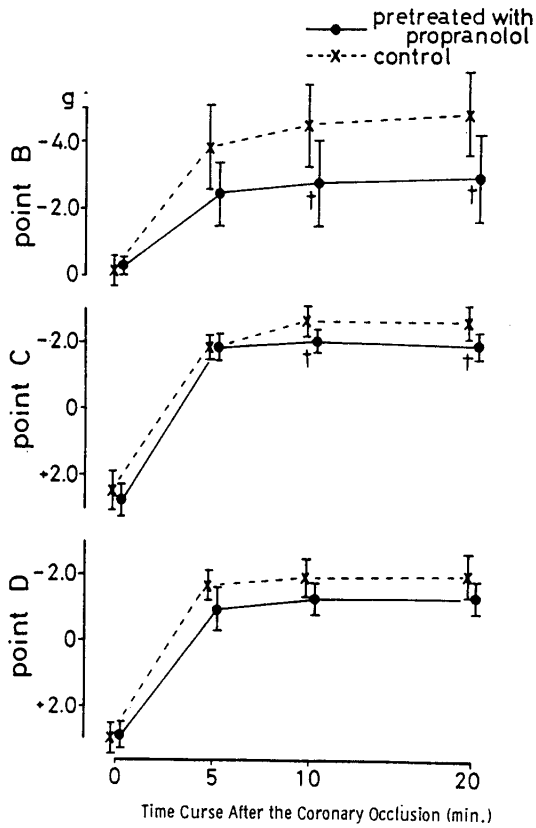

Fig. 4. Dimensional changes in points of the segment-length curve in the ischemic zone during coronary occlusion maintained for 20 min.
Significant difference between the two groups: $^{+}P<0.05$.

difference in the dimensions of point D was observed between the two groups. A small increase in paradoxical lengthening in point C seen in the control group from five to ten min after the occlusion was lost in the propranolol group (Table 4, Fig. 4).

In the normal area of the propranolol group, point B progressively lengthened throughout the experiments. In contrast to this, point B in the control group was rather increased in shortening following an initial slight reduction. Points C and D in propranolol group decreased gradually in shortening, similar to those in the control group. A significant difference in the dimension of point D, however, was observed between the two canine groups at 5, 10 and 20 min after the occlusion ($P<0.01$). Point C also showed significant differences in dimension between the two groups at 5 and 20 min after the occlusion (Fig. 5).

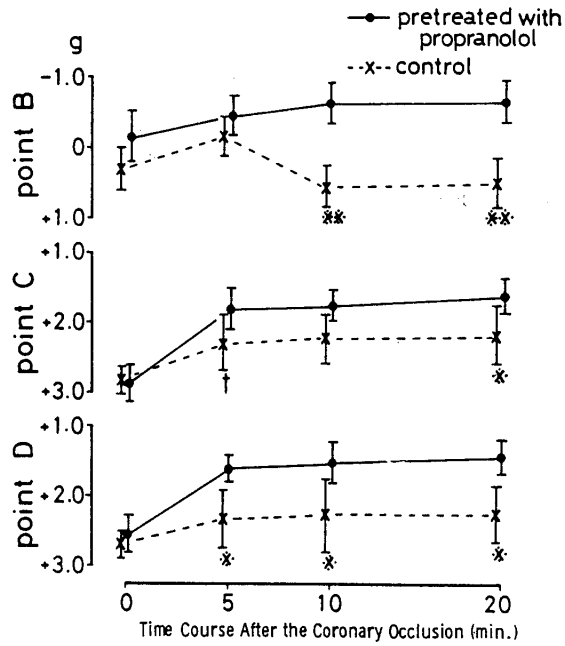

Fig. 5. Dimensional changes in poins of the segment-length curve in the normal zone during coronary occlusion maintained for 20 min.
Significant difference between the two groups: **P<0.001, *P<0.01, +P<0.05.

TABLE 5. PERCENT CHANGES OF HEMODYNAMIC MEASUREMENTS DURING LAD OCCLUSION (%)

		Pretrated with propranolol				Control			
		LVET	SV	sBP	dBP	LVET	SV	sBP	dBP
5 min	M	97.3	88.0	95.0	90.6	102.5	81.0	93.0	93.7
	SD	8.5	9.2	6.5	8.1	5.3	5.3	7.3	12.6
10 min	M	100.6	88.4[a]	96.9	94.4	102.0	80.4	93.9	94.6
	SD	2.2	5.3	5.0	9.0	5.0	6.7	3.6	10.6
20 min	M	99.9	89.0[a]	94.1	94.0	101.6	80.9	91.2	93.9
	SD	3.6	6.9	5.6	7.6	5.9	5.5	5.5	7.0

LVET=left ventricular ejection time, SV=stroke volume, sBP=systolic blood pressure, dBP=diastolic blood pressure. M=mean, SD=standard deviation.
Significant difference from control, *a* P<0.05.
Data represent the percentage ratio of each hemodynamic measurement to preocclusion values.

The occlusion of the LAD maintained for 20 min resulted in a fall in stroke volume and blood pressure in both groups. The propranolol group showed a lesser reduction of stroke volume which was significantly different at 10 and 20 min from that of the control group ($P<0.05$). This was in association with the difference in the dimensions of points B and C of the two groups. Blood pressure tended to fall less in the propranolol group than in the control group, though no significant difference existed between the groups (Table 5).

DISCUSSION

Recently, attention has been focused on decreasing the degree of myocardial injury (6–8). The fate of endangered ischemic tissue depends upon the balance between oxygen requirement and supply. The ability of propranolol to decrease the heart rate and myocardial contractility should favourably reduce myocardial oxygen consumption. Furthermore possible redistribution of blood flow from non-ischemic zones to the ischemic zone could be attributed to the improvement of the impaired local myocardial function (9–11). Coronary occlusion produced minor changes in systemic hemodynamics and function in normal myocardial zones, but caused progressively greater impairment of function in the ischemic segment. In the ischemic segment, paradoxical systolic lengthening was initiated from the end-systolic point (point D) and extended rapidly to the early ejection phase (point B). Primzmetal *et al.* (12) using high-speed cinematography, described early systolic contraction with ballooning late in systole and sometimes throughout systole. Hood *et al.* (13) also showed the segment lengthening normally observed during isovolumetric systole greatly increased during ischemia and that shortening during the ejection phase disappeared. These are consistent with the present findings, and the paradoxical systolic expansion resulted from inability to sustain active tension development with increased myocardial compliance in the ischemic segment (14). Propranolol pretreatment exerted apparent effects on regional function in normal and ischemic segments. In the normal segment, propranolol reduced the extent of shortening, minimally during and after the brief coronary occlusion, but significantly during coronary occlusion maintained for 20 min. In contrast, in the ischemic segment, propranolol suppressed the extent of end-systolic abnormal contraction which was induced by one min occlusion of the LAD and facilitated an improvement of paradoxical lengthening during systole. Furthermore, the extent of passive stretching induced by maintaining coronary occlusion fell significantly with propranolol pretreatment in early systole. The depressant action of propranolol on systemic hemodynamics and regional myocardial function in the normal zone was predictable, a finding which is consistent with our previous report (15), and those of Mueller *et al.* (16) and Vatner *et al.* (17). The ability of propranolol to decrease the amount of ische-

mia and necrosis after experimental coronary ligation was investigated recently (18–20). The drug reduced the infarction size as estimated histologically (21). The epicardial ECG mapping technique also confirmed the protective effects of propranolol from ischemic injury (22, 23). Theroux *et al.*. reported, using ultrasonic dimension gauges, a protecting effect of the drug, observing that the reduction in the extent of shortening was substantially less after propranolol administration than it was during the control occlusion in both open-chest anesthetized (24) and conscious (25) dogs. Vatner *et al.* (17) observed that in the ischemic segment with paradoxical expansion during systole, propranolol decreased the extent of paradoxical motion in contrary to the effect in the normal and moderately ischemic segments in which the extent and velocity of shortening were decreased by the drug. In the present study, in accord with these reports, favourable effects of propranolol were most evident in the dimension of early systole of the ischemic segment at 10 and 20 min during the coronary occlusion. This might suggest that propranolol had the favourable effect of maintaining developing tension during the isovolumetric contraction phase. One of the important findings in this investigation was that propranolol accelerated the improvement of the impaired segment-function after the release of a brief coronary occlusion. An attack of angina pectoris with or without organic coronary lesions produced severe myocardial ischemia that caused a transient paradoxical segmental expansion in systole (26–28). Propranolol-accelerated restoration of segment function might affect favourably left ventricular function in patients with angina pectoris in addition to protecting patients from angina attack. Though the mechanisms of the beneficial effects of propranolol pretreatment were not clear in the present study, slowing heart rate might be the most important. A reduction of contractility and an increase in oxygen supply to the ischemic segment might play little or no role in the beneficial effects, since the loss of contractile force in the severe ischemic zone was almost complete (29) and propranolol had no ability to cause redistribution of blood flow to ischemic areas in acutely induced myocardial ischemia (30, 31). Of interest propranolol impeded normal segment in a compensatory increase in shortening during the maintaining coronary occlusion. This was most apparent in early systole when the drug significantly decreased the extent of paradoxical systolic elongation in ischemic zone. Two possible mechanisms of the effects, which would resulted in disturbing a compensatory increase in shortening of normal segment, are the blocking effect of β-adrenergic receptor of myocardium and a lessened effect of the Frank-Starling mechanism because of a smaller residual volume in diastole.

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