Noninvasive Evaluation of Cardiovascular Effects of β-Adrenergic Blockers with Different Pharmacological Properties

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The effects of nadolol (Nad), indenolol (Idn), metoprolol (Met), pindolol (Pid), arotinolol (Art, S-596), and propranolol (Prp) on the cardiovascular system were studied noninvasively in healthy male volunteers. Exercise testing with a bicycle ergometer was performed both before and after single oral administration of these β-blockers, and any changes in the exercise-induced increase in heart rate-systolic blood pressure product (ΔDP) were studied. Systolic time intervals were measured from the simultaneous recording of carotid pulse, phonocardiogram, and electrocardiogram at rest. Left ventricular dimensions were measured by echocardiography, and ejection fraction (EF), stroke index (SI), and cardiac index (CI) were calculated by the standard techniques. Systemic vascular resistance (SVR) was computed from these data. ΔDP was decreased with all β-blockers. According to the degree of this effect, the relative potency of these drugs was estimated to be as follows : Pid > Art > Idn ≒ Prp > Nad ≒ Met. The ratio of pre-ejection period to left ventricular ejection time was increased with all β-blockers. EF, SI, and CI were decreased by all β-blockers except Pid, by which SI and CI were kept almost unchanged, and EF was significantly increased. Therefore, Pid was thought to be less cardiosuppressive than the other β-blockers. SVR was significantly decreased by Pid, while it was increased

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by all the other β-blockers. These results suggest that the acute hemodynamic response to β-blockers is determined primarily by the property of intrinsic sympathomimetic activity. Neither β_1-selectivity nor membrane stabilizing effect was shown to be a major factor modifying the central or peripheral hemodynamic response to β-blockers.

Key words : β-blockers, cardiovascular effect, systolic time intervals, echocardiography

Introduction

The value of β-adrenoceptor blockade has been well established in clinical medicine for the management of hypertension, angina pectoris, and cardiac arrhythmias. Recently, an increasing number of new β-adrenergic blocking drugs have been introduced into clinical practice. They differ in pharmacodynamic and pharmacokinetic properties such as cardioselectivity, intrinsic sympathomimetic activity (ISA), membrane stabilizing activity, duration of effect, absorption rate, and elimination half-time. β-Blockers were classified into 5 groups by Fitzgerald[1] according to differences in their pharmacological properties. In clinical application, the pharmacological properties of β-blockers should be carefully considered to minimize the associated untoward effects and to attain the best therapeutic results.

Of the β-blockers now clinically available, propranolol (Prp) has been the drug of choice. The pharmacological properties of the other β-blockers have been studied in comparison with those of Prp. Nadolol (Nad) is a new non-cardioselective β-adrenergic blocking agent which lacks both membrane activity and ISA. It has the longest plasma half-life of any known β-blocking drug, and can be administered once daily[2][3]. Indenolol (Idn) is also a non-cardioselective β-blocking agent with membrane activity and ISA[4][5]. Metoprolol (Met) is a new β-blocking drug that has cardioselectivity, but does not possess either ISA or membrane activity[6]. Pindolol (Pid) is a very potent β-adrenergic blocking drug that has pronounced ISA. It lacks both membrane activity and cardioselectivity[7]. Arotinolol (Art) is a newly developed compound in Japan that, like labetalol, has antagonist properties at both α- and β-adrenoceptors[8]. It is devoid of cardioselectivity, ISA, and membrane activity[9].

This study was undertaken in order to comparatively investigate the cardiovascular effects of these β-blocking drugs in normal men. For this purpose, the resting hemodynamics and the cardiac response to ergometer exercise were evaluated noninvasively before and after single oral administration of these β-blockers.

Subjects and Methods

Thirty-six healthy male volunteers participated in this study after giving informed consent. They ranged in age from 21-40 years (mean 27 years) and in weight from 51-80 kg (mean 64 kg). Each β-blocking drug was given to 6 subjects orally in a dose of 40 mg except for Pid and Art, the doses of which were 5 mg and 15 mg, respectively.

The subjects performed a single stage supine ergometer exercise for three minutes immediately before the drug administration, and repeated

it at 1, 2, 4, 6, 8, 12, and 24 hours after the drug dosing. The work loads of the exercise tests were determined for each subject before the experiment so that the heart rate would be increased by about 60/min from the resting state. They ranged from 100 to 175 watts (mean 135 watts). Measurement of blood pressure (BP) was performed by sphygmomanometer just prior to and during the last 30 seconds of the exercise tests. Heart rate (HR) was assessed from the ECG recordings. The product of HR and systolic blood pressure (BPs) or double product (DP) was obtained for each resting and exercise state, and the increase in DP (ΔDP) was calculated. Phonocardiograms and external carotid pulse tracings were recorded simultaneously with ECG before the exercise tests using a microphone (Nihon-kohden, TA-501 T) and a pulse transducer (Nihon-kohden, TF-112 S). From these recordings, the pre-ejection period (PEP) and the left ventricular ejection time (LVET) were obtained according to the standard technique (Weissler)[10]. Since it has been shown that the ratio of PEP to LVET (PEP/ET) correlates well with left ventricular performance[10][11], the value of PEP/ET was calculated. In all intances, several cardiac cycles were analysed, and mean values were obtained. Echocardiograms were recorded with the subject in the supine position from the third or fourth intercostal space using an echocardiograph (Fukuda-denshi, EM-401-A). Adequate echocardiograms were recorded in all subjects for the measurement of left ventricular minor axis dimensions. End-diastolic diameter was defined as the distance between the septal and posterior wall endocardial echo at the peak of the R waves of simultaneously recorded ECG, and end-systolic diamter was measured at the point of least perpendicular separation of the endocardial surfaces. As in the case with systolic time intervals, the echocardigraphic measurements were performed for several cardiac cycles, and mean values were calculated. The left ventricular end-diastolic and end-systolic volumes were estimated according to the method of Pombo et al.[12]. Stroke volume was derived from the difference of the two volumes. Cardiac output was obtained by multiplying stroke volume by heart rate. Stroke volume and cardiac ouput were standardized as stroke volume index (SI) and cardiac index (CI), respectively, by dividing the values by body surface area (m^2). Ejection fraction was obtained as stroke volume divided by the end-diastolic volume. Mean blood pressure was calculated as (BPs-diastolic blood pressure (BPd))/3. Systemic vascular resistance (SVR) was derived from the formula (mean blood pressure$\times$1.33$\times$60)/cardiac output, and the result was expressed in dy$\cdot$sec$\cdot$cm^{-5}.

A blood sample was collected before each exercise test until 12 hours after administration in order to assess the drug concenration. For Nad and Art, the drug concentration was additionally determined at 24 hours after the drug administration, due to their reported longacting effects[2][3][9]. The drug concentration was determined as plasma level for each drug except Art, which was assayed as serum level. The plasma levels of Nad and Met were assayed by gas-chromatography, and Idn and Prp by gas-chromatography mass-spectrometry. Plasma Pid was determined by the method of Pacha[13]. The serum level of Art was measured by thin layer chromatography with fluorescence detection. Statistical significance was tested by the paired t-test for changes in the hemodynamic variables. Analysis of variance was used for the comparison between the drugs. A p value of $<$

0.05 was considered as significant. The values are given as the mean±SEM.

Results

The time course of drug concentration in the blood is shown in Fig. 1. The peak concentration (C_{max}) of Art was 95.0 ng/ml and that of Idn was 7.7 ng/ml, which were much higher and lower, respectively, than the C_{max} of the other four β-blockers. The C_{max} of these four β-blockers were between 36.0 and 47.3 ng/ml. The peak concentration time (T_{max}) of the β-blockers was around 2 hours after the oral administration except for Pid and Nad, which peaked at around 1 and 4 hours, respectively. The C_{max}, T_{max}, and elimation half-time ($T_{1/2}$) of the β-blockers are summarized in Tab. 1. These results agreed well with the previous reports[2)3)6)7)].

Tab. 2 and Tab. 3 summarize the changes in HR and BP at rest and during ergometer exercise, respectively. There were significant reductions in HR and BPs after administration of each β-blocker. This was more prominent during the ergometer exercise than the resting state. In contrast with HR and BPs, the resting BPd was increased significantly after administration of Nad and Idn. At the maximum, it was increased from 64.3±3.1 to 70.3±2.9 mmHg with Nad, and from 61.0±3.4 to 71.0±2.5 mmHg with Idn. After administrations of Met, Pid, and Prp, the resting BPd was lowered significantly, from 68.7±4.9 to 52.0±2.8, from 69.7±1.7 to 57.7±1.7, and from 66.7±2.3 to 58.3±3.9 mmHg, respectively. This was not changed significantly with Art.

BPd during exercise was significantly increased with Met 1 hour after administration, and significantly lowered with Idn and Met 6 hours after administration. It was not significantly changed with the other β-blockers.

Fig. 2 shows the time course of ΔDP follwing administration of the β-blockers, expressed as % value of control. As shown in the same figure, the maximum suppression of ΔDP was observed near the T_{max} of each β-blocker. With Nad, Idn, and Met, ΔDP was suppressed, at maximum, to 65.0±5.3, 57.6±3.4, and 69.4±3.0% of control, respectively. After administra-

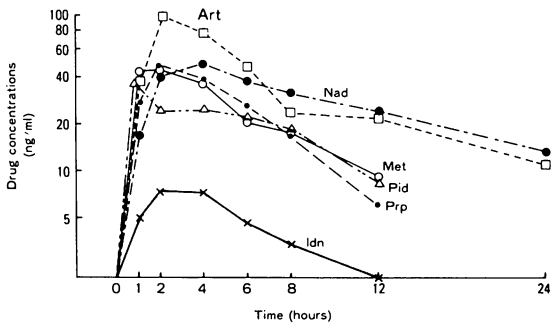

Fig. 1 Time course of serum concentrations of arotinolol (Art, 15 mg □---□) and plasma concentrations of nadolol (Nad, 40 mg ●——●), indenolol (1 dn, 40 mg ×——×), metoprolol (Met, 40 mg ○——○), pindolo (Pid, 5 mg △—·—△) and propranolol (Prp, 40 mg ●——●) after a single oral administration. Each point represents the mean of 6 subjects.

Tab. 1 Pharmacokinetic Parameters of β-Blockers

β-blocker	Dose (mg)	Cmax (ng/ml)	Tmax (hours)	T 1/2 (hours)
nadolol	40	47.3	4.0	14.0
indenolol	40	7.7	2.3	3.0
metoprolol	40	43.7	1.6	3.7
pindolol	5	36.0	1.3	4.6
arotinolol	15	95.0	2.2	7.2
propranolol	40	45.1	2.0	4.2

Abbreviations : C_{max}, peak drug concentration ; T_{max}, peak concentration time ; $T_{1/2}$, elimination half-time.

Tab. 2 Changes in Heart Rate and Blood Pressure at Rest after Single Oral Administration of β-Blockers

		Control	Time after administration (hours)						
			1	2	4	6	8	12	24
HR (bests /min)	Nad	66.3±3.9	**51.2±2.3	**49.2±2.0	**54.5±2.4	**50.8±2.2	**50.8±1.4	**52.5±2.1	**52.8±2.8
	Idn	56.0±4.7	*46.7±2.6	49.0±2.8	55.0±2.9	50.5±2.4	48.5±2.3	52.8±3.7	*47.5±2.5
	Met	64.2±3.8	*55.5±4.4	*54.7±4.8	*56.0±4.8	62.8±5.8	63.3±5.7	63.7±5.7	70.3±4.9
	Pid	63.3±3.3	*56.8±1.9	*56.0±1.7	61.8±1.7	60.5±1.1	59.0±1.1	61.5±1.9	59.3±1.2
	Art	54.7±3.0	53.3±2.7	**49.0±2.5	54.5±2.2	52.8±2.6	53.7±2.6	55.3±2.5	52.7±3.0
	Prp	64.0±3.6	*55.5±2.8	**54.0±3.3	58.5±5.3	*57.0±3.0	**55.2±2.2	*56.2±4.2	60.8±3.5
BPs (mmHg)	Nad	115.7±4.5	111.0±1.8	*107.0±3.9	**106.0±3.4	*104.7±2.9	107.3±3.2	109.3±3.3	108.0±4.0
	Idn	115.3±4.1	109.7±4.2	110.0±4.4	*111.3±3.7	111.0±3.0	108.7±3.1	112.2±5.7	*107.7±4.9
	Met	128.3±5.6	**114.7±4.8	**110.7±5.6	*112.7±6.6	118.3±4.2	119.0±4.2	122.0±4.1	128.3±3.2
	Pid	112.0±5.0	105.3±3.3	**102.0±2.8	108.3±4.7	111.3±2.7	115.3±2.5	117.7±3.2	113.0±4.1
	Art	116.7±1.6	112.7±2.0	**106.0±2.1	99.7±6.0	**105.7±1.6	109.7±4.0	109.3±3.1	**104.3±2.3
	Prp	114.7±3.4	**106.0±2.3	*105.0±4.4	*105.3±4.8	109.3±4.0	*108.0±4.3	114.0±5.8	114.0±6.4
BPd (mmHg)	Nad	64.3±3.1	**70.0±3.2	**70.3±2.9	65.0±2.5	66.7±1.5	67.7±1.8	63.3±1.5	62.0±2.5
	Idn	61.0±3.4	*71.0±2.5	*70.0±2.9	58.3±4.8	62.0±4.0	59.3±2.7	58.8±3.1	60.5±5.8
	Met	68.7±4.9	67.3±5.2	62.7±4.2	*58.7±4.8	**52.0±2.8	57.2±5.2	57.7±5.3	**57.7±4.9
	Pid	69.7±1.7	64.0±3.2	**63.0±2.2	**57.7±1.7	*62.0±2.0	65.0±1.7	*61.7±2.8	66.3±1.7
	Art	60.0±3.7	60.7±2.4	59.7±2.2	51.7±2.7	57.3±2.6	58.3±3.2	56.7±2.1	57.0±2.8
	Prp	66.7±2.3	69.3±3.0	67.7±4.3	61.7±3.8	60.3±2.9	63.3±4.8	59.0±3.2	*58.3±3.9

Abbreviations : HR, heart rate ; BPs, systolic blood pressure ; BPd, diastolic blood pressure : Nad, nadolol ; Idn, indenolol ; Met, metoprolol ; Pid, pindolol ; Art, arotinolol ; Prp, propranolol. Values are the mean ± SEM of 6 subjects. Statistics relate to comparison with control : $^{*}P<0.05$; $^{**}P<0.01$

tion of Pid, Art, and Prp, ΔDP was suppressed to 51.8±4.0, 58.3±2.6, and 53.6±3.7% of control, respectively. The differences in these ΔDP suppressing effects were not statistically significant. After administration of Nad, Pid, and Art, significant reduction in ΔDP continued until 24 hours, when ΔDP was suppressed to 77.3±6.4, 82.1±6.4, and 84.8±3.9% of control, respectively. The significant reduction in ΔDP continued up to 4 hours with Met, and up to 8 hours with Idn and Prp.

Tab. 4 summarizes the changes in PEP/ET, EF, SI, and CI at rest. PEP/ET was increased significantly 1-2 hours after administration of Pid, Art, and Prp. It was increased from 0.30±0.01 to 0.33±0.01, from 0.31±0.01 to 0.35±0.01, and from 0.35±0.03 to 0.41±0.04 with these β-blockers, respectively. Although not significantly, PEP/ET was also increased with the other β-blockers. EF was decreased signi-

Tab. 3 Changes in Heart Rate and Blood Pressure During Ergometer Exercise after Single Oral Administration of β-Blockers

		Control	Time after administration (hours)						
			1	2	4	6	8	12	24
HR (beats /min)	Nad	121.3± 3.9	*105.7±2.5	**101.2±2.7	**102.5±1.2	**103.5±1.0	**102.5±1.2	*106.0±1.3	**103.7±1.6
	Idn	128.8± 2.0	**103.7±1.7	**105.5±0.8	**110.7±1.6	**113.0±1.3	**114.0±0.6	**117.2±1.3	**117.5±1.9
	Met	129.3± 6.1	**111.0±4.2	**112.0±4.4	**114.7±4.3	*120.7±5.1	**119.8±5.9	**118.8±5.0	126.0±5.5
	Pid	133.2± 1.3	**109.0±2.9	**110.8±2.9	**113.7±3.1	**116.0±3.2	**116.2±3.3	*122.3±4.2	123.3±5.8
	Art	119.3± 2.2	110.7±2.4	**99.7±2.8	**100.8±1.9	**102.2±2.0	**104.8±1.2	**108.5±1.6	**109.3±1.9
	Prp	127.0± 4.1	**104.3±3.6	**101.0±4.5	**109.7±2.5	**111.7±2.4	**112.7±2.9	**116.8±3.7	122.3±1.8
BPs (mmHg)	Nad	160.7± 4.8	**138.3±3.9	**127.7±5.0	**131.7±5.3	**134.7±7.4	**136.3±8.8	**140.3±8.0	*142.7±7.1
	Idn	171.0± 7.6	**134.3±4.6	**134.7±5.3	**148.0±4.1	*159.3±7.5	*159.7±7.9	169.7±8.0	166.3±7.0
	Met	197.3±10.2	**164.0±7.2	**167.0±8.3	*176.3±7.5	188.3±6.2	190.0±8.6	195.0±7.9	207.0±8.9
	Pid	188.3±10.3	**139.3±6.8	**142.0±6.1	**154.3±5.0	*161.0±4.9	*168.3±5.0	180.3±6.7	172.0±4.2
	Art	190.0± 8.6	**161.7±4.2	**146.7±5.3	**154.3±3.5	*164.3±3.9	*172.3±6.7	171.3±5.7	*175.3±4.9
	Prp	166.7± 7.7	**133.7±2.8	**129.0±3.2	*143.7±4.9	**146.3±6.6	*151.3±4.4	167.0±5.1	171.7±6.5
BPd (mmHg)	Nad	78.3± 2.4	78.0±2.5	73.3±5.3	78.7±2.9	79.7±3.2	83.0±3.3	79.3±4.0	69.3±2.5
	Idn	80.3± 4.9	83.3±2.4	80.0±2.7	76.0±4.1	*73.0±3.1	77.2±3.4	80.5±3.7	81.7±2.1
	Met	89.0± 5.4	*95.3±5.0	89.0±3.8	92.7±6.1	*77.0±3.7	85.3±3.6	88.7±4.9	84.7±6.5
	Pid	83.7± 8.5	78.0±1.6	77.7±3.4	76.7±5.8	77.0±5.5	74.0±5.9	77.3±5.5	81.0±3.8
	Art	86.3± 4.7	80.0±3.9	82.0±3.8	81.0±3.8	86.3±3.6	83.7±2.9	83.3±3.8	84.0±2.3
	Pid	53.3±12.6	65.0±3.9	63.0±6.1	59.3±6.6	62.3±4.0	62.7±7.3	60.0±7.9	50.3±8.5

Abbreviations and asterisks : See Tab. 2

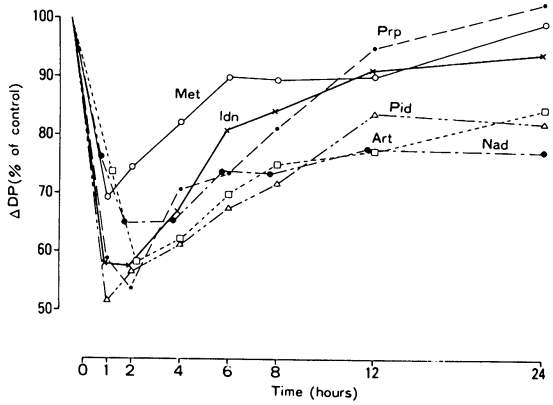

Fig. 2 Percentage change in the exercise-induced increase in the heart rate-systolic blood pressure product (△ DP) after single oral administration of β-blockers. Each point reprepents the mean in 6 subjects. Symbols and abbreviations are as in Fig. 1.

Tab. 4 Changes in Systolic Time Intervals, Ejection Fraction, Stroke Index and Cardiac Index at Resting State after Single Oral Administration of β-Blockers

		Control	Time after administration (hours)						
			1	2	4	6	8	12	24
PEP /ET	Nad	0.34±0.02	0.40±0.01	0.42±0.02	0.35±0.01	0.38±0.01	0.39±0.02	0.38±0.02	0.35±0.02
	Idn	0.32±0.02	0.36±0.02	0.36±0.02	0.28±0.02	0.30±0.02	0.31±0.01	0.31±0.02	0.32±0.01
	Met	0.36±0.02	0.39±0.02	0.37±0.02	0.39±0.04	0.34±0.03	0.39±0.02	0.39±0.03	0.36±0.03
	Pid	0.30±0.01	0.32±0.02	*0.33±0.01	0.28±0.01	0.33±0.02	0.34±0.01	*0.31±0.01	0.31±0.01
	Art	0.31±0.01	*0.35±0.01	0.34±0.01	0.34±0.02	0.32±0.02	0.32±0.01	0.31±0.01	0.35±0.02
	Prp	0.35±0.03	0.39±0.04	**0.41±0.04	0.33±0.03	0.37±0.03	0.36±0.04	0.35±0.03	0.35±0.05
EF	Nad	0.79±0.02	*0.71±0.03	0.73±0.03	0.79±0.02	0.77±0.02	0.77±0.03	0.80±0.03	0.77±0.02
	Idn	0.75±0.02	**0.69±0.02	**0.69±0.02	0.75±0.02	0.76±0.02	0.74±0.02	0.76±0.03	0.74±0.04
	Met	0.73±0.02	**0.66±0.02	0.71±0.02	0.72±0.02	0.74±0.02	0.75±0.02	**0.77±0.02	0.75±0.02
	Pid	0.72±0.03	0.74±0.04	*0.76±0.02	**0.82±0.01	*0.80±0.01	0.78±0.03	*0.80±0.03	*0.76±0.02
	Art	0.77±0.02	0.73±0.01	*0.70±0.02	0.75±0.02	0.77±0.02	0.77±0.03	0.77±0.02	*0.71±0.02
	Prp	0.74±0.01	0.70±0.01	0.69±0.02	0.72±0.02	0.77±0.02	0.75±0.02	0.77±0.02	0.76±0.02
SI (ml /m^2)	Nad	53.5 ±5.5	*43.7 ±2.4	*43.0 ±2.1	50.5 ±3.5	47.1 ±2.5	43.8 ±2.4	50.6 ±1.7	47.6 ±1.5
	Idn	46.6 ±3.5	*40.7 ±2.6	*39.4 ±3.6	44.3 ±3.2	45.1 ±2.6	44.1 ±3.2	42.5 ±4.8	42.0 ±3.6
	Met	43.9 ±4.7	38.9 ±4.0	42.2 ±3.8	42.6 ±3.0	45.4 ±3.4	47.3 ±4.0	47.7 ±5.0	45.6 ±4.3
	Pid	41.5 ±5.7	44.4 ±6.9	42.7 ±6.1	44.6 ±4.3	44.3 ±5.0	44.7 ±7.3	45.8 ±6.4	41.5 ±5.2
	Art	48.7 ±2.9	47.3 ±6.2	*40.3 ±2.3	46.1 ±3.4	47.7 ±4.1	45.4 ±3.3	49.5 ±5.0	*43.1 ±2.9
	Prp	45.6 ±2.4	46.8 ±3.5	42.6 ±2.3	42.8 ±3.2	46.5 ±2.4	44.8 ±4.9	49.0 ±3.7	42.4 ±4.7
CI (l/ min /m^2)	Nad	3.61±0.56	*2.23±0.13	*2.11±0.14	2.78±0.29	2.41±0.20	*2.22±0.13	2.67±0.18	2.53±0.20
	Idn	2.65±0.35	*1.93±0.21	*1.97±0.25	2.45±0.25	2.30±0.22	2.16±0.23	2.20±0.24	2.01±0.24
	Met	2.79±0.31	*2.07±0.08	2.22±0.07	2.33±0.13	2.77±0.16	2.94±0.29	2.96±0.24	3.14±0.23
	Pid	2.63±0.38	2.57±0.42	2.39±0.35	2.76±0.27	2.68±0.31	2.64±0.44	2.81±0.41	2.46±0.31
	Art	2.67±0.22	2.55±0.26	*1.97±0.15	2.50±0.18	2.50±0.20	2.41±0.12	2.71±0.25	*2.26±0.16
	Prp	2.91±0.19	2.58±0.19	*2.30±0.19	2.48±0.24	2.64±0.17	2.47±0.27	2.77±0.31	2.60±0.33

Abbreviations : PEP/ET, pre-ejection period/left ventricular ejection time ; EF, ejection fraction ; SI, stroke index ; CI, cardiac index ; Nad, Nadolol ; Idn, indenolol ; Met, metoprolol ; Pid, pindolol ; Art, arotinolol ; Prp, propranolol.
Values are the mean ± SEM in 6 subjects. Statistics relate to comparison with control : : *$P<0.05$; **$P<0.01$

ficantly with Nad, Idn, Met, and Art 1-2 hours after their administration. Although not significantly, it was also decreased with Prp. On the other hand, Pid induced sustained increase in EF. Its effect reached a maximum 4 hours after administration, when EF was significantly increased from 0.72±0.03 to 0.82±0.01. SI was reduced significantly with Nad, Idn, and Art from 53.5±5.5 to 43.0±2.1, from 46.6±3.5 to 39.4 ± 3.6, and from 48.7 ± 2.9 to 40.3 ± 2.3 ml/m^2, respectively. Although not signfifcantly, it was also decreased from 43.9±4.7 to 38.9± 4.0 ml/m^2 with Met, and from 45.6±2.4 to 42.6 ± 2.3 ml/m^2 with Prp. Pid, on the other hand, did not exert a decreasing effect on SI. CI was decreased significantly with all β-blockers ex-

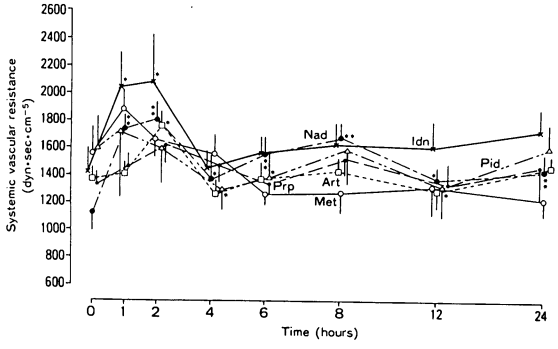

Fig. 3 Changes in the systemic vascular resistance at rest after a single oral administration of β-blockers. Symbols and abbreviations are as in Fig. 1. Each point represents the mean ± SEM of 6 subjects. Statistics relate to comparison with the pre-dosing state : $^{*}P<0.05$; $^{**}P<0.01$.

cept Pid. After administration of Nad, CI was decreased most prominently from 3.61±0.56 to 2.11±0.14 l/min/m^2. With Pid, it was not changed significantly.

SVR at resting state was changed as shown in Fig. 3. After administration of Nad, Idn, and Art, it was increased significantly, from 1116±128 to 1817±133, from 1424±175 to 2074±351, and from 1370±92 to 1754±111 dyn·sec·cm^{-5}, respectively. The increase in SVR was sustained after the administration of Nad. SVR was also increased with Met and Prp, although not significantly. Contrary to these β-blockers, Pid induced a significant decrease in SVR, from 1606±266 to 1292±146 dyn·sec·cm^{-5}.

Discussion

β-Blockers were classified by Fitzgerald[1] into 5 groups according to their pharmacological properties. Nad, Idn, Met, Pid, and Prp belong to each group of this classification. Art was added in this study because of its unique pharmacological property, in that it has both α- and β-adrenoceptor blocking effect.

Prp in a single dose of 40 mg is clinically admitted, and is thus considered here as the control dose for the other β-blockers. The doses of the other β-blockers were determined so as to be approximately equipotent to that of Prp according to the reported potency ratio[3)4)7)9)].

The C_{max} of Nad, Met, Pid, and Prp were almost equal. The plasma concentration of Idn was much lower than that of the other β-blockers. The T_{max} of Nad was 4.0 hours, which was later than with the other β-blockers, possibly because Nad is poorly absorbed from the gastrointestinal tract. According to Vukovich et al.[14)], only 34% of oral nadolol is absorbed.

After the administration of Idn, Pid, and Art, ΔDP was suppressed to almost the same degree as with Prp. The maximum ΔDP suppressions with Nad and with Met were less than with Prp, although not significantly. According to the ΔDP suppressing effects, the potency of these drugs was estimated as follows. On a mg.-for-mg. basis, Pid was the most potent, and Art the second most potent among these β-blockers. Idn and Prp were equally potent following Art. The potencies of Nad and Met were approximately equal following those of Idn and Prp. In short, the β-blocking potency of these drugs was grossly ranked in the following order : Pid > Art > Idn ≒ Prp > Nad ≒ Met. In general, this order of potency agreed with previous reports[4)7)9)], though Nad and Met were estimated to be less potent than Prp in this study.

It is well known that cardiac function is more or less suppressed by β-blockers. In this study, one of the authors' goals was to evaluate the cardiosuppressive effects of β-blockers noninvasively. For this purpose, studies using systolic time intervals and echocardiography were performed repeatedly before and after the ad-

ministration of β-blockers, although these methods are not regarded as sufficiently reliable for accurate hemodynamic evaluations. PEP/ET was increased significantly with Pid, Art, and Prp, and with the other β-blockers, although not significantly. Thus, it was suggested from the systolic time intervals that the cardiac function was suppressed with these β-blockers. The changes in EF, SI, and CI also suggested cardiosuppressive effects of the β-blockers other than Pid, since all these parameters decreased after drug administration. With Pid, however, SI and CI remained almost unchanged and EF was significantly increased. This was consistent with the result reported by Svendsen et al.[15] that the cardiac output measured by thermodilution was decreased with Prp, but not with Pid. Therefore, from the echocardiographic examination, Pid was suggested to be not only not suppressive, but even promotive, of the cardiac function. The systolic time intervals and echocardiography were inconsistent as to the evaluation of the cardiac effects of Pid. However, it may be possible that Pid is at least less cardiosuppressive than the other β-blockers examined in this study. This characteristic of Pid may be ascribed to its ISA. Nad is devoid of membrane stabilizing effects, and, for this reason, has been expected to be less cardiosuppressive. Compared to Prp, Nad was shown to be 20-50 times less suppressive in the canine myocardium in vivo[16]. However, in this study, Nad was not found to be less cardiosuppressive than Prp.

The changes in SVR were opposite after the administration of Pid and the other β-blockers ; SVR was decreased significantly with Pid, while it was increased with all the other β-blockers. Accordingly, it was suggested that the effect of Pid on the peripheral vessels was dilatative, and the effects of the other β-blockers were constrictive. The vasodilating effect of Pid was considered to be due to its ISA. Idn also has the property of ISA[4]. However, the hemodynamic changes with Idn were like those after the administration of β-blockers without ISA. This may be because the ISA of Idn is weak in potency.

Met is a highly selective antagonist for β_1-adrenoceptors. From in vivo studies in the cat, it was demonstrated that Met had 15-50 times higher affinity to β_1- than to β_2- adrenoceptors[17][18]. Art shows the antagonistic property at both α- and β- adrenoceptors. Its α- blocking potency was reported to be 1/10 of that of phentolamine[8]. Because of these unique pharmacological properties, it was expected that Met and Art might produce less vasoconstriction and induce a cardiac response different from that of Prp. However, after their administration, SVR was increased and cardiac function was suppressed as with Prp.

These results may indicate that the acute hemodynamic response to β-blockers at rest is determined primarily by the property of ISA. It seems that neither β_1-selectivity nor membrane stabilizing effect is a major factor modifying the central or peripheral hemodynamic responses to β- blockers. The hemodynamic effects of β_1-selectivity and of ISA were discussed by Svendsen[19], and the present study was in good agreement with that report.

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