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Changes in regional blood flows and myocardial performance after administration of bisoprolol to pigs

P. D. VERDOUW, D. J. DUNCKER, I. O. L. SCHMEETS, L. J. v. WOERKENS AND P. R. SAXENA

*Laboratory for Experimental Cardiology, Thoraxcenter and *Department of Pharmacology, Erasmus University Rotterdam, Rotterdam, The Netherlands.*

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The cardioselective beta-adrenoceptor antagonist bisoprolol (4–1024 μg kg^{-1}) caused in anaesthetized open-chest pigs a dose-dependent decrease in cardiac output, which was primarily due to a negative chronotropic action as heart rate decreased more than stroke volume. The decrease in stroke volume apparently resulted from a negative inotropic action of the drug, reflected by a decrease in max LV dP/dt in animals both with and without atrial pacing. A mild increase in systemic vascular resistance prevented serious hypotension. Pulmonary artery pressure was not affected, as pulmonary vascular resistance increased although the increase was statistically significant only with the highest concentration. The dose-related decreases in left ventricular blood flow were equally distributed over all myocardial layers and were the consequence of the reduced metabolic needs of the myocardium. Cerebral blood flow was well preserved but the changes in blood flow to some other organs and tissues (kidneys, stomach and skeletal muscle) paralleled that in cardiac output. The systemic haemodynamic effects of bisoprolol (16–1024 μg kg^{-1}; i.v.) in conscious pigs resembled closely those observed in anaesthetised animals and were similar to those exerted by propanolol (25–300 μg kg^{-1}; i.v.) in the same preparation. The effectiveness of bisoprolol and propranolol in antagonizing isoprenaline-induced changes in heart rate and max LV dP/dt were, however, markedly different. While propranolol inhibited both parameters to the same extent, bisoprolol was more effective in inhibiting max LV dP/dt than heart rate responses in conscious animals, probably due to beta$_1$-adrenoceptor selectivity.

Beta-adrenoceptor antagonists are often the drugs of choice in the treatment of myocardial ischaemia, because they not only decrease heart rate and arterial blood pressure and thereby lower the metabolic needs of the myocardium but also because they favourably influence the maldistribution of oxygen-supply to the ischaemic myocardium.[1–3] It is now widely accepted that blockade of the beta$_1$-adrenoceptors in the heart is of paramount importance for protection of the myocardium. The use of beta$_1$-selective adrenoceptor antagonists has therefore increased progressively in recent years. It has also been shown that this class of beta-adrenoceptor antagonists has less adverse effects on maximum workload[4,5] and is less frequently the cause of dehydration and hyperthermia during heavy exercise[6].

Bisoprolol ((±)-1-[4-(2-isopropoxyethoxymethyl)-phenoxyl]-3-isopropylamino-2-propanol-fumarate (2:1), EMD 33512) is a new beta$_1$-selective adrenoceptor antagonist, which in anaesthetized animals has been shown to have a much higher beta$_1$/beta$_2$-adrenoceptor antagonism ratio than either atenolol or metoprolol[7,8]. Knowledge of the effects of bisoprolol on cardiovascular performance is rather limited[9]. We now report in detail on the cardiovascular effects of bisoprolol in anaesthetised and conscious pigs. In the anaesthetized animals special emphasis has been placed on regional blood flow and regional myocardial performance, whereas in the conscious animals the

Address for correspondence: P. D. Verdouw, PhD, Laboratory for Experimental Cardiology, Thoraxcenter, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

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systemic haemodynamic and beta-antagonistic actions of bisoprolol were compared to those of propranolol.

Materials and methods

ANAESTHETIZED PIGS

Studies were performed on Yorkshire pigs (22–28 kg) which, after sedation with 120 mg azaperone, were anaesthetized with 150 mg metomidate *i.v.* and subsequently intubated for artificial ventilation with a mixture of oxygen and nitrous oxide (1:2). Respiratory rate and tidal volume were set to keep arterial blood gas-values (ABL-3, Radiometer, Copenhagen, Denmark) in the normal range.

A cannula was placed in the descending aorta for collection of blood, while the superior caval vein was catheterized for administration of 100 mg kg^{-1} -D(+)-gluco-chloralose (Merck, Darmstadt, F.R.G.) and haemaccel® (Behringwerke, Marburg, F.R.G.) to replace blood loss. Tips of catheters (Honeywell and Philips Medical Electronics Group, Eindhoven, The Netherlands) 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.

After exposure of the heart via a midsternal split, an electromagnetic flow probe (Skalar, Delft, The Netherlands) was placed around the ascending aorta for measurement of the ascending aortic blood flow. The left atrial appendage was catheterized for the injection of microspheres (15 ± 1 μm, 3 NEN Company, Dreieich, F.R.G.) labelled with either ^{141}Ce, ^{113}Sn, ^{103}Ru, ^{95}Nb or ^{46}Sc for determination of regional blood flows. Details of this technique have been described elsewhere[10]. Myocardial wall thickness tracings, monitored with a 5 MHz ultrasonic transducer (Krautkramer–Branson, Lewistown, PA, USA) 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[11]. Haemoglobin concentration and oxygen-saturation in arterial and coronary venous blood samples were determined with an OSM2-hemoximeter (Radiometer, Copenhagen, Denmark). The difference in the arterial and coronary venous oxygen-contents was multiplied by the left ventricular blood flow to calculate left ventricular oxygen-consumption.

Concentrations of bisoprolol in arterial plasma were determined by high-performance liquid chromatography. The lower limit of detection was 1–2 ng ml^{-1} [12].

CONSCIOUS PIGS

After an overnight fast Yorkshire pigs (18–20 kg; $N = 7$), pretreated with a mixture of procaine penicillin-G and benzathine penicillin-G (Duplocillin®), both 300 000 U i.m. were sedated with 30 mg kg^{-1} ketamine HCl i.m. The animals were intubated and connected to a respirator for artificial ventilation while anaesthesia was maintained with a mixture of oxygen and nitrous oxide (1:2) to which 1% halothane was added. A jugular vein and a common carotid artery were cannulated for administration of drugs and measurement of mean arterial blood pressure, respectively. After access to the heart was obtained via the left fifth intercostal space, a pressure transducer (Konigsberg Instruments Inc, Pasadena, CA, USA) was implanted near the apex for recording the left ventricular pressure. The aorta was approached through the third intercostal space and an electromagnetic flow probe (Skalar, Delft, the Netherlands) was positioned around the ascending aorta for the determination of cardiac output. Catheters and wires were tunneled subcutaneously to the back, the chest was closed and the animals allowed to recover. Catheters were flushed daily to prevent blood clotting. Details of the surgery and antibiotic treatment during the postoperative period have been reported in detail elsewhere[13]. Following recovery from surgery, at least 4 sessions were held to adapt the animals to the experimental and laboratory facilities, before the experimental protocol was executed.

EXPERIMENTAL PROTOCOLS

Five cumulative doses of bisoprolol (4, 16, 64, 256 and 1024 μg kg^{-1}), administered over a period of 2 minutes at 20 minute intervals, were used to evaluate the effects on systemic haemodynamic effects and regional (including coronary) blood flows in 10 anaesthetized pigs.

In the conscious animals the systemic haemodynamic and beta adrenoceptor blocking properties of bisoprolol (16, 64, 256 and 1024 μg kg^{-1}; $N = 7$), injected over a period of 2 minutes at 30 minute intervals were compared with those of propranolol. The latter was administered over 2 minute periods at 15 min intervals in doses of 25, 25, 50 and 200 μg kg^{-1} (total dose 25, 50, 100 and 300 μg kg^{-1}; $N = 6$). Dose–response curves were constructed with isoprenaline (0·25, 0·5, 0·1, 0·2 and

$0{\cdot}4\,\mu g\,kg^{-1}$ injected before and after the administration of different doses of the two antagonists. Doses of isoprenaline eliciting increases in heart rate (20 beats m^{-1}) and in max LV dP/dt (1000 mmHg s^{-1}) were calculated to determine the dose ratio of isoprenaline before and after each dose of the antagonists.

Finally, a group of anaesthetized pigs was subjected to 3 successive occlusions of the proximal left anterior descending coronary artery for 10 minutes at 30 minutes intervals. These animals received no medication ($N = 6$) or were pretreated with either $300\,\mu g\,kg^{-1}$ ($N = 4$) or $1000\,\mu g\,kg^{-1}$ ($N = 5$) bisoprolol. The incidence of ventricular arrhythmias during occlusion and reperfusion and the recovery of regional myocardial wall function was assessed. Animals which encountered a ventricular fibrillation but could not be defibrillated within 30 seconds were excluded from further study. No antiarrhythmic drugs were administered at any time.

DATA PRESENTATION AND STATISTICAL ANALYSIS

The data in some figures have been presented as percentage change from baseline. Statistical analysis was, however, performed on the actual data using a parametric two-way analysis of variance (randomized block design) followed by Duncan's new multiple range test. P values of less than 0·05 were considered statistically significant.

Results

SYSTEMIC CIRCULATION IN ANAESTHETIZED PIGS

Dose-dependent decreases were observed in heart rate (up to 22%), mean arterial blood pressure (up to 14%), cardiac output (up to 30%) and max LV dP/dt (up to 46%) whereas systemic vascular resistance increased up to 28% (Fig. 1).

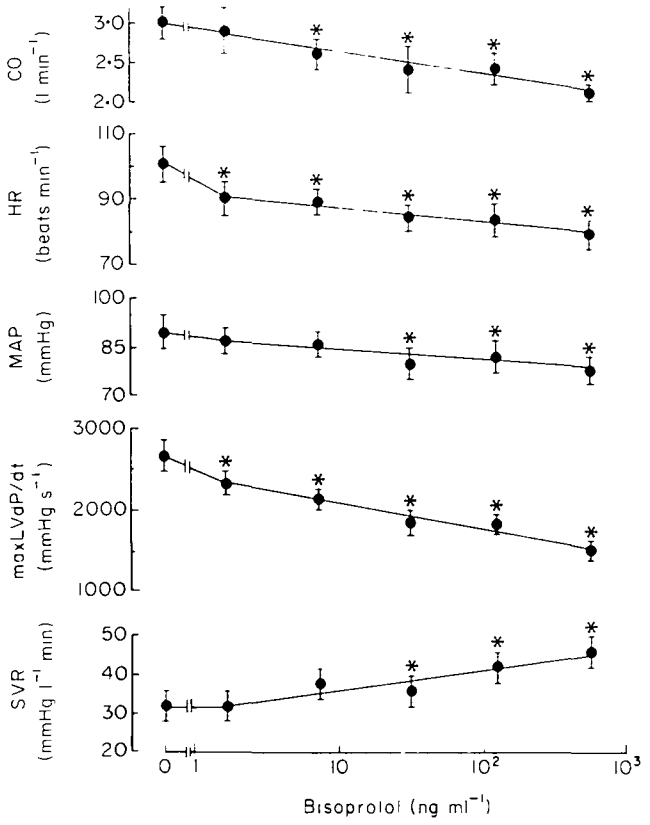

Figure 1 Changes in systemic haemodynamics with increasing plasma levels of bisoprolol in 10 anaesthetized pigs. Shown are cardiac output (CO), heart rate (HR), mean arterial blood pressure (MAP), the maximum rate of rise in left ventricular pressure (max LV dP/dt) and systemic vascular resistance (SVR). Data have been presented as mean ±SEM. $^*P < 0{\cdot}05$ *vs* pre-drug value.

For concentrations lower than 30 ng ml^{-1}, the relative decrease in cardiac output was less than that in heart rate but for higher concentrations the reverse was true. Consequently, stroke volume initially increased but decreased with higher concentrations. Amongst the determinants of stroke volume, myocardial contractility (max LV dP/dt) was most affected. The negative chronotropic action of bisoprolol did not contribute to the decrease in max LV dP/dt because raising heart rate to pre-drug levels by means of atrial pacing had no effect on max LV dP/dt.

PULMONARY CIRCULATION

Mean pulmonary artery pressure (24 ± 3 mmHg) was not affected by bisoprolol. Pulmonary vascular resistance (baseline 5·1 ± 0·7 mmHg min l^{-1}) remained therefore constant until 600 ng ml^{-1} when there was an increase to 7·3 ± 1·0 mmHg min l^{-1} ($P < 0·05$).

CORONARY CIRCULATION

Left ventricular blood flow decreased with increasing plasma concentrations down to 44 ± 5% of its pre-drug value of 144 ± 8 ml min^{-1} 100 g^{-1} (Fig. 2). The decrease in perfusion was uniformly distributed over the myocardial layers (endo/epi blood flow ratio was 1·13 ± 0·04 at baseline and 1·09 ± 0·06 during the last measurement, $P > 0·05$). Since the fall in mean arterial blood pressure (Fig. 1) was considerably less than the decrease in left ventricular blood flow (Fig. 2), the calculated coronary vascular resistance showed a dose-related increase. Myocardial oxygen extraction was only minimally affected as coronary venous oxygen saturation (baseline 15 ± 2%) was only different from the pre-drug value at plasma concentrations of 30 ng ml^{-1} (not shown). Left ventricular oxygen consumption therefore decreased in accordance with the decrease in left ventricular blood flow (Fig. 2).

Wall thickness at end-diastole (pre-drug 10·4 ± 0·5 mm) did not change significantly after administration of bisoprolol. The velocity of systolic wall thickening decreased gradually from a pre-drug value of 7·7 ± 0·5 mm s^{-1} to 6·0 ± 0·6 mm s^{-1} at 125 ng ml^{-1} and than more abruptly to 4·7 ± 0·5 mm s^{-1} at 600 ng ml^{-1}. The lengthening of the left ventricular ejection period, due to the bradycardiac action of bisoprolol, prevented that the wall thickness at end-systole (pre-drug 15·4 ± 0·05 mm) was reduced until the last dose was administered (14·4 ± 0·7 mm, $P < 0·05$). Consequently systolic wall thickening (pre-drug; 48 ± 2%) was not affected until the last dose was administered (34 ± 3%, $P < 0·05$).

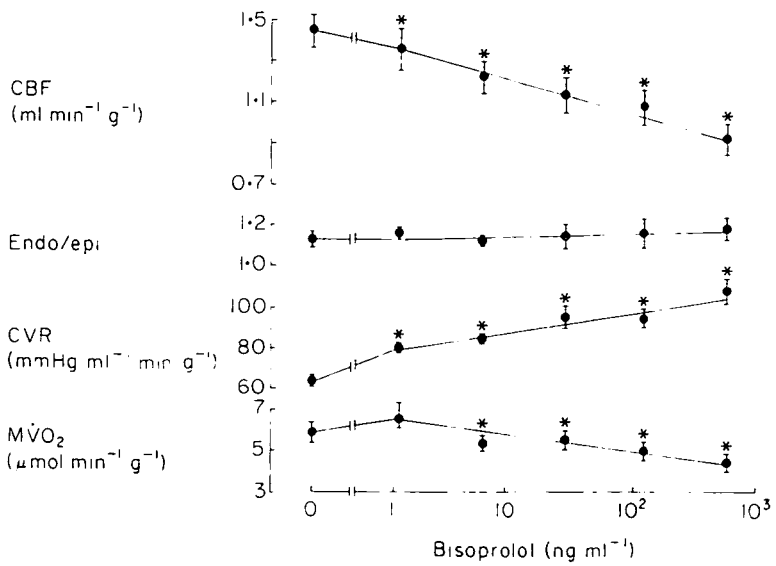

Figure 2 Changes in coronary circulation with increasing plasma concentrations of bisoprolol in 10 anaesthetized pigs. Shown are transmural left ventricular blood flow (CBF), subendocardial–subepicardial blood flow ratio (endo/epi), coronary vascular resistance (CVR) and left ventricular oxygen consumption ($MV̇O_2$). Data have been presented as mean ±SEM. *$P < 0·05$ *vs* pre-drug value.

REGIONAL BLOOD FLOWS AND RESISTANCES

With the exception of cerebral blood flow, which did not decrease until the last dose (15%), perfusion of other organs and tissues decreased dose-dependently. For some (stomach, muscle and kidneys) the decreases (up to 30%) were similar to those in cardiac output (Fig. 3). For the small intestine they tended to be less (up to 20%), whereas perfusion of the spleen and hepatic artery flow decreased more (up to 45% and 60%, respectively). Flow to the skin and adrenals did not change significantly (not shown).

Resistances of the regional vascular beds perfusing brain, kidneys and small intestines were only minimally affected (0%, +15% and +15%, respectively), but dose-dependent increases occurred in other regional vascular beds (spleen, up to 60%; muscle, up to 40.%; and stomach, up to 30%).

MULTIPLE CORONARY ARTERY OCCLUSIONS AND REPERFUSION

Administration of 300 or 1000 $\mu g\,kg^{-1}$ bisoprolol had no significant effect on systolic wall thickening. Immediately after its occlusion the area perfused by the left anterior descending coronary artery ceased to contract as indicated by the complete loss of systolic wall thickening. Bisoprolol did neither affect the magnitude nor the time course of loss of function. Ventricular arrhythmias occurred in all 3 groups, but ventricular fibrillation was only seen in one of the six untreated animals, two of the four animals pretreated with 300 $\mu g\,kg^{-1}$ bisoprolol and in none of the animals which received 1000 $\mu g\,kg^{-1}$ bisoprolol. Recovery of systolic wall function was similar for all three groups of animals: from $33 \pm 4\%$ (pre-occlusion) to $21 \pm 5\%$ at the end of reperfusion for the untreated animals and from $30 \pm 2\%$ to $21 \pm 6\%$ for the animals pretreated

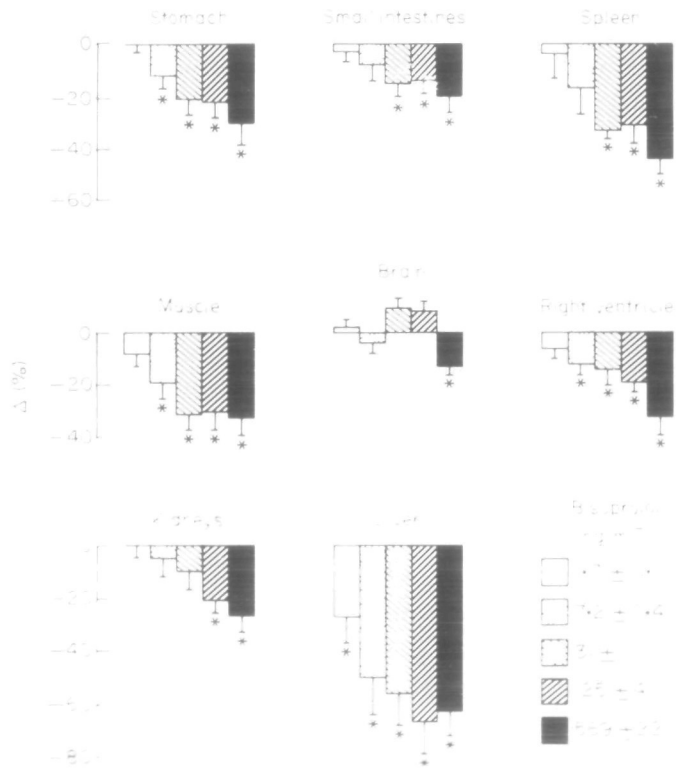

Figure 3 Changes in regional blood flows with increasing plasma concentrations of bisoprolol in 10 anaesthetized pigs. Pre-drug values [in ml $min^{-1}(100\,g)^{-1}$] were 19 ± 4 (stomach), 34 ± 2 (small intestine), 121 ± 17 (spleen), $2{\cdot}7 \pm 0{\cdot}3$ (muscle), 24 ± 1 (brain), 107 ± 6 (right ventricle), 241 ± 17 (kidneys) and 33 ± 9 (liver, hepatic artery flow only).

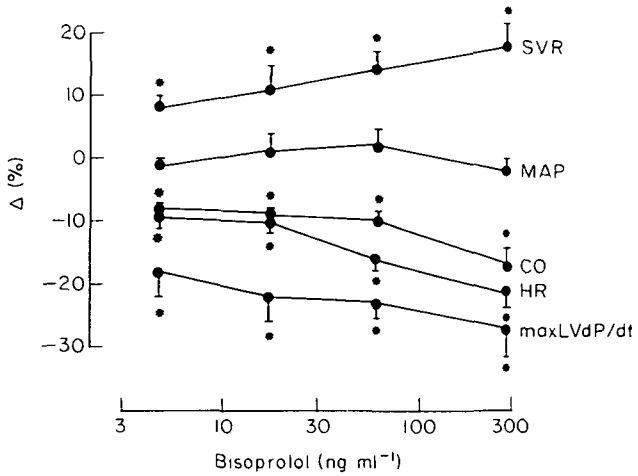

Figure 4 Changes in systemic haemodynamics with increasing doses of bisoprolol in 7 conscious pigs. The pre-drug values of heart rate (HR), cardiac output (CO), mean arterial blood pressure (MAP), the maximum rate of rise in left ventricular pressure (max LV dP/dt) and systemic vascular resistance (SVR) were 128 ± 3 beats min^{-1}, $2{\cdot}7 \pm 0{\cdot}11$ min^{-1}, 111 ± 3 mmHg, 2480 ± 120 mmHg s^{-1} and 42 ± 3 mmHg $min\ l^{-1}$, respectively. For further details see legends of Fig. 1.

with 1000 $\mu g\ kg^{-1}$ bisoprolol. No representative data could be obtained in the group which received the lower dose of the antagonist because of the low number of animals. During a subsequent second and third occlusion-reperfusion period, ventricular fibrillation occurred in two animals of each group. After a third occlusion-reperfusion period none of the untreated, only one of the animals which received 300 $\mu g\ kg^{-1}$, and two of the animals which received 1000 $\mu g\ kg^{-1}$ were still alive. Evaluation of recovery of function during reperfusion was therefore not possible after the second and third occlusion.

SYSTEMIC CIRCULATION IN CONSCIOUS PIGS

Bisoprolol caused dose-related decreases in cardiac output (up to 17%), heart rate (up to 21%) and max LV dP/dt (up to 27%). In spite of the decrease in cardiac output, mean arterial blood pressure was maintained because systemic vascular resistance increased up to 18% (Fig. 4). Left ventricular filling pressure (not shown) increased from $8{\cdot}6 \pm 0{\cdot}6$ mmHg to $15{\cdot}0 \pm 2{\cdot}1$ mmHg. With propranolol similar dose-related changes in these parameters were observed. This is illustrated in Fig. 5 which depicts the relation between the changes in max LV dP/dt and cardiac output and the changes in heart rate of both substances. One must bear in mind, however, that the dose range of bisoprolol (16–1024 $\mu g\ kg^{-1}$) was considerably wider than that of propranolol (25–300 $\mu g\ kg^{-1}$).

ANTAGONISM OF CARDIAC RESPONSES TO ISOPRENALINE IN CONSCIOUS PIGS

Modifications of the isoprenaline-induced changes in heart rate and max LV dP/dt by

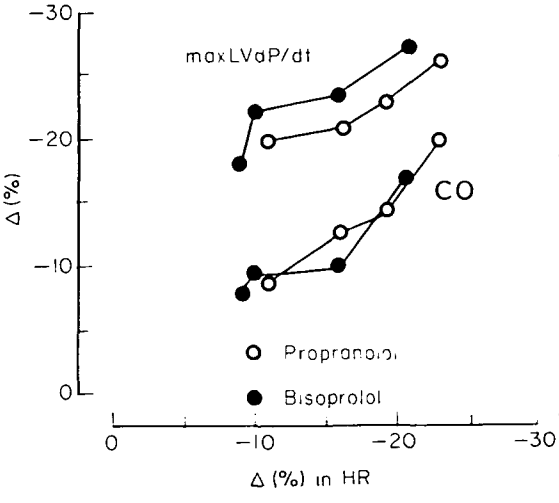

Figure 5 Relation between the changes in max LV dP/dt and cardiac output (CO) and the changes in heart rate (HR) after bisoprolol (16–1024 $\mu g\ kg^{-1}$) and propranolol (25–300 $\mu g\ kg^{-1}$).

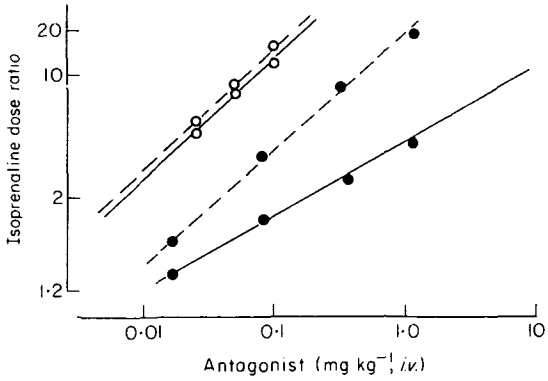

Figure 6 Antagonism by intravenously (*i.v.*) administered bisoprolol (●) and propranolol (○) of responses to isoprenaline-induced changes in heart rate (—) and max LV dP/dt(– – –) in 6 conscious pigs. Notice the split in the heart rate and max LV dP/dt responses after administration of bisoprolol.

bisoprolol and propranolol have been presented in Fig. 6. The figure shows that bisoprolol is more effective in antagonizing the effects on max LV dP/dt than those on heart rate, whereas propranolol was equi-effective in inhibiting the increase in these parameters. Furthermore, on a $\mu g\,kg^{-1}$ basis, propranolol was more potent than bisoprolol in antagonizing the isoprenaline-induced increases in heart rate and max LV dP/dt.

Discussion

SYSTEMATIC AND REGIONAL HAEMODYNAMICS

Beta-adrenoceptor antagonists usually decrease cardiac output because of their negative chronotropic and (or) inotropic actions. In this study, in the conscious animals the decrease in heart rate was the only factor for the reduced myocardial pump function, while in the anaesthetized animals a small decline in stroke volume also contributed. The observations that stroke volume was not affected in the conscious animals, but decreased slightly in the anaesthetized animals deserve some comments. Myocardial contractility, reflected by max LV dP/dt, was already slightly depressed in the anaesthetized animals and a further reduction by bisoprolol may have exerted a negative effect on stroke volume. Another factor could be the increase in left ventricular filling pressure in the conscious animals, which was conspicuously absent in the anaesthetized open-chest preparations. With two other beta-adrenoceptor antagonists (propranolol and the $beta_1$-selective antagonist bevantolol[3]), investigated under the same experimental conditions, similar observations were made[3,14].

In the anaesthetized animals, myocardial work was decreased due to a reduction in both cardiac output and, though of a smaller magnitude, mean arterial blood pressure. This was accompanied by similar decreases in left ventricular oxygen consumption and, because myocardial oxygen extraction was virtually unaffected, in left ventricular blood flow. This is again similar to our observations with bevantolol and propranolol under the same experimental conditions, although we observed a slight decrease in myocardial oxygen extraction with bevantolol[3] and a slight increase with propranolol[14]. That the decrease in coronary flow in non-ischaemic hearts was uniformly distributed over the different myocardial layers was also not unexpected[2,3].

The decreases in regional flows were in general parallel to those in cardiac output, but the finding that cerebral perfusion was so well preserved is encouraging but, again, not different from that observed with bevantolol[3].

Although in the conscious animals the systemic haemodynamic actions of propranolol and bisoprolol were very similar, the effectiveness of bisoprolol and propranolol in antagonizing the isoprenaline-induced changes in heart rate and max LV dP/dt, were markedly different. Propranolol inhibited the max LV dP/dt and heart rate increases to a similar extent, whereas bisoprolol was more effective in inhibiting max LV dP/dt than heart rate. This "splitting" is probably due to $beta_1$-adrenoceptor selectivity and has also been described for atenolol[8]. Isoprenaline decreases arterial blood pressure via vascular $beta_2$-adrenoceptors. This, in turn, invokes the baroreceptor-reflex to enhance sympathetic tone but to reduce parasympathetic tone. As the atria are richly innervated by the parasympathetic system[15], the withdrawal of parasympathetic tone also contributes in increasing heart rate which, in contrast to the tachycardia mediated via $beta_1$-adrenoceptors (both reflexogenic and directly due to isoprenaline) can not be suppressed by beta-adrenergic blockade. Since the ventricles are only scarcely innervated by the parasympathetic nervous system, both the reflex-mediated and 'directly'-induced increases in max LV dP/dt after isoprenaline administration are a consequence of $beta_1$-adrenoceptor stimulation. Therefore, it is to be expected that $beta_1$-adrenoceptor selective antagonists, such as bisoprolol, would antagonize the increase in

max LV dP/dt more than in heart rate. Propranolol, on the other hand, blocks both types of beta-adrenoceptors, thereby attenuating the fall in arterial blood pressure and, in turn, the contribution of parasympathetic withdrawal to the isoprenaline-induced tachycardia. Indeed Brick *et al.*[16] observed that after their patients had been atropinized, practolol, another $beta_1$-selective agent, became almost as potent as propranolol in blocking the isoprenaline-induced tachycardia. In addition to the above explanation, however, the involvement of cardiac $beta_2$-adrenoceptors in the tachycardiac response to isoprenaline can not be excluded[17].

RECOVERY OF SYSTOLIC WALL FUNCTION AFTER MULTIPLE CORONARY ARTERY OCCLUSIONS

Pigs are very susceptible to ventricular arrhythmias following occlusion of a coronary artery[18,19]. In pigs these arrhythmias nearly always terminate in ventricular fibrillation within 30 min after a proximal occlusion of the left anterior descending coronary artery. As we intended to study recovery of regional wall function after coronary artery occlusion we used multiple occlusions of 10 minutes at 30 minute intervals to circumvent a high loss of animals. Although propranolol and a low dose of bevantolol ($0{\cdot}5\ mg\ kg^{-1}$) did not protect against ventricular fibrillation in this model, a dose of $1{\cdot}5\ mg\ kg^{-1}$ of bevantolol offered a nearly complete protection against fatal arrhythmias and the study of short-term recovery of regional myocardial function could be accomplished[3]. In the present study, however, a high dose of bisoprolol ($1\ mg\ kg^{-1}$), providing adequate beta-adrenoceptor blockade, did not protect against ventricular fibrillation during the later occlusion and reperfusion periods and the analysis of short-term recovery of regional function could not be accomplished. Most beta-adrenoceptor antagonists have been found ineffective in pigs against arrhythmias induced by acute coronary artery ligation[20–23]. Re-entry is very likely the mechanism leading to ventricular arrhythmias immediately following coronary artery occlusion. Thus, from our animal experiments unequivocal conclusions regarding the possible antiarrhythmic effects of beta blockers in the clinical setting (chronic ventricular arrhythmias) are not justified.

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