COMPARISON OF HEMODYNAMIC EFFECTS BETWEEN β -BLOCKING AGENTS AND A NEW ANTIANGINAL AGENT, DILTIAZEM HYDROCHLORIDE

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DILTIAZEM hydrochloride (diltiazem) is a new antianginal drug of 1,5-benzothiazepine derivative synthesized recently by Kugita et al.¹ In experimental animals the drug exerts a powerful coronary vasodilator action and slight negative inotropic and chronotropic actions.² Clinically, diltiazem is effective on effort angina and rest angina.³⁻⁵ However, the mechanism of antianginal action of diltiazem is not elucidated entirely. Angina commonly results from imbalance between myocardial oxygen consumption and myocardial oxygen availability. There are two ways in the treatment of angina; one is to induce actively an increase in myocardial oxygen availability through coronary vasodilation and another is to reduce myocardial oxygen consumption. Among drugs for this purpose, β -blocking agents are used widely because the agents can reduce myocardial oxygen consumption.^{6,7} In this connection the attention of investigators has been attracted to the hemodynamic effects of anti-anginal drugs. In a previous paper, we reported the hemodynamic effects of diltiazem at rest.⁸ The present work was designed to throw some light on the anti-anginal mechanism of diltiazem in comparison of the hemodynamic

action of diltiazem after bicycle ergometric exercise with that of β -blocking agents after the exercise.

METHODS

Twenty four subjects including 22 Japanese men and 2 Japanese women ranging in age from 26 to 72 years were selected for this study. They were composed of 8 normal subjects, 11 with hypertension, 3 with effort angina, 1 with rest angina and 1 with old myocardial infarction. All subjects had showed neither the change in ST-T segments of ECG nor enlargement of the heart, and the cardiac functional capacity by NYHA classification was in Classes I and II (Table I). Cardiac output (CO) was determined by radiocardiography as reported previously.^{9,10} Briefly a scintillation probe having NaI crystals of 2.5 x 5.0 cm was collimated over the left sternal margin of the third intercostal space. One milliliter each of physiological saline solution containing ¹³¹I-albumin and ^{99m}Tc-albumin was injected via the right medial antecubital vein to measure CO at rest and during exercise respectively. Immediately after the injection, it was flushed with about 10 ml of physiological saline solution. The output of the probe was recorded by magnetic tape recorder. During the replay the energy levels of ¹³¹I and ^{99m}Tc were separated by pulse height analyzer and rate-meter respectively, and the radiocardiograms of both nuclides were obtained. Thus, we yielded a total of 4 radiocardiograms, twice each by ¹³¹I-albumin (doses:

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TABLE I

No.	Name	Age	Sex	Diagnosis	BSA (m ²)
<i>Propranolol-treated group</i>					
1	K.N.	26	M	Hypertension	1.77
2	T.K.	42	M	Effort angina	1.48
3	K.N.	42	M	Rest angina	1.64
4	T.I.	57	M	Normal	1.47
5	S.T.	36	M	Normal	1.84
6	K.S.	38	F	Hypertension	1.41
7	T.Y.	41	F	Hypertension	1.57
8	K.T.	49	M	Normal	1.59
9	K.W.	66	M	Effort angina	1.87
10	T.S.	26	M	Hypertension	1.42
<i>Pindolol-treated group</i>					
11	T.Y.	35	M	Normal	1.63
12	M.H.	43	M	Normal	1.74
13	S.K.	61	M	Hypertension	1.50
14	K.H.	57	M	Hypertension	1.65
<i>Diltiazem-treated group</i>					
15	S.T.	54	M	Hypertension	1.65
16	T.M.	47	M	Hypertension	1.73
17	M.T.	27	M	Normal	1.75
18	S.K.	39	M	Normal	1.69
19	T.K.	39	M	Hypertension	1.57
20	T.K.	48	M	Hypertension	1.62
21	F.S.	65	M	Old MI	1.50
22	I.T.	72	M	Effort angina	1.42
23	T.N.	47	M	Hypertension	1.59
24	O.N.	47	M	Normal	1.69

Legends: BSA=Body surface area; M=Male; F=Female; MI=Myocardial infarction

20, 40 μ Ci) and ^{99m}Tc -albumin (doses: 100, 200 μ Ci), by this method.

All medications were restricted for 24 hr before the test. The subjects were fasted for 14 hr before the test, with exception of water. They were kept in a recumbent position for 30 min before the test. After the first measurements of CO using ^{131}I -albumin, blood pressure (BP) and heart rate (HR) in a supine position, the subjects were instructed to exercise for 4 min with bicycle ergometer (Monark Co., Sweden) in a supine position. The exercise load was 30 watt which did not cause anginal exhaustion in all cases. The second determination of CO was done 3'30" after the start of the exercise by using ^{99m}Tc -albumin. Subsequently, 60 mg of diltiazem and 20 mg of propranolol were given orally to

10 cases each respectively. At a dose level of 5 mg, pindolol which is a β -blocking agent somewhat different from propranolol in action was also given orally in 4 cases. The measurement of CO at rest and on exercise was repeated 90 min after the medications. The following indices were calculated from the values obtained by the above measurements.

$$\text{CO (L/min)} = \text{BV} \times \frac{\text{FDV}}{\int_0^\infty f(t)dt}$$

where $\int_0^\infty f(t)dt$: The area under the isotope dilution curve.

FDV: The value at the equilibrium after injection of radioisotope.

BV: The blood volume determin-

ed by the totally injected radioisotope count which was divided by one blood count at the equilibrium.

The ratio of CO at blood volume (CO/BV) =

$$\frac{\text{FDV}}{\int_0^\infty (t) dt}$$

Stroke volume (SV) (ml/beat) =

$$\text{CO} \times 1000 / \text{heart rate (HR)}$$

Mean blood pressure (mBP) (mmHg) =

$$\text{DBP} + 1/3 (\text{PP})$$

where DBP represents diastolic pressure and PP represents pulse pressure.

Cardiac work index (CWI) ($\text{g} \cdot \text{m}/\text{min}/\text{m}^2$) =

$$\frac{\text{CO} \times \text{mBP} \times 13.6}{1,000 \times \text{BSA}}$$

where BSA represents body surface area.

Stroke work index (SWI) ($\text{g} \cdot \text{m}/\text{beat}/\text{m}^2$) =

$$\frac{\text{SV} \times \text{mBP} \times 13.6}{1,000 \times \text{BSA}}$$

Total systemic resistance (TSR)

$$(\text{dynes} \cdot \text{sec} \cdot \text{cm}^{-5}) =$$

$$\text{mBP} \times 80 / \text{CO}$$

Rate-Pressure-Products (RPP) =

$$\text{HR} \times \text{SBP}$$

where SBP represents systolic pressure.

The data were analyzed by paired Student *t*-test and one-way layout analysis of variance.¹¹

RESULTS

None of the 24 subjects had anginal pain during the exercise. Only a few subjects complained of fatigue of lower extremities. Table II shows the effects of propranolol, pindolol and diltiazem on hemodynamic indices. Analysis of variance was applied to assess equality of each index of 3 groups at rest before the medication, which proved the absence of significant difference on equality among them. In addition to this, equality of the changes of each index among the groups due to exercise was examined before the medications, but there existed no significant differences on 11 indices among 3 groups except

Fig.1. Heart rate (HR) at rest and during exercise. Solid lines indicate the control value and dotted lines, that after the medications.

HR is significantly decreased at rest and during exercise on propranolol only.

for DBP. Therefore, as far as the 11 indices are concerned, there were no differences for amount of exercise load among 3 groups. DBP was different statistically between propranolol-treated and diltiazem-treated groups at less than 1% level of significance, i.e., because DBP elevated after exercise in diltiazem group (before medication), the change in DBP after administration of diltiazem was evaluated carefully.

1. Effect on HR (Fig. 1)

HR was decreased after administration of propranolol in all 10 cases, viz., HR at rest was decreased by 18.3% and HR after exercise was decreased by 15.5%, indicating significant decrease in HR.

The values of HR at rest and after exercise were decreased by 9.1% and 11.2% respectively after pindolol, revealing no statistically significant decrease. Though 3 of the 4 subjects showed the decrease in HR, the remaining 1 showed a slight increase in HR after the drug.

HR at rest was decreased by 6.2% after administration of diltiazem, while the postexercise value remained unchanged after the drug. This indicated that the drug had no effect on HR at rest as well as on exercise.

TABLE II HAEMODYNAMIC PARAMETERS BEFORE AND AFTER MEDICATION

Case No.	Condition	HR (/min)	SBP/DBP (mmHg)	CO (l/min)	CI (l/min/m ²)	SV (ml)	SI (ml/m ²)	SWI (g·m/m ²)	CWI (g·m/min/m ²)	TSR (dynes·sec·cm ⁻⁵)	RPP (HR × Ps)
1	Rest	66	136/85	7.01	3.97	106	60	83.2	5507	1164	8976
	B.M. Exercise	96	152/90	14.40	8.14	150	85	128.3	12288	617	14592
	Rest	57	132/84	5.70	3.23	100	57	77.5	4393	1403	7524
	A.M. Exercise	88	132/98	7.78	4.41	88	50	74.1	6537	1121	11616
2	Rest	54	112/80	4.52	3.05	84	57	70.5	3775	1610	6048
	B.M. Exercise	100	138/82	11.07	7.48	111	75	103.0	10274	730	13800
	Rest	46	102/65	4.43	2.99	96	65	68.1	3131	1391	4692
	A.M. Exercise	92	128/85	8.65	5.84	94	64	86.2	7863	917	11776
3	Rest	67	108/76	7.09	4.34	106	65	76.9	5135	982	7236
	B.M. Exercise	108	156/95	11.76	7.19	109	67	104.8	11245	782	16848
	Rest	58	110/76	5.19	3.17	89	55	65.1	3750	1341	6380
	A.M. Exercise	100	142/85	10.63	6.50	106	65	91.9	9194	782	14200
4	Rest	54	146/76	4.53	3.08	84	57	76.7	4147	1748	7884
	B.M. Exercise	108	196/95	12.08	8.22	112	76	133.3	14421	854	21168
	Rest	48	150/72	4.91	3.34	102	70	93.3	4452	1597	7200
	A.M. Exercise	87	182/95	8.73	5.94	100	68	117.4	10259	1163	15834
5	Rest	57	119/80	6.68	3.63	117	64	80.9	4591	1113	6783
	B.M. Exercise	92	138/85	12.11	6.58	132	72	100.9	9217	680	12696
	Rest	50	122/82	5.88	3.20	118	64	82.7	4134	1293	6100
	A.M. Exercise	81	142/85	11.17	6.07	138	75	106.1	8585	744	11502
6	Rest	80	149/90	6.55	4.66	82	58	86.8	6971	1343	11920
	B.M. Exercise	128	162/95	9.74	6.93	76	54	85.9	11027	961	20736
	Rest	60	129/75	4.84	3.44	81	57	72.1	4351	1538	7740
	A.M. Exercise	105	149/85	10.54	7.50	100	71	102.4	10812	805	15645
7	Rest	69	136/80	9.65	6.15	140	89	119.8	8280	821	9384
	B.M. Exercise	104	156/84	14.28	9.09	137	87	127.8	13351	605	16224
	Rest	60	140/80	7.26	4.62	121	77	105.0	6283	1101	8400
	A.M. Exercise	92	146/65	11.74	7.48	128	81	101.3	9359	627	13432
8	Rest	75	126/78	6.77	4.26	90	57	72.9	5446	1110	9450
	B.M. Exercise	112	138/80	10.74	6.75	96	60	80.8	9088	737	15456
	Rest	63	115/80	4.85	3.05	77	48	60.1	3816	1518	7245
	A.M. Exercise	96	148/85	8.98	5.65	93	59	85.1	8145	944	14208
9	Rest	69	136/90	5.97	3.20	87	46	67.6	4700	1448	9384
	B.M. Exercise	112	152/88	11.20	6.00	100	54	81.5	9058	793	17024
	Rest	59	110/75	4.98	2.67	84	45	53.2	3159	1397	6490
	A.M. Exercise	93	132/85	9.40	5.04	101	54	74.2	6922	860	12276

10	B.M.	Rest	93	128/98	5.67	3.99	61	43	63.2	5861	1524	11904
		Exercise	132	146/105	11.50	8.11	87	61	98.7	13125	765	19272
	A.M.	Rest	66	148/105	3.57	2.52	54	38	61.5	4078	2667	9768
		Exercise	108	146/115	8.29	5.84	77	54	91.8	9928	1206	15768
11	B.M.	Rest	60	108/70	5.85	3.60	97	60	67.7	4064	1135	6480
		Exercise	99	128/84	13.26	8.16	134	82	109.5	10876	591	12672
	A.M.	Rest	63	102/64	7.77	4.78	123	76	79.6	5006	793	6426
		Exercise	100	132/58	11.72	7.21	117	72	80.3	8041	560	13200
12	B.M.	Rest	63	122/80	5.87	3.39	93	54	68.3	4288	1268	7696
		Exercise	104	172/100	14.00	8.07	134	78	131.5	13609	709	17888
	A.M.	Rest	53	106/75	5.44	3.13	103	59	68.2	3618	1250	5618
		Exercise	96	145/90	11.21	6.46	117	67	98.4	9488	771	13920
13	B.M.	Rest	64	172/95	5.65	3.76	88	59	97.1	6188	1714	11008
		Exercise	124	206/108	12.18	8.12	98	65	124.6	15570	926	25544
	A.M.	Rest	54	152/80	6.47	4.31	120	80	113.2	6096	1285	8208
		Exercise	90	162/108	7.73	5.15	86	57	97.7	8825	1304	14580
14	B.M.	Rest	78	132/84	7.41	4.50	95	58	80.5	6242	1101	10296
		Exercise	112	186/100	11.10	6.75	99	60	105.3	11842	929	20832
	A.M.	Rest	68	132/85	6.60	4.01	97	59	83.4	5672	1261	8976
		Exercise	100	164/105	7.64	4.64	76	46	78.2	7888	1308	16400
15	B.M.	Rest	69	126/82	7.51	4.57	109	66	87.1	6029	1033	8694
		Exercise	93	138/85	11.07	6.73	119	72	100.9	9427	744	12834
	A.M.	Rest	70	120/75	7.89	4.79	112	68	83.2	5863	912	8400
		Exercise	93	136/85	10.97	6.67	118	72	99.9	9253	743	12648
16	B.M.	Rest	56	126/80	6.50	3.76	116	67	86.6	4858	1169	7056
		Exercise	92	152/100	11.09	6.41	121	70	111.4	10200	844	13984
	A.M.	Rest	56	109/68	6.51	3.76	116	67	74.7	4193	1008	6104
		Exercise	88	154/100	10.24	5.92	116	67	107.5	9500	922	13552
17	B.M.	Rest	69	128/72	7.84	4.48	114	65	80.4	5544	929	8832
		Exercise	111	166/108	12.16	6.95	110	63	108.8	12004	836	18426
	A.M.	Rest	62	122/70	6.32	3.61	102	58	68.6	4271	1101	7564
		Exercise	102	154/85	11.76	6.72	115	66	98.9	9870	735	15709
18	B.M.	Rest	78	129/88	7.66	4.55	98	58	82.8	6497	1097	10062
		Exercise	120	162/108	17.00	10.07	141	84	143.9	17256	593	19440
	A.M.	Rest	66	124/72	5.87	3.48	89	53	64.2	4212	1213	8184
		Exercise	111	162/100	11.17	6.63	101	60	98.7	10910	867	17982
19	B.M.	Rest	57	152/98	6.22	3.96	109	69	108.9	6247	1492	8664
		Exercise	108	184/112	11.92	7.59	110	70	129.5	14039	913	19872
	A.M.	Rest	56	132/85	6.40	4.07	114	73	101.3	5646	1275	7392
		Exercise	116	196/100	14.68	9.35	127	81	145.4	16785	719	22736

Case No.	Condition	HR (/min)	SBP/DBP (mmHg)	CO (l/min)	CI (l/min/m ²)	SV (ml)	SI (ml/m ²)	SWI (g·m/m ²)	CWI (g·m/min/m ²)	TSR (dynes·sec·cm ⁻⁵)	RPP (HR × Ps)
20	Rest	56	126/78	6.42	3.92	115	71	83.0	4585	1072	7056
	B.M. Exercise	93	164/105	11.10	6.85	119	74	125.8	11645	901	15252
	Rest	62	116/70	5.74	3.54	93	57	65.9	4092	1185	7192
	A.M. Exercise	112	166/105	11.72	7.23	105	65	110.5	12291	853	18592
21	Rest	75	122/60	5.96	3.91	79	53	56.4	4307	1087	9150
	B.M. Exercise	104	142/75	7.53	5.02	72	48	63.3	6622	1031	14768
	Rest	66	110/60	5.18	3.45	79	52	54.5	3613	1189	7260
	A.M. Exercise	100	142/70	8.02	5.35	80	53	65.6	6621	908	14200
22	Rest	72	134/70	6.06	4.26	84	59	73.0	5272	1201	9648
	B.M. Exercise	120	182/100	10.47	7.37	87	61	105.4	12730	970	21840
	Rest	66	126/75	6.03	4.24	91	64	80.1	5305	1221	8316
	A.M. Exercise	112	174/84	9.96	7.01	89	63	97.7	10868	915	19488
23	Rest	60	156/85	6.11	3.85	102	64	94.9	5707	1427	9360
	B.M. Exercise	108	186/100	14.10	8.90	131	82	145.0	15735	737	20088
	Rest	57	116/60	7.03	4.44	123	78	81.7	4650	876	6612
	A.M. Exercise	108	172/75	14.00	8.81	129	82	119.3	12820	611	18576
24	Rest	46	122/84	4.53	2.69	99	58	76.5	3549	1713	5612
	B.M. Exercise	92	146/95	11.89	7.06	129	77	106.8	9794	686	13432
	Rest	42	121/80	4.45	2.64	106	63	83.1	3483	1743	5082
	A.M. Exercise	84	136/82	10.28	6.10	122	73	99.3	8296	778	11424

Legends: B.M.=Before medication; A.M.=After medication; HR=Heart rate; SBP/DBP=Systolic blood pressure/Diastolic blood pressure;
 CO=Cardiac output; CI=Cardiac index; SV=Stroke volume; SI=Stroke index; SWI=Stroke work index; CWI=Cardiac work index;
 TSR=Total systemic resistance; RPP=Rate pressure products.

Fig. 2. Systolic blood pressure (SBP) at rest and during exercise.

Solid lines indicate the control value and dotted lines, that after the medications.

SBP is decreased during exercise on propranolol and at rest on diltiazem.

Fig. 3. Cardiac index (CI) at rest and during exercise.

Solid lines indicate the control value and dotted lines, that after the medications.

CI is decreased both at rest and during exercise on propranolol, and only during exercise on pindolol.

2. Effect on BP (Fig. 2)

BP at rest was not influenced by propranolol, but only postexercise SBP was decreased significantly by 5.2% after the drug. DBP at rest and during exercise remained unchanged after the drug. DBP and SBP at rest were decreased in 3 of the 4 subjects after pindolol whereas in the remaining one case both pressures did not change after the drug. The decrease of BP after the drug was 8.3% in average. DBP and SBP after exercise were decreased and increased in 3 and 1 subject respectively after pindolol, indicating the decrease of 12.7%. Diltiazem induced a slight fall in BP in all 10 cases with an average of 9.1% which was statistically significant ($p < 0.01$). However, diltiazem elicited only a 1.9% lowering of BP after exercise and the lowering was not significant statistically.

3. Effect on CO and cardiac index (CI) (Fig. 3)

CO and CI at rest were reduced by 21.0% each respectively after administration of propranolol. Both values after exercise were also decreased by

the same degrees as those at rest ($p < 0.01$). CO and CI at rest were not influenced by pindolol while the postexercise values were decreased by 24.1% after the drug ($p < 0.05$). The changes in rest and postexercise CO and CI were not significant statistically after administration of diltiazem, being only 5.2% in the mean decrease ($p > 0.1$).

4. Effect on stroke volume (SV) and stroke index (SI)

SV and SI at rest remained unchanged after propranolol. In all cases the rest SV and SI were increased by 19.4% in average after administration of pindolol, but the changes were not significant statistically because the subjects examined might be few in number. The postexercise changes in SV and SI were significant after pindolol, the mean decrease being 14.7% ($p < 0.01$). There were no significant changes in rest and postexercise SV and SI of diltiazem-treated group.

5. Effect on stroke work index (SWI) (Fig. 4)

Fig.4. Stroke work index (SWI) at rest and during exercise.

Solid lines indicate the control value and dotted lines, that after the medications.

SWI is decreased during exercise on pindolol and at rest on diltiazem.

Fig.5. Cardiac work (CW) at rest and during exercise.

Solid lines indicate the control value and dotted lines, that after the medications.

CW is decreased both at rest and during exercise on propranolol, during exercise on pindolol, and at rest on diltiazem.

Fig.6. Total systemic resistance (TSR) at rest and during exercise.

Solid lines indicate the control value and dotted lines, that after medications.

There is no significant change between control and posttreatment values.

SWI at rest and after exercise was decreased by 9.2% and 8.9% respectively in propranolol-treated group, but the decreases were not significant statistically. The rest SWI was increased by 9.8% after pindolol, but the change was not significant statistically. On the other hand, the postexercise SWI was decreased significantly by 24.6% in pindolol-treated group ($p < 0.01$). The SWI at rest was decreased with the average of 8.8% which was significant at the level of 5%, but the decrease in the postexercise SWI in 8 of the 10 cases was not statistically significant in diltiazem-treated group ($0.05 < p < 0.1$).

6. Effect on cardiac work index (CWI) (Fig. 5)

The rest and postexercise CWI were decreased significantly by 23.7% and 22.5% respectively in propranolol-treated group ($p < 0.01$). Although the rest CWI remained unchanged in pindolol group, the drug caused the greatest decrease of the postexercise CWI (34%) among 3 groups ($p < 0.05$). CWI at rest was decreased by 13.8% in diltiazem group at 1% level of significance while

Fig. 7. Rate-pressure-product (RPP) at rest and during exercise.

Solid lines indicate the control value and dotted lines, that after the medications.

RPP is decreased both at rest and on exercise on propranolol, and only at rest on diltiazem.

Pindolol shows a decrease in RPP which is not statistically significant.

the postexercise CWI was not decreased significantly (10.2%, $p < 0.1$).

7. Effect on TSR (Fig. 6)

The rest and postexercise values of TSR were increased by 22.7% and 21.9% respectively in propranolol group, but the values varied greatly to show no statistical differences before and after administration of the drug. Pindolol induced 12.1% decrease and 25.0% increase at rest and postexercise TSR respectively, but the changes were not significant statistically. The rest and postexercise values of TSR were decreased by 4.1% and 2.5% respectively in diltiazem group, indicating no appreciable change.

8. Effect on RPP (Fig. 7)

RPP was decreased significantly after administration of propranolol ($p < 0.01$), decrease

being 19.6% and 18.8% at rest and after exercise respectively. The rest and postexercise values of RPP were decreased by 17.6% and 24.5% respectively in pindolol group, but the decreases were not statistically significant. RPP at rest was significantly decreased in 9 of the 10 subjects of diltiazem group with the average of 14.3% ($p < 0.01$). RPP after exercise was decreased in 8 of the 10 diltiazem-treated subjects with the average of 3.0%, indicating no significant change statistically.

DISCUSSION

1. HR

The hemodynamic actions of β -blocking agents, propranolol and pindolol, were somewhat different each other. Propranolol induced decreases in rest and post-exercise HR to the same extent while pindolol exerted a greater action of decreasing only postexercise HR. The intrinsic sympathomimetic action of pindolol may underlie the difference of actions between pindolol and propranolol.^{12,13} The range of decrease in rest HR due to propranolol is reported to be between 9 and 27%.¹⁴⁻¹⁶ The result obtained by the present work (18.3%) was also within the range of reports. Propranolol produces a similar decrease in postexercise HR.^{7,17} Winsor¹⁸ demonstrated that rest and postexercise values of HR were decreased by 8% and 11% respectively after pindolol in a dose of 5 mg (equal to the dose given in this study). The negative chronotropic action of 1 mg of propranolol was also found to be stronger than that of 1 mg of pindolol.¹⁸ Tsukiyama et al.¹³ and Matsunaga et al.¹⁹ reported the results similar to this. Our study indicated that diltiazem not induce a significant decrease in HR. However, animal experiments prove the presence of a negative chronotropic action in the drug. This is assumed to be the fact that diltiazem being a Ca-antagonist inhibits the spontaneous electric discharge of sinoatrial pacemaker cells.²⁰

2. BP

Pritchard et al.²¹ mentioned first the anti-hypertensive effect of propranolol. The CO lowering action,²² the inhibitory action against renin²³ and the action through the central nervous system²⁴ have been proposed as the mechanism of the hypotensive action of propranolol, but its mechanism is still not yet established. The decrease in CO and increase in TSR are major changes which manifest im-

mediately after administration of propranolol and therefore the lowering of mBP is slight.^{14,15} In fact, a significant fall in BP was not seen in our study. Because the β -effect is peripheral vasodilation, β -blocking agents elicit the augmentation of TSR. In this context the result obtained by our study on propranolol was reasonable. A rise of BP after exercise was blocked significantly by propranolol, indicating that the increased CO due to exercise is inhibited by the drug. Pindolol caused a decrease in BP at rest and TSR without CO change. These actions differed from those of propranolol, which were not β -blocking effects. Ogino²⁵ found that pindolol has an anti-hypertensive action, but it has no action to increase TSR. TSR is assumed to be decreased through the intrinsic sympathomimetic action of pindolol.

In experimental animals, diltiazem elicits a fall of BP, particularly a fall of diastolic pressure.² However, clinically the drug does not exert a significant hypotensive action in normotensive patients and in contrast the drug exerts an hypotensive effect on patients with hypertension and the drug effect is potentiated by concurrent use with other anti-hypertensive drug.²⁶ We could observed the hypotensive effect only at rest and not after exercise. The hypotensive action of diltiazem at rest differed from that of propranolol, i.e., the action of the former was consequent to the decreased TSR and not due to the decreased CO.

3. CO, CI and SV

CO and CI are influenced by preload, HR and myocardial contractility. CO at rest and after exercise was decreased by propranolol in our data. This decrease was due to the decrease in HR because SV remained unchanged. Tsukiyama et al.¹³ Robin et al.¹⁴ and Aronow et al.¹⁵ confirmed the action of propranolol to decrease CO. A decrease in CO after exercise similar to that at rest by propranolol was reported by Aronow et al.¹⁷ Dwyer et al.²⁷ showed that CI was decreased by 39% in patients whose anginal pain disappeared whereas the change in CI was unremarkable after administration of propranolol in patients whose anginal pain did not disappear. Unlike propranolol, in our data pindolol was unable to induce the decrease in CO at rest while it reduced postexercise CO markedly. The reason for this may be that when the basal sympathetic activity at rest is not high, pindolol causes a tendency to increase SV through the intrinsic sympathomi-

metic action rather than exerting its β -blocking action. Since pindolol exhibited sufficiently the β -blocking action on the postexercise CO, the reason for no change of CO at rest should not be attributed to insufficiency in the dose of pindolol. Since 10 mg of pindolol is reported to be equivalent to 40 mg of propranolol,²⁸ the dose of the former given in this study was also equal to that of the latter. That pindolol does not reduce CO in a basal state is an advantageous property of the drug because heart failure would be aggravated rarely by this drug, i.e., pindolol can be used advantageously in the treatment of angina of effort.

Although diltiazem shows experimentally a weak negative inotropic action,²⁹ its strong vasodilator action leads to an increase in CO².

Clinically, CO is not always increased by diltiazem and it is rather decreased.⁸ According to our data, CO tended to decrease slightly without significant change after administration of diltiazem. An increase in CO of experimental animals may be attributed to the increased myocardial contractility resulting from the decrease in afterload. Clinically, as the negative inotropic effect is not seen clearly after oral administration of diltiazem (60 mg), the decrease in CO would result from a decrease in preload due to reduction of venous return.⁸

4. CWI, SWI and RPP

We found that the rest and postexercise CWI are decreased equally by propranolol. CWI at rest was not decreased by pindolol while the postexercise CWI was markedly decreased. The postexercise SWI was decreased by pindolol, but both propranolol and pindolol produced no change in the rest SWI. The reason why pindolol does not reduce the rest CWI is assumed to counterbalance the β -blocking action by the intrinsic sympathomimetic action. Therefore, the β -blocking action of pindolol may surpass the intrinsic sympathomimetic action after exercise. This action of pindolol is favorable to the treatment of effort angina because a risk to induce heart failure would be little.

Diltiazem elicited decreases in both CWI and SWI at rest, but such changes were not seen in the post-exercise CWI and SWI.

Kusukawa et al.⁸ confirmed a significant decrease in CWI by diltiazem. However, the results did not always coincide with that of animal experiments in which CO is increased significantly by diltiazem.² An increase in CWI

after exercise was not inhibited by diltiazem. The fact suggests that diltiazem has no β -blocking action.

RPP which is determined instead of tension time index is correlated with myocardial oxygen consumption.³⁰ RPP at rest and after exercise was decreased by about 20% each respectively after administration of propranolol, indicating that the drug induced a decrease in myocardial oxygen consumption. Similarly, RPP was decreased by pindolol, but the decrease was greater after exercise than at rest. RPP at rest was decreased significantly by diltiazem while that after exercise was not affected by the drug at all. Oyama et al.³¹ confirmed the effect of diltiazem to reduce RPP and mentioned that the antianginal effect of the drug should partly result from its inhibitory action against myocardial oxygen demand. Sublingual administration of nifedipine which is a Ca-antagonistic agent like diltiazem induces almost no or slight increase in HR, lowering of mBP and significant decrease in TSR, but nifedipine has no action to reduce tension time index.^{20,32} Nifedipine is somewhat different from diltiazem in these actions. As discussed above, diltiazem exerts an anti-anginal effect at least partly through the inhibitory mechanism on myocardial oxygen demand at rest. However, the drug has no action like β -blockade and it rather exhibits an anti-anginal effect through the coronary vasospasmolytic mechanism resulting in an increase in coronary blood flow after exercise. This can be understood by the fact that the drug is more effective on rest angina than on effort angina and its effect is particularly remarkable on variant angina.⁵

SUMMARY

The effects of propranolol, pindolol and diltiazem on systemic hemodynamics at rest and during bicycle exercise were studied in 24 patients. Radiocardiographic determination of cardiac output (CO) was done by using ¹³¹I-albumin and ^{99m}Tc-albumin at rest and on exercise, respectively. CO was determined 4 times in 90 min during the experiment.

Patients were divided into 3 groups: Group I (N = 10) was administered propranolol, group II (N = 4) pindolol and group III (N = 10) diltiazem. Heart rate (HR), CO, cardiac work index (CWI) and rate-pressure-product (RPP) were decreased equally at rest and during exercise after propranolol. The decrease in HR, CO, CWI and RPP at rest after pindolol was not significant statis-

tically, whereas that during exercise was significant after the drug. Diltiazem caused significant decrease in HR, BP, CWI and RPP at rest, but there was no appreciable change in these values during exercise.

It may be concluded that myocardial oxygen consumption is decreased by propranolol at rest and during exercise, by pindolol during exercise only and by diltiazem at rest only. Evidences suggest that diltiazem has no β -blocking action and its anti-anginal effect is mediated through the coronary vasodilator action.

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