Hemodynamic Effect of Bunitrolol on Patients with Ischemic Heart Disease

Comparison with Propranolol

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SUMMARY

Acute hemodynamic changes induced by two beta-blocking agents, bunitrolol and propranolol, in patients with ischemic heart disease were studied.

Besides possessing negative chronotropic and inotropic effects which were demonstrated by decreased heart rate (HR), cardiac index (CI) and double product (DP) of the heart, propranolol significantly increased systemic vascular resistance (SVR, 12%, $p<0.05$) and the time constant of left ventricular (LV) isovolumic pressure fall (T, 10%, $p<0.01$). With bunitrolol, no significant changes were observed in indexes reflecting chronotropic and inotropic states of the heart, and CI and DP were essentially unchanged. Only LV systolic pressure (−5%, $p<0.01$), LV end-diastolic pressure (EDP, −17%, $p<0.01$) and T (−10%, $p<0.05$) decreased significantly. Systemic vascular resistance (SVR) decreased, though insignificantly.

Myocardial oxygen supply-demand balance in the resting state was not improved by propranolol as evidenced by the fact that CI decreased in proportion to the decline in DP. In contrast, ischemia at rest was apparently improved by bunitrolol because LV wall stress decreased due to the reduction in LV volume which was suggested by the decline in LV systolic pressure and LVEDP while CI remained constant. Improvement of the time constant T might be strong evidence of relief from ischemia.

Bunitrolol might be effective even in patients with overt heart

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failure, especially that due to ischemic heart disease because of its lack of negative inotropic action and its ameliorating effect on ischemia at rest.

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BETA-BLOCKING agents are widely used for the treatment of ischemic heart disease and high blood pressure. However, untoward side effects of these agents such as heart failure, decreased coronary blood flow and increased myocardial oxygen demand due to dilatation of the left ventricle secondary to the negative inotropic and chronotropic actions of these drugs are sometimes observed.

Bunitrolol (Kö 1366, Boehringer Ingelheim, West Germany) is a very potent nonselective beta-blocking agent in terms of its ability to antagonize the chronotropic and inotropic effects of isoproterenol.[1)-3)] Furthermore, moderate but consistent positive chronotropic and inotropic effects, i.e. ISA, at relatively low dosage in the resting state[3)] and potent vasodilator action[2),3)] have also been reported and these characteristics favor its use in the treatment of hypertension. The mechanisms of the vasodilator action have not been clarified as yet, but selective alpha-1 blocking activity[4)] and Ca^{++} antagonist activity[5)] have been reported recently.

Bunitrolol is also effective in exercise induced ischemia because of its strongly antagonistic activity to sympathetic nerve stimulation,[6)] but there have been very few actual hemodynamic assessments of this unique beta-blocking agent in patients with ischemic heart disease.[7),8)] The purpose of this study is to assess the actual hemodynamic effects of bunitrolol in patients with ischemic heart disease and to clarify the differences between those of propranolol.

Patients and Methods

Using a protocol approved by the Human Subjects Ethical Committee of Tokyo University Hospital, we studied 17 patients with ischemic heart disease. All patients were referred for cardiac catheterization, including coronary cineangiography, because of chest pain and/or positive exercise tolerance test; a greater than 75% stenosis in at least one major coronary artery was documented in all cases. Administration of drugs such as nitrates, beta-blockers and Ca^{++} antagonists was stopped the morning before patients had catheters inserted. After informed consent had been obtained, patients

were premedicated with 10 mg diazepam. Catheterization of the right and left sides of the heart was performed via either the brachial or femoral approach under local lidocaine anesthesia.

After routine diagnostic catheterization, 15 min were allowed for recovery from the effects of injected contrast material. A 7F balloon-tip thermodilution catheter (Gould Inc., Calif.) was advanced into the pulmonary artery and connected to a Statham P23 DI pressure transducer (Gould Inc.). A 7F Millar-micromanometer tipped catheter (Millar Inc., Texas) was also advanced into the left ventricle. Measurements of cardiac output by thermodilution were performed in triplicate using a Fukuda Denshi EH-11 thermodilution computer (Fukuda Denshi Ltd., Tokyo). Signals were amplified by a Sanei Sokki 146 polygraph system (Nihon Denki Sanei, Tokyo) and stored on magnetic tape by a data recorder A-49 (Sony Magnescale Inc., Tokyo). Signals were also recorded on a Mingograf ink jet recorder (Erma-Schonander, Sweden). Stored data were analyzed by a DEC LSI 11/2 microcomputer system (Digital Equipment Co., Massachusetts).

Using this system, heart rate (HR), right atrial pressure (RAP), pulmonary wedge pressure (PCW), aortic pressure (AOP) and left ventricular systolic (LVSP) and end-diastolic pressure (LVEDP) were obtained. Parameters derived from left ventricular pressure such as LV dp/dt, LV dp/dt/p, LV(−)dp/dt and the time constant of left ventricular isovolumic pressure fall (T) by Weiss's method,[9] were calculated by computer. However, in the event that the micromanometer tipped catheter could not be advanced into the left ventricle these parameters were not obtained.

Systemic vascular resistance (SVR) in dynes·sec·cm^{-5} was calculated by the following formula: $[(MAP-RAP)/CO]\times 80$. Double product (DP) of the heart in mmHg/min was calculated by the following formula: HR$\times$ LVSP, where MAP and CO are mean aortic pressure and cardiac output, respectively.

After control measurements were done, either 5 mg bunitrolol (9 patients) or 20 mg propranolol (8 patients) were slowly administered intravenously. No serious side effects were observed in either group, and 10 min later the hemodynamic measurements were repeated.

We compared measurements before and after bunitrolol or propranolol administration, using Student's t-test for paired data, and between the effects of two drugs, using Student's t-test for unpaired data. Values are expressed as means$\pm$SD.

Results

Effects of bunitrolol (Table I)

Following administration of bunitrolol, LVSP, LVEDP and T decreased significantly. HR, CI, DP, LV dp/dt, LV dp/dt/p and LV(−)dp/dt were

Table I. Hemodynamic

Case	Age, Sex	Diagnosis	HR (/min)		LVSP (mmHg)		LVEDP (mmHg)		CI (L/min/m²)	
			(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)
1. TY	47 M	LAD, CX, RCA	68	71	136	128	20	14	3.72	4.31
2. TE	47 M	CX	60	64	123	119	26	19	3.64	3.55
3. KK	52 M	LAD, CX, RCA	66	66	119	114	17	13	3.70	3.89
4. SS	48 M	RCA	93	84	109	101	13	13	3.61	3.32
5. MM	61 F	LAD, CX, RCA	54	60	192	183	18	16	2.64	2.41
6. TS	56 M	LAD, CX	69	69	—	—	—	—	3.46	3.76
7. HY	48 M	LAD, CX	66	68	145	139	25	22	3.93	3.61
8. SO	50 M	LAD	63	60	—	—	—	—	4.03	3.31
9. TK	72 M	LAD	54	54	—	—	—	—	3.02	3.22
		mean	66	66	137	131	20	16	3.53	3.49
		SD	12	9	30	29	5	4	0.44	0.53
		p	NS		0.01		0.01		NS	

LAD=anterior descending branch of coronary artery; CX=circumflex branch; RCA=right coronary artery; RA=ramus medianus; LMT=left main trunk. Greater than 50% stenosis in LMT and more than 75% stenosis in other coronary arteries were documented. HR=heart rate;

Table II. Hemodynamic

Case	Age, Sex	Diagnosis	HR (/min)		LVSP (mmHg)		LVEDP (mmHg)		CI (L/min/m²)	
			(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)
1. MM	60 M	LMT, LAD, RA	63	63	127	132	11	18	2.95	2.80
2. MY	55 M	LAD, RCA, RA	—	—	119	112	13	13	—	—
3. SS	54 M	LAD, CX, RCA	77	66	118	117	5	9	2.85	2.43
4. KN	53 M	LAD, CX, RCA	—	—	—	—	—	—	3.25	2.93
5. IT	48 M	RCA	70	51	123	125	13	14	3.57	3.08
6. RI	67 F	LAD, CX, RCA	60	54	217	208	28	27	2.45	2.05
7. NK	64 M	LAD, CX, RCA	66	52	110	119	11	16	2.33	1.71
8. SY	51 M	LAD, CX, RCA	70	52	128	108	22	16	3.18	2.54
		mean	68	56	135	132	15	16	2.94	2.51
		SD	6	7	37	35	8	6	0.44	0.49
		p	0.01		NS		NS		0.01	

Abbreviations are same as Table I.

not changed. SVR tended to decrease, though insignificantly.

Effects of propranolol (Table II)

HR, CI, DP, LV dp/dt, LV dp/dt/p and LV(−)dp/dt fell significantly in the propranolol group. There were no significant changes in LVSP and LVEDP. SVR and T increased significantly.

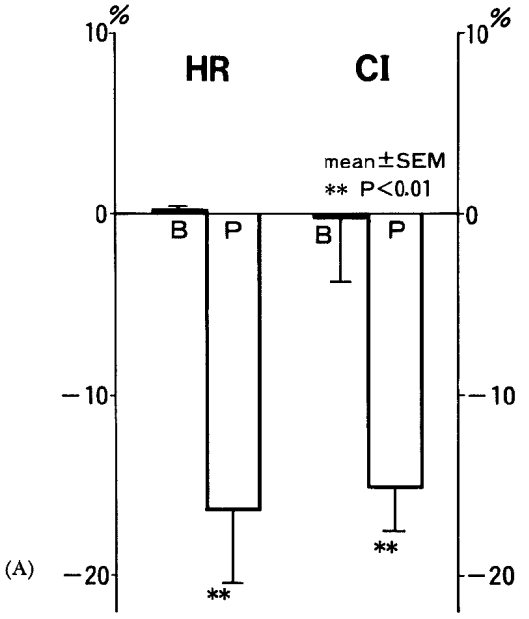
Effects of Bunitrolol

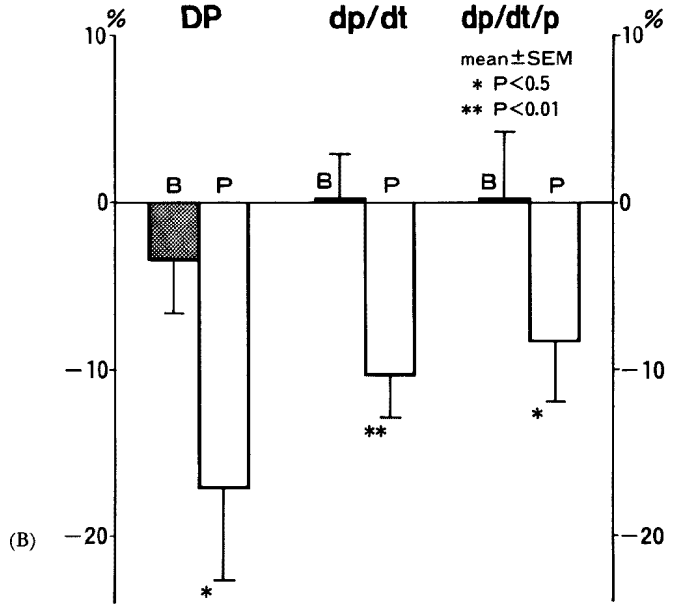
DP (mmHg/min)		SVR (dynes·sec·cm^5)		LV dp/dt (mmHg/sec)		LV dp/dt/p (/sec)		LV(−)dp/dt (mmHg/sec)		T (msec)	
(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)
9248	9230	1246	1067	1757	1763	30.3	29.8	1751	1670	51.0	46.7
7380	7378	1297	1147	1711	1912	27.6	31.0	1618	1531	58.7	55.2
7854	7128	1292	1111	2002	1874	27.0	25.0	1517	1606	53.6	50.5
10137	8484	1343	1459	1535	1542	27.0	29.5	1549	1522	44.2	42.5
10368	10980	2864	3025	1522	1452	22.5	20.1	1839	1704	51.8	53.2
—	—	1407	1266	—	—	—	—	—	—	—	—
9570	9452	—	—	2048	2163	31.4	33.9	1954	2068	61.6	56.9
—	—	1163	1147	—	—	—	—	—	—	—	—
—	—	1701	1628	—	—	—	—	—	—	—	—
9093	8775	1575	1481	1763	1784	27.6	28.2	1705	1684	53.5	50.8
1220	1434	634	653	224	260	3.1	4.9	173	202	6.2	5.4
NS		NS		NS		NS		NS		0.05	

LVSP=left ventricular peak systolic pressure; LVEDP=left ventricular end-diastolic pressure; CI=cardiac index; DP=double product; SVR=systemic vascular resistance; T=time constant of left ventricular isovolumic pressure fall. (b), (a): before and after administration of drug.

Effects of Propranolol

DP (mmHg/min)		SVR (dynes·sec·cm^5)		LV dp/dt (mmHg/sec)		LV dp/dt/p (/sec)		LV(−)dp/dt (mmHg/sec)		T (msec)	
(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)
8001	8316	2079	1968	1777	1679	33.1	30.3	2750	2450	41.7	49.4
—	—	—	—	1596	1491	28.4	26.9	2342	2225	39.3	43.2
9086	7722	1726	1865	1560	1379	25.0	22.7	1986	1875	38.7	46.8
—	—	1553	1704	—	—	—	—	—	—	—	—
8610	6375	1303	1493	1553	1488	26.9	26.4	2089	1896	45.9	49.5
13020	11232	3247	3667	2067	1566	24.3	19.3	1796	1686	64.1	64.7
7260	6188	1918	2481	1268	1170	25.7	20.9	1733	1593	55.0	59.8
8960	5616	1174	1310	1310	1142	20.1	21.4	1894	1558	57.6	61.1
9156	7575	1857	2070	1590	1416	26.2	24.0	2084	1898	48.9	53.5
2010	2057	691	798	273	200	4.0	4.0	356	333	10.0	8.2
0.01		0.05		0.05		0.05		0.01		0.01	





Comparison between bunitrolol and propranolol (Fig. 1)

Percent changes of these parameters induced by the two drugs differed significantly in HR(1.2±6.1 vs −16.4±10.4%, $p<0.01$), CI(−1.0±10.7 vs

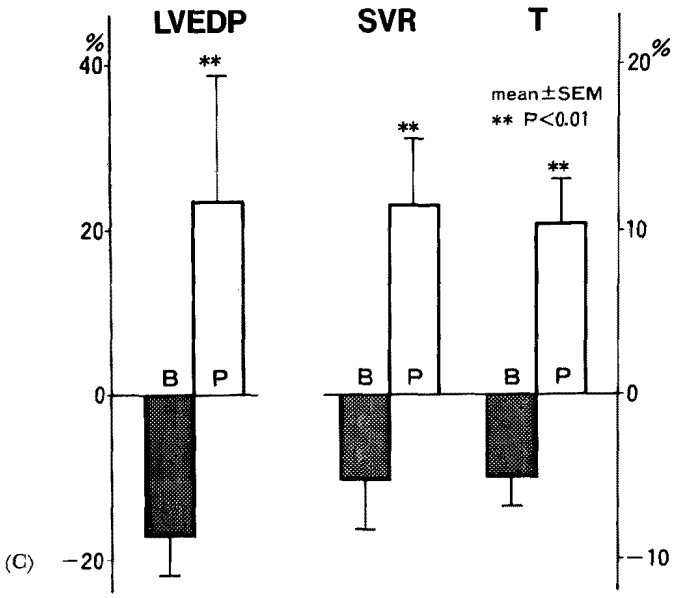


Fig. 1. Comparison between bunitrolol and propranolol.
(A) Percent changes in heart rate (HR) and cardiac index (CI). B= bunitrolol; P=propranolol; mean±SEM. ** $p<0.01$. (B) Percent changes in double product (DP), LV dp/dt and LV dp/dt/p. * $p<0.05$. Abbreviations are same as (A). (C) Percent changes in left ventricular end-diastolic pressure (LVEDP), systemic vascular resistance (SVR) and T. Abbreviations are same as (A).

$-15.2\pm6.9\%$, $p<0.01$), DP(-3.4 ± 7.9 vs $-17.1\pm13.8\%$, $p<0.05$), SVR (-5.2 ± 8.9 vs $11.6\pm10.2\%$, $p<0.01$), LV dp/dt(1.2 ± 6.7 vs $-10.4\pm6.9\%$, $p<0.01$), LV dp/dt/p(1.6 ± 9.6 vs $-8.2\pm9.4\%$, $p<0.05$), LV (−)dp/dt (-1.2 ± 5.8 vs $-8.9\pm4.4\%$, $p<0.05$), T(-4.0 ± 4.0 vs $10.4\pm7.0\%$, $p<0.01$) and LVEDP(-17.3 ± 11.5 vs $23.7\pm39.6\%$, $p<0.01$). In particular, HR and CI were significantly reduced in the propranolol group but unchanged in the bunitrolol group. Furthermore, LVEDP, SVR and T decreased in the bunitrolol group but increased in the propranolol group.

Discussion

In the pentobarbital anesthetized dog, bunitrolol was more than 10 times more potent than propranolol[2),3)] in terms of its ability to antagonize the chronotropic and inotropic effects of isoproterenol. Slight but consistently positive inotropic action of this drug in relatively low doses (less than 100 μg/kg) in the anesthetized dog was also reported.[3)] Studies in healthy human volun-

teers showed that 2.5–3.0 mg of bunitrolol was roughly equivalent in potency to 10 mg of propranolol.[8] Also, it was reported that up to 10 mg of this drug had been administered intravenously to patients with ischemic heart disease or high blood pressure without any serious side effects.[7),10] We administered a relatively low dose of bunitrolol intravenously, 5 mg (65—100 μg/kg) and compared the results with the acute effects of 20 mg propranolol given intravenously.

Significant positive chronotropic and inotropic actions which were observed in animal experiments[3] were not shown in this study in that bunitrolol demonstrated no apparent effects on myocardial contractility and cardiac output, and as a result myocardial oxygen demand-supply balance was not altered. Moreover, the fact that both left ventricular systolic and end-diastolic pressures fell following drug administration suggested a decline in left ventricular volume secondary to afterload reduction. Subsequently, ventricular wall stress fell, and considering that coronary flow was unaltered, myocardial ischemia should have been relieved through this mechanism.

Slight, though insignificant, increments in LV dp/dt and LV dp/dt/p suggested the possibility of enhanced left ventricular contractility through improved myocardial oxygen balance. These findings might also suggest the existence of positive inotropism of this beta-blocking agent, but which of these two possibilities is more likely remains to be determined.

The time constant T has been considered to be a good indicator of left ventricular relaxation properties, especially sensitive to changes in myocardial inotropic and ischemic states. Shortening of T may be attributed to improvement of ischemia rather than to altered myocardial contractility in this case.

Decreased systemic vascular resistance contributed to left ventricular systolic pressure fall and afterload reduction. Recent studies reported that bunitrolol, with moderate ISA, might play a role in vasodilating peripheral vascular vessels.[11] In addition to this action of bunitrolol, alpha-blocking[4] and Ca^{++} antagonist actions[5] were shown in animals; however, these were too weak to explain its vasodilator action, and the actual mechanisms remain unclear.

Intravenous propranolol at a dose of 20 mg showed both significant negative chronotropic and inotropic actions in patients with ischemic heart disease. In proportion to the decline in double product, an index of cardiac oxygen demand and cardiac output also decreased to almost the same degree following propranolol and systemic vascular resistance, which is roughly analogous to coronary vascular resistance, increased. Thus, the reduction in double product by propranolol might not be beneficial to the relief of myocardial ischemia in the resting state. Even the small increment in left ventricular

end-diastolic pressure, which suggested dilatation of the left ventricle, indicated a worsened myocardial oxygen balance. Prolongation of the time constant T might be the summation of the effects of both direct negative inotropic action and worsened ischemia.

In conclusion, besides its effectiveness in exercise induced angina due to its potent negative chronotropic activity and hypotensive effects during exercise,[6)~8)] bunitrolol is effective in relieving ischemia at rest without any deterioration of cardiac contractility. This beta-blocking agent is safe enough to be administered to the aged and/or to patients with overt heart failure.

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