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Cardiovascular Profile of the Cardioselective Beta-Adrenoceptor Antagonist Bisoprolol in Anesthetized Pigs

Pieter D. Verdouw, Ilona O.L. Schmeets, and Rob J. Rensen

Laboratory for Experimental Cardiology, Thoraxcenter, Erasmus University Rotterdam, 3000 DR Rotterdam, The Netherlands

ABSTRACT

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The cardioselective beta-adrenoceptor antagonist bisoprolol ((±)-1-[4-(2-isopropoxyethoxymethyl)-phenoxy]-3-isopropylamino-2-propanol-hemifumarate, EMD 33512) was studied for its effects on cardiac performance in ten anesthetized open-chest pigs. Radioactive labelled microspheres (15 ± 1 μm) were used to determine regional blood flows. In doses of 4, 16, 64, 256, and 1,024 $\mu g \cdot kg^{-1}$(arterial plasma concentrations 1.65 ± 0.07 to 569 ± 22 $ng \cdot ml^{-1}$) the drug caused dose-dependent decreases in cardiac output (4–31%, $P <$ .05) that were primarily due to a negative chronotropic action as heart rate, which had already been slowed down by 9% ($P <$ .05) after the lowest dose, decreased up to 22% ($P <$ .05). Stroke volume was not significantly affected at any dose, although it tended to decrease after the highest dose of bisoprolol (– 10%, $P <$ .05). Myocardial contractility, reflected by maxLVdP/dt, fell dose dependently from 12% (after 4 $\mu g \cdot \mu g \cdot kg^{-1}$, $P <$ .05) up to 46% (after 1,024 $\mu g \cdot kg^{-1}$, $P <$ .05). Raising the heart rate to predrug levels revealed that this reduction in maxLVdP/dt was not related to the bradycardic action of the drug. Mean arterial blood pressure decreased slightly (<15%, $P <$ .05) after the highest three doses, but a larger fall was prevented by a mild vasoconstriction of the systemic arterial vascular bed as systemic vascular resistance increased up to 28% ($P <$ .05). Pulmonary artery pressure was not affected, because pulmonary vascular resistance increased with the highest doses. Left ventricular blood flow, which had already decreased significantly with the lowest dose (11%, $P <$ .05), also decreased dose dependently (up to 44% after 1,024 $\mu g \cdot kg^{-1}$, $P <$ .05). These decreases were equally distributed over all myocardial

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Address reprint requests to P.D. Verdouw, Ph.D., Laboratory for Experimental Cardiology, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

layers as the endo/epi blood flow ratio (1.13 ± 0.04) was not affected. Myocardial O_2 consumption was not affected by the lowest dose, but decreased progressively up to 43% ($P < .05$) with the higher doses. These changes occurred parallel to those in blood flow as myocardial O_2 extraction did change. Cerebral blood flow was well preserved but decreases in perfusion of some other organs and tissues (kidneys, stomach, and skeletal muscle) were similar to those in cardiac output.

In conclusion, bisoprolol has a cardiovascular profile similar to that of other beta-adrenoceptor agents. The finding that no serious adverse cardiovascular affects are observed over a wide dose range warrants further studies in models of myocardial ischemia and hypertension.

Key words: systemic hemodynamics, distribution of cardiac output, pulmonary circulation, coronary circulation

INTRODUCTION

Bisoprolol ((±)-1-[4-(2-isopropoxyethoxymethyl)-phenoxy]-3-isopropylamino-2-propanol-hemifumarate, EMD 33512; Fig. 1) is a new beta-adrenoceptor antagonist without intrinsic sympathomimetic activity [Harting et al., 1986]. Binding studies revealed a high selective affinity for $beta_1$-adrenoceptors, a property confirmed in several studies performed with anesthetized dogs, guinea pigs, and cats [Schliep and Harting, 1984; Schliep et al., 1986]. Bisoprolol also reduced ST-segment elevation of the epicardial electrocardiogram during short-lasting, intermittent occlusions of the left anterior descending coronary artery in anesthetized dogs [Harting et al., 1986].

Although the drug has been shown to exert a bradycardic action and to decrease cardiac output [Harting et al., 1986], a detailed description of its cardiovascular actions, in particular on the coronary circulation, is not available. In this study we report on the effects of cumulative doses of bisoprolol on the systemic, pulmonary, and coronary circulation of anesthetized pigs.

MATERIALS AND METHODS

Studies were performed on Yorkshire pigs (22–28 kg) after an overnight fast. After sedation with 120 mg of the butyrophenon derivative azaperone [Heykants et al., 1971], the animals were anesthetized with 150 mg metomidate i.v. [Dimigen and Reetz, 1970] and subsequently intubated for artificial ventilation with a mixture of oxygen and nitrous oxide (1:2). Respiratory rate and tidal volume were set to control arterial blood gas values (ABL-3, Radiometer, Copenhagen).

Catheters were placed in the descending aorta for the withdrawal of arterial reference samples to calibrate regional flow measurements and to collect blood for the determination of

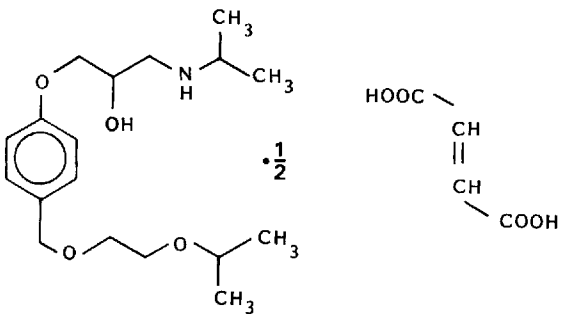

Fig. 1. Chemical structure of bisoprolol.

plasma levels of bisoprolol, and in the superior caval vein for administration of α-D(+)-glucochloralose (100 mg·kg^{-1},Merck, Darmstadt, F.R.G.) and Haemaccel [Behringwerke, Marburg, F.R.G.] to replace the blood withdrawn during the collection of the reference sample at the time of injection of microspheres (see below). Tips of Millar catheters were positioned in the left ventricle and in the root of the ascending aorta for measurement of local blood pressures. The tip of a triple lumen Swan-Ganz catheter was positioned in the pulmonary artery for pressure recordings and administration of bisoprolol, while a pacing catheter was positioned in the coronary sinus.

After exposure of the heart, an electromagnetic flow probe (Skalar, Delft, The Netherlands) was placed around the ascending aorta for measurement of the cardiac output. The left atrial appendage was catheterized for the injection of microspheres (15 ± 1 μm, 3 NEN Company, Dreieich, F.R.G.) labelled with ^{46}Sc, ^{103}Ru, ^{141}Ce, ^{95}Nb, or ^{113}Sn. The withdrawal of an arterial reference sample was started (flow rate 10 ml·min^{-1}) just prior to the start of the injection of the microspheres (10^6 per batch) and continued until 1 min after the injection was completed. Full details of the calculation of regional blood flows from the radioactivity in the organs and tissues have been reported earlier [Saxena and Verdouw, 1982, 1985].

Myocardial wall thickness tracings, monitored with a 5-MHz ultrasonic transducer (Krautkramer-Branson, Lewistown, PA) sutured onto the epicardial surface of a myocardial segment perfused by the left anterior descending coronary artery were used to calculate regional systolic wall thickening and the velocity of wall thickening [Verdouw et al., 1981]. Hemoglobin and coronary venous O_2 saturation were determined in blood samples drawn from the great cardiac vein. Myocardial O_2 consumption was calculated as the product of the left ventricular blood flow and the difference in the arterial and coronary venous O_2 contents.

Arterial plasma concentrations were determined by high-performance liquid chromatography [Bühring and Garbe, 1986]. The lower limit of detection was 1 ng·ml^{-1}.

Cardiovascular Effects of Bisoprolol

Baseline values were obtained after the preparation had been stable for 30 min. Subsequently five doses (4, 16, 64, 256, and 1,024 μg·kg^{-1}) were administered to each of ten pigs over a period of 2 min at 20-min intervals. Fifteen minutes after administration of each dose all hemodynamic measurements were repeated. At that time also an arterial blood sample was drawn for the determination of plasma concentrations of bisoprolol (8 ml), and a batch of radioactive microspheres was injected. Because only five batches of microspheres were available, in each experiment regional blood flow measurements could only be obtained during baseline and after four of the five different doses.

In order to evaluate the effect of heart rate on max LVdP/dt, the former was raised in all animals to prebisoprolol values by means of electrical stimulation via the pacing catheter, after the microsphere measurements were completed. After 2 min all hemodynamic parameters were again determined and the pacing was discontinued.

Statistics

Statistical analysis was performed on the actual data by using parametric two-way analysis of variance (randomized block design) followed by the Duncan New Multiple-Range test. Statistical significance was accepted at $P < .05$. All data have been expressed as means ± SEM.

RESULTS

Arterial Plasma Concentrations

Fifteen minutes after administration of 4 μg·kg^{-1} of bisoprolol, plasma concentrations (1.65 ± 0.07 ng·ml^{-1}) were at the lower limit of detection. With the other doses (16, 64, 256, and 1,024 μg·kg^{-1}), concentrations of 7.2 ± 0.4 ng·ml^{-1}, 31 ± 1 ng·ml^{-1}, 125 ± 4 ng·ml^{-1}, and 569 ± 22 ng·ml^{-1}, respectively, were achieved.

Systemic Circulation

In Figure 2 the bisoprolol-induced changes in a number of systemic hemodynamic variables have been depicted. Mean arterial blood pressure decreased only moderately (< 15%) after administration of the three highest doses, but the decreases in heart rate (up to 22%), cardiac output (up to 30%), and maxLVdP/dt (up to 46%) were dose dependent and more pronounced. The fall in cardiac output was less than the negative chronotropic action of the drug for the lowest three doses but slightly larger for the highest two doses. Consequently stroke volume tended to increase after administration of the lower doses ($P > .05$) and to decrease after administration of 1,024 $\mu g \cdot kg^{-1}$ bisoprolol (total dose 1,364 $\mu g \cdot kg^{-1}$), but none of the changes was statistically significant. Myocardial contractility, reflected by maxLVdP/dt, was most affected. The negative chronotropic actions of bisoprolol did not contribute to this decrease in maxLVdP/dt since raising the heart rate to predrug levels had no effect on this parameter (Table 1). Left ventricular end-diastolic pressure decreased slightly from 8.2 ± 0.7 mmHg to 6.4 ± 0.7 mmHg, but this change was only significant for the two lower concentrations. When the heart rate was raised to predrug levels the fall in filling pressure was more pronounced and caused a significant decrease in stroke volume (Table 1). Particularly at higher

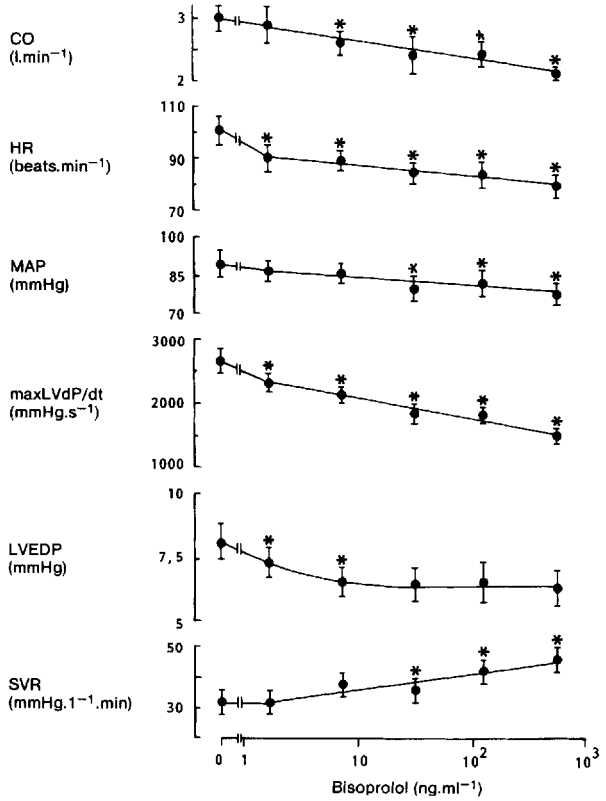

Fig. 2. Effect of cumulative doses of bisoprolol, administered at 20-min intervals, on the systemic hemodynamics of ten anesthetized pigs. CO=cardiac output; HR=heart rate; MAP=mean arterial blood pressure; maxLVdP/dt=maximum rate of rise of left ventricular pressure; LVEDP=left ventricular end-diastolic pressure; SVR=systemic vascular resistance. All data were collected 15 min after administration of each dose and have been presented as mean ± SEM. For the sake of clarity the SEM bars (<4% of the mean value for each data point) of the plasma concentrations have been omitted. *P < .05 vs. predrug value (0 ng · ml^{-1}).

TABLE 1. Effect of Heart Rate on Myocardial Contractility and Other Systemic Hemodynamic Parameters in Six Anesthetized Pigs Treated With Bisoprolol.†

		Δ% by bisoprolol				
Cumulative doses:		4	16	64	256	1,024
Total doses:		4	20	84	340	1,364
[Bisoprolol]:	0	1.65 ± 0.07	7.2 ± 0.4	31 ± 1	125 ± 4	569 ± 22
Heart rate						
NSR	104 ± 12	−9 ± 2*	−17 ± 3*	−21 ± 3*	−24 ± 3*	−25 ± 5*
P	104 ± 12	—	—	—	—	—
maxLVdP/dt						
NSR	2710 ± 10	−11 ± 3*	−18 ± 5*	−25 ± 6*	−32 ± 5*	−46 ± 3*
P	2710 ± 10	−10 ± 10	−18 ± 8*	−31 ± 2*	−33 ± 4*	−44 ± 3*
LVEDP						
NSR	8 ± 1	−7 ± 3*	−13 ± 5*	−18 ± 10	−9 ± 12	−12 ± 11
P	8 ± 1	−7 ± 9	−24 ± 7*	−18 ± 12	−31 ± 12*	−27 ± 6*
Stroke volume						
NSR	31 ± 2	4 ± 3	2 ± 4	6 ± 8	−2 ± 8	−11 ± 7
P	31 ± 2	−12 ± 9	−13 ± 7*#	−20 ± 7*#	−28 ± 7*#	−35 ± 7*#

†Doses of bisoprolol are in $\mu g \cdot kg^{-1}$. [Bisoprolol] = arterial plasma concentrations of bisoprolol ($ng \cdot ml^{-1}$); heart rate ($beats \cdot min^{-1}$); maxLVdP/dt ($mmHg \cdot s^{-1}$); LVEDP=left ventricular end-diastolic pressure (mmHg); stroke volume (ml); NSR=normal sinus rhythm; P=pacing rate; *$P < .05$ vs. predrug −(0 $ng \cdot ml^{-1}$); #$P < .05$ vs. NSR value at the same bisoprolol concentration. All data have been presented as means ± SEM.

doses of bisoprolol the decrease in mean arterial blood pressure was considerably less than in cardiac output (14% vs. 31% after 1,024 $\mu g \cdot kg^{-1}$ bisoprolol, respectively). Consequently systemic vascular resistance was increased (up to 30%, $P < .05$) during the period immediately following intravenous administration of the highest three doses of bisoprolol.

Pulmonary Circulation

Mean pulmonary artery pressure (24 ± 3 mmHg) was not affected by bisoprolol. Hence, pulmonary vascular resistance (baseline 5.1 ± 0.7 $mmHg \cdot min \cdot L^{-1}$) remained constant until the administration of the highest two doses, when there was an increase to 7.3 ± 1.0 $mmHg \cdot min \cdot L^{-1}$ ($P < .05$).

Coronary Circulation

Left ventricular blood flow decreased with increasing doses up to 44 ± 5% of its predrug value of 144 ± 8 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ (Fig. 3). The decrease in perfusion was uniformly distributed over all myocardial layers (endo/epi blood flow ratio was 1.13 ± 0.04 at baseline and 1.09 ± 0.06 during the last measurement, $P > .05$).

Because the fall in mean arterial blood pressure was considerably less than in left ventricular blood flow, bisoprolol must have caused vasoconstriction of the coronary vasculature. Myocardial O_2 extraction was only minimally affected as coronary venous O_2 saturation (baseline 15 ± 2%) was only different from the predrug value after administration of 64 $\mu g \cdot kg^{-1}$ bisoprolol (not shown). Left ventricular O_2 consumption therefore decreased in accordance with the decrease in left ventricular blood flow (Fig. 3).

Wall thickness at end-diastole (prebisoprolol 10.4 ± 0.5 mm) did not change, although a slightly reduced value (10.1±0.7 mm, $P > .05$) was observed with the last dose (Fig. 4). The velocity of systolic wall thickening decreased gradually from a predrug value of 7.7 ± 0.5 $mm \cdot s^{-1}$ to 6.0 ± 0.6 $mm \cdot s^{-1}$ after 256 $\mu g \cdot kg^{-1}$ bisoprolol and then more abruptly to 4.7 ± 0.5 $mm \cdot s^{-1}$ after the last dose. Due to prolongation of the left ventricular ejection period resulting from the bradycardic action of bisoprolol, wall thickness at end-systole (prebisoprolol

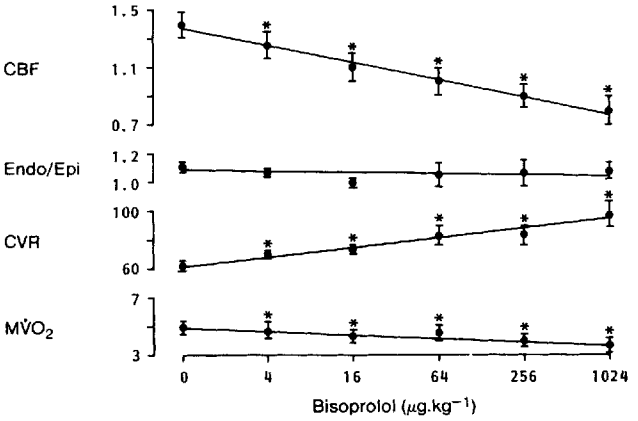

Fig. 3. Effect of cumulative doses of bisoprolol on the coronary circulation of ten anesthetized pigs. CBF=transmural left ventricular blood flow; Endo/Epi= ratio of normalized blood flow to subendo- and subepicardial layers; CVR=coronary vascular resistance; $M\dot{V}O_2$=left ventricular O_2 consumption. For further details see legend of Figure 2.

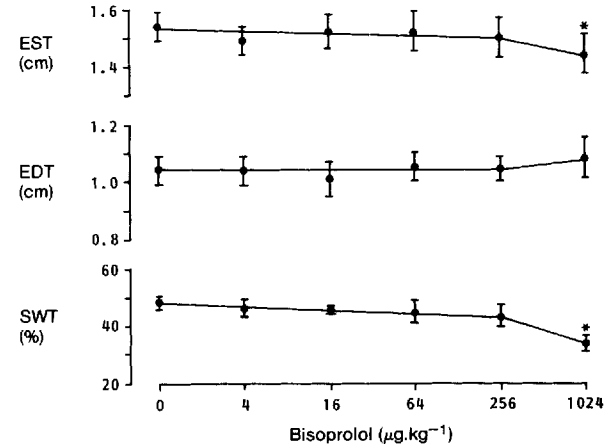

Fig. 4. Effect of cumulative doses of bisoprolol on regional myocardial performance in ten anesthetized pigs. EDT and EST are the left ventricular wall thickness at end diastole and end systole, respectively, while SWT stands for systolic wall thickening (=(EDT−EST)/EDT × 100%). For further details see legend of Figure 2.

15.4 ± 0.5 mm) was not reduced until the last dose (14.4 ± 0.7 mm, $P < .05$). Consequently systolic wall thickening was not affected until the highest concentration (Fig. 4).

Perfusion of the right ventricle also decreased dose dependently but the changes were less (up to 32%) than for the left ventricle (Fig. 4). The changes in atrial blood flow were only significant for the highest two doses of bisoprolol (−25 ± 8% and −35 ± 8%, respectively; both $P < .05$ vs. the prebisoprolol value of 101 ± 11 ml · min^{-1} · 100 g^{-1}).

Regional Blood Flows and Resistances

With the exception of cerebral blood flow, which did not decrease until the last dose (15%), perfusion of the other organs and tissues decreased dose dependently (Fig. 5). For some (stomach, muscle, and kidneys) the decreases (up to 30%) were similar to those in cardiac output. For the small intestine they tended to be less (up to 20%), whereas the

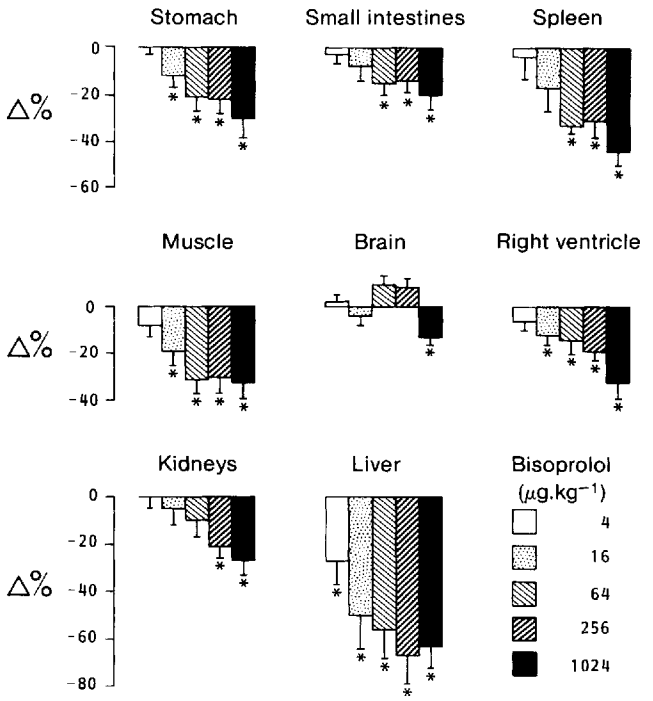

Fig. 5. Effect of cumulative doses of bisoprolol on regional blood flows in ten anesthetized pigs. Because of the limited number of microspheres for each dose the data were obtained in eight of the ten animals. Therefore we have been presented these data as change from prebisoprolol values which were in ml·min^{-1} 100 g^{-1}): 18.7 ± 4.1 (stomach); 33.6 ± 1.9 (small intestine), 121 ± 17 (spleen), 2.73 ± 0.25 (muscle), 23.6 ± 0.8 (brain), 107 ± 6 (right ventricle), 241 ± 17 (kidneys), and 32.5 ± 9.5 (liver). For further details see legend of Figure 2.

decreases in perfusion of the liver, via the hepatic artery, and spleen were higher (up to 60 and 45%, respectively). The changes in renal blood flow were only significant after administration of the highest two doses, but for most organs the decreases in perfusion were already significant after administration of lower doses. Flow to the skin (0.48 ± 0.13 ml·min^{-1}·100 g^{-1}) and adrenals (170 ± 25 ml·min^{-1}·100g^{-1}) did not change significantly (not shown). The decrease in the flows to the brains, kidneys, and small intestine were parallel to those in mean arterial blood pressure. Consequently the vascular resistances of these organs were only minimally affected (Table 2). On the other hand, dose-dependent increases in resistance were observed in spleen (up to 60%), muscle (up to 40%), and stomach (up to 30%). Hepatic artery resistance more than doubled, but the results of the individual experiments varied considerably.

DISCUSSION

Stability of the Preparation and Reproducibility of Microsphere Data

In an earlier report we have described the global hemodynamic parameters as changing less than 5% of their respective baseline values during the period of time necessary to execute the experimental protocol (Wolffenbuttel and Verdouw, 1983). Except for the myocardium, brains, and kidneys, we have, however, no such data for the regional blood flows [Schamhardt, 1980; Saxena and Verdouw, 1982]. For the aforementioned organs reproducibility of flow data was good, as four determinations with isotopes, injected either simultaneously or consecutively, showed a variability of less than 10%.

TABLE 2. Effect of Bisoprolol on the Resistance of Regional Vascular Beds and Tissues in Ten Anesthetized Pigs†

Cumulative doses:		4	16	64	256	1,024
Total doses:		4	20	84	340	1,364
[Bisoprolol]:	0 (n=10)	1.65 ± 0.07 (n=8)	7.2 ± 0.4 (n=8)	31 ± 1 (n=8)	125 ± 4 (n=7)	569 ± 22 (n=7)
Kidneys	0.39 ± 0.03[a]	0.38 ± 0.04	0.38 ± 0.04	0.45 ± 0.05	0.44 ± 0.04	0.45 ± 0.02
Adrenals	0.69 ± 0.15	0.68 ± 0.13	0.77 ± 0.15	0.97 ± 0.15	1.06 ± 0.19	0.93 ± 0.24
Liver[b]	6.3 ± 2.4	6.7 ± 2.5*	20.7 ± 9*	26.9 ± 11.5*	23.7 ± 8*	19.6 ± 7.1*
Stomach	5.9 ± 0.7	5.7 ± 0.8	6.2 ± 1.0	7.1 ± 1.2*	7.3 ± 0.7	8.1 ± 1.0
Small intestine	2.8 ± 0.3	2.8 ± 0.3	2.7 ± 0.2	3.2 ± 0.3	3.0 ± 0.4	3.2 ± 0.4
Spleen	0.91 ± 0.16	1.11 ± 0.25	1.21 ± 0.24	1.04 ± 0.12*	1.10 ± 0.15*	1.37 ± 0.28*
Muscle	36 ± 4	37 ± 4	38 ± 3	48 ± 4*	51 ± 6*	50 ± 5*
Brain	3.9 ± 0.3	3.0 ± 0.2	3.7 ± 0.2	4.0 ± 0.2	3.9 ± 0.2	3.9 ± 0.2
Right ventricle	0.87 ± 0.07	0.87 ± 0.08	0.88 ± 0.07	0.95 ± 0.08	1.07 ± 0.09	1.18 ± 0.09*
Right atrium	1.05 ± 0.14	0.90 ± 0.14	1.00 ± 0.19	1.29 ± 0.21	1.45 ± 0.25*	1.70 ± 0.21*
Left atrium	0.96 ± 0.09	1.04 ± 0.16	0.89 ± 0.05	1.10 ± 0.11	1.23 ± 0.18	1.29 ± 0.17

†Doses of bisoprolol are in $\mu g \cdot kg^{-1}$. [Bisoprolol] = arterial plasma concentrations of bisoprolol ($ng \cdot ml^{-1}$). (= number of observations. Because of the limited number of microspheres available measurements could not l made at each concentration; [a] in $mmHg \cdot min \cdot ml^{-1} \cdot 100g^{-1}$; [b]hepatic artery flow only; *$P < .05$ vs. predrug $ng \cdot ml^{-1}$. All data have been presented as means ± SEM.

Systemic Hemodynamics

Beta-adrenoceptor antagonists usually decrease cardiac output by negative chronotropic and inotropic actions. This study shows that when the reduction in heart rate is related to that in maxLVdP/dt, bisoprolol behaves very similarly to some other beta-adrenoceptor antagonists such as bevantolol (cardioselective) and propranolol (noncardioselective), which have been evaluated in the same model [Wolffenbuttel and Verdouw, 1983; Hartog et al., 1986; Verdouw et al., 1986].

In the present study heart rate had only a minor effect on maxLVdP/dt, which is in agreement with the results reported earlier for the same species [Scheffer and Verdouw, 1983]. This implies that the decrease in maxLVdP/dt mainly reflects a decrease in myocardial contractility, because the changes in pre- and afterload were of minor importance. Since autonomic cardiac innervation was preserved, we cannot conclude whether this decrease in maxLVdP/dt was the result of a direct myocardial depressant effect, or the result of inhibition of the sympathimometic activity, or (most probably) a combination of both. Stroke volume did not change until the highest doses. Hence, the prolongation of the left ventricular ejection phase, a consequence of the negative chronotropic activity of bisoprolol, compensated for the negative actions on stroke volume caused by the decreases in myocardial contractility. Left ventricular end-diastolic blood pressure decreased slightly in spite of the bradycardia. When the heart was stimulated at the predrug rate, left ventricular end-diastolic pressure decreased, which may have contributed to the decrease in stroke volume in this situation.

As described for other beta-adrenoceptor antagonists devoid of partial agonist activity, we observed an acute fall in cardiac output while mean arterial blood pressure was virtually unchanged [Man in 't Veld and Schalekamp, 1983; Wolffenbuttel and Verdouw, 1983; Verdouw et al., 1986]. Consequently systemic vascular resistance must have increased. Man in 't Veld and Schalekamp [1983] also pointed out that although arterial blood pressure hardly changes for hours after the acute intravenous administration, all beta-adrenoceptor antagonists ultimately lower arterial blood pressure to the same extent (10–15%). This occurs without further changes in cardiac output but by a lowering of the systemic vascular resistance. There is, at present, no evidence that bisoprolol will exhibit a different pattern during chronic treatment.

Myocardial Performance

The decrease in myocardial work, calculated as the product of mean arterial blood pressure and cardiac output, was accompanied by a similar decrease in myocardial O_2 consumption. The changes in left ventricular O_2 consumption were very closely related to those in blood flow as myocardial O_2 extraction was not significantly affected. The reduction in flow was uniformly distributed over all myocardial layers, which was not surprising in view of the relative minor changes in the cardiovascular parameters which determine the distribution of transmural myocardial blood flow [see Feigl, 1983]. Similar results have been described for other beta-adrenoceptor antagonists [Saxena, 1983; Verdouw et al., 1986].

The regional myocardial function data do not contribute significantly to the characterization of the cardiovascular profile of pharmacological agents in animals with an intact coronary circulation but are very informative when the coronary circulation is impeded. In that situation a beta-adrenoceptor may improve function by a redistribution of blood flow (see Saxena, 1983). On the other hand, the negative inotropic actions of these agents could mask this improvement. Knowledge about the actions of these agents on regional function therefore facilitates interpretation of the data obtained during myocardial ischemia.

Regional Blood Flows

The decreases in cardiac output were fairly uniformly distributed over most regional vascular beds, although it is encouraging that in view of the possible clinical applications of this drug, cerebral blood flow was well preserved and renal and skeletal muscle blood flows were also only moderately affected. The most dramatic decreases were, however, observed in spleen and hepatic artery blood flow. Similar results have been reported for bevantolol [Verdouw et al., 1986]. Tsuchiya et al. [1978] have reported that, at least in untreated conscious rats, hepatic artery flow measurements are not very reproducible but that the flow data increased with each following batch of microspheres. Since in the present hepatic artery flow decreased, it is unlikely that this decrease is caused by lack of reproducibility of the microsphere method. Besides, hepatic artery flow data obtained with the microsphere method were reproducible in conscious pigs when measurements were repeated 24 hr later (Duncker et al., 1987).

In summary, we conclude that the cardiovascular profile of bisoprolol is similar to that of other beta-adrenoceptor antagonists and may therefore be useful in the treatment of hypertension and myocardial ischemia.

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