Br. J. Pharmac. (1984), **83**, 203–210

Influence of heart rate on the effects of prenalterol on regional myocardial blood flow and function during coronary stenosis in dogs

A. Berdeaux, C. Bonhenry, P. Duhazé, J.F. Giudicelli & C. Thuillez

Département de Pharmacologie, Faculté de Médecine Paris-Sud, 63, rue Gabriel Péri, 94270 Le Kremlin-Bicêtre, France

1 The effects of prenalterol, a selective β_1-adrenoceptor agonist with potent cardiac positive inotropic properties have been investigated on regional myocardial blood flow (RMBF) (microspheres) and contractile function (ultrasonic crystals) during partial circumflex coronary artery stenosis in 8 open-chest anaesthetized dogs.

2 Prenalterol was investigated at two intravenous doses: 5 $\mu g\,kg^{-1}$, which increased myocardial contractility (*dP/dt max*: +29%) more than heart rate (+12%, up to 150 beats min^{-1}) and 20 $\mu g\,kg^{-1}$ which induced almost similar increases in contractility (+35%) and heart rate (+31% up to 175 beats min^{-1}). The induced modifications of regional flow and function were then compared to those produced in another series of 6 dogs by atrial pacing at 150 and 175 beats min^{-1} respectively.

3 Prenalterol significantly increased RMBF and segment length (SL)-shortening in a dose-dependent manner in the nonischaemic zone. In the ischaemic zone, RMBF was maintained and SL-shortening increased with prenalterol, 5 $\mu g\,kg^{-1}$ whereas both RMBF and contractile function were severely decreased with prenalterol, 20 $\mu g\,kg^{-1}$.

4 Atrial pacing had almost no effect on RMBF and SL-shortening in the nonischaemic zone. In the ischaemic zone, atrial pacing rate-dependently decreased both RMBF and SL-shortening.

5 Thus, a significant increase in contractility, associated with little tachycardia (prenalterol, 5 $\mu g\,kg^{-1}$), induces beneficial effects on RMBF and function in both the nonischaemic and ischaemic myocardium. In contrast, a strong tachycardia, whether accompanied by positive inotropic effects (prenalterol, 20 $\mu g\,kg^{-1}$) or not (atrial pacing at 175 beats min^{-1}) induces deleterious effects on RMBF and cardiac function in the ischaemic myocardium.

Introduction

Although it is generally considered that sympathomimetic amines have deleterious effects on evolving ischaemic damage by increasing oxygen demand (through their positive inotropic and chronotropic effects) and/or by decreasing oxygen supply (through coronary arterial hypotension), several authors have recently pointed out that in some circumstances, administration of these agents is not necessarily accompanied by an augmentation of the functional severity of ischaemic injury. For instance, after coronary occlusion in dogs, low doses of dopamine or dobutamine can decrease intramyocardial P_{CO_2} (Rude *et al.*, 1983), improve the regional contractility of the ischaemic zone (Vatner & Baig, 1979) and even reduce the ultimate infarct size (Liang *et al.*, 1981) providing that heart rate remains unchanged. These results tend to support the view that the increase in heart rate induced by β-adrenoceptor stimulation is more deleterious for the ischaemic myocardium than the concomitant increase in cardiac contractility, the latter being possibly associated with a lesser myocardial oxygen cost than the former.

Accordingly, the purpose of the present study was to compare the effects on regional myocardial blood flow (RMBF) and contractility of normal and ischaemic canine myocardium of (a) prenalterol (a selective β_1-adrenoceptor agonist with predominant inotropic vs chronotropic effects) (Manders *et al.*, 1980) and of (b) identical increases in heart rate produced by atrial pacing.

Methods

Materials and preparation

Fourteen mongrel dogs of either sex weighing 19 to 27 kg, were anaesthetized with sodium pentobarbitone (35 mg kg^{-1}, i.v.). Artificial ventilation with room air was performed through an endotracheal tube by means of a Harvard Respirator 907 and blood gases were analyzed at regular intervals. After thoracotomy in the fifth left intercostal space, the pericardium was opened and the heart suspended in a pericardial cradle. Catheters were inserted in the left ventricular (LV) cavity through the cardiac apex and in the ascending aorta. Catheters were placed in the left atrial appendage for microsphere injections and in the femoral artery for withdrawal of reference arterial blood samples used for RMBF calculation. The circumflex coronary artery was dissected free near its origin and a flow probe (Statham SP 7515, 2 to 3 mm i.d.) placed around the vessel. Coronary blood flow was recorded by use of an electromagnetic flowmeter (Statham 2202). A hydraulic occlusive snare was placed distal to the probe so that no branches were present between the probe and the occluder. The zero flow reference was obtained by mechanical occlusion with an arterial clamp. In six dogs pacing electrodes were sutured on the right atrium.

Aortic and LV pressures were measured by a hydraulic system (catheter connected to a Hewlett-Packard 1280C pressure transducer) and LV dP/dt was obtained by electronic differentiation of the LV pressure pulse. Heart rate was determined from the electrocardiogram (lead II). All data were recorded on a Hewlett-Packard 8800 multichannel recorder.

Regional myocardial contractility

To monitor myocardial segment shortening, two pairs of piezoelectric crystals were implanted 10–15 mm apart, parallel to the muscle fibres, at a depth of 7–11 mm within the subendocardial layer of the LV wall. The location of the crystals on the endocardial surface was confirmed at autopsy. One pair was placed in the area exhibiting maximum cyanosis during a brief temporary occlusion of the circumflex artery (ischaemic segment), the other pair was implanted in a distant nonischaemic area, supplied by the left anterior descending coronary artery (nonischaemic segment).

The ultrasonic technique used to obtain continuous measurements of the dimensions of these two myocardial segments has been described previously (Théroux *et al.*, 1974). Small 6MHz piezoelectric discs were excited by a 0.2 μs, 200 V pulse at a repeated rate of 1 KHz and segment length was obtained after calibration by measuring the transit time of ultrasounds with a sonocardiometer (Schuessler, model 401). End diastolic (EDL) and end systolic segment (ESL) lengths were defined as the instantaneous lengths at the onset of isovolumic contraction and at the onset of isovolumic relaxation, respectively. The values for segment length were normalized to a 10 mm initial dimension by dividing the observed length by the control EDL and multiplying by 10. This procedure was necessary for comparing data from different dogs because the distance between each pair of crystals was variable and arbitrary in relation to the actual circumference of each heart. The stroke excursion of segment length from end diastole to end systole was corrected by dividing by end diastolic dimension and expressed as percentage shortening.

All myocardial segment lengths were recorded on a Hewlett-Packard 8800 multichannel recorder at a paper speed of 100 mm s^{-1} and measurements were made at end expiration with the respirator turned off.

Regional myocardial blood flow (RMBF)

The distribution of RMBF was determined by use of the radioactive microsphere technique. The carbonized plastic microspheres used were 15 ± 5 μm in diameter and labelled with the gamma emitting nuclides: ^{141}Ce(10.8 mCi g^{-1}), ^{103}Ru (11.5 mCi g^{-1}), ^{96}Nb (12.6 mCi g^{-1}) and ^{46}Sc (12.4 mCi g^{-1}) (NEN Company). They were obtained as 1 mCi of nuclide suspended in 10 ml of 10% dextran to which one drop of Tween 80 was added to minimize aggregation. After appropriate dilution, the mixture was shaken before injection by vigorous stirring with a Teflon-covered magnet and by applying 50 W of ultrasound (10 min) with an Ultrasonic NSU 144 ultrasound generator. Approximately 2 million beads were injected into the left atrium for each RMBF determination, without significant changes in coronary haemodynamics during or immediately after microsphere injection (Berdeaux *et al.*, 1978).

The sequence of the isotopes used was chosen at random. Beginning simultaneously with each microsphere injection and continuing for 90 s, a reference sample of arterial blood was collected from the femoral catheter at a constant rate of 20 ml min^{-1} using a Sage Instruments model 351 withdrawal pump. Each arterial blood reference sample was collected in 6 separate 15 s aliquots which were counted individually to ensure that all radioactivity had been cleared from the circulation within the sampling interval. After the animals had been killed the heart was excised and fixed in 4% formaldehyde for 48 h. One transmural tissue sample (1 to 2 g) of each zone in which a pair of ultrasonic crystals was implanted was then subdivided in epicardial and

endocardial layers, weighed and counted with appropriately selected energy windows in a gamma well counter (Compugamma, LKB Co.). The raw counts were then corrected for background and energy cross-over and compared with the reference sample to obtain the flow (ml $min^{-1} g^{-1}$ of tissue): knowing the rate of withdrawal of the reference sample (Qr) and its radioactivity (Cr), we used myocardial activity (Cm) to compute myocardial blood flow (Qm) as : $Qm = Qr \times Cm/Cr$. Endocardial and epicardial blood flows and endo/epi ratios were then determined for each of the nonischaemic and ischaemic zones.

Experimental design

The experimental protocol was similar to that previously described by Thuillez *et al.* (1983a, b). Two groups of dogs were used: a prenalterol-treated group ($n = 8$) and an atrial pacing-treated group ($n = 6$).

In the prenalterol group, after instrumentation, control haemodynamic, coronary blood flow and segmental shortening parameters were measured and a first set of microspheres was injected for the pre-stenosis RMBF determination. The circumflex coronary artery was then gradually constricted with the hydraulic occluder and a stenosis sufficient to abolish reactive hyperaemia and to reduce coronary blood flow by 40–50% was produced. Ten minutes later, when a stable pattern of segmental hypofunction within the ischaemic zone was obtained, haemodynamic, contractility and RMBF (2nd set of microspheres) parameters were measured. Then prenalterol was infused (1 $\mu g\,kg^{-1}\,min^{-1}$) during 5 min (total dose: 5 $\mu g\,kg^{-1}$) and a 3rd set of microspheres was injected. Finally, prenalterol was reinfused at a dose of 4 $\mu g\,kg^{-1}\,min^{-1}$ for 5 min (total dose: 20 $\mu g\,kg^{-1}$) and a last series of measurements and microspheres injection (4th set) was performed.

In the atrial pacing group, the same experimental protocol was followed but saline was infused instead of prenalterol (in the same volume and at the same infusion rate) and measurements were made before stenosis, 10 min after a stable pattern of stenosis-induced effects and then after atrial pacing (rectangular pulses, 2 V, 2 ms) at the two mean heart rate values recorded in the prenalterol group during the two types of infusions (5 and 20 $\mu g\,kg^{-1}$), i.e. respectively 150 and 175 beats min^{-1}.

Drugs

The laevo-isomer of prenalterol, (−)-[1-(4-hydroxyphenoxy - isopropyl - amino - 2 - propanol) hydrochloride], was used. It was dissolved at the required concentrations in saline. Doses are expressed in terms of the base.

Data analysis

All values quoted in the text are means ± s.e.mean. All data were compared to pre-stenosis control values by a paired *t* test.

Intragroup comparison of data from multiple time periods was performed by an analysis of variance (ANOVA) for repeated measures followed by the Newman-Keul's multiple range test.

Table 1 The haemodynamic values before, after left circumflex coronary (LCx) stenosis and after subsequent intravenous prenalterol (5 and 20 $\mu g\,kg^{-1}$) or atrial pacing (AP) (150 and 175 beats min^{-1}) treatments

	Heart rate (beats/min)	*Mean arterial blood pressure* (mmHg)	*LV systolic blood pressure* (mmHg)	*LVEDP* (mmHg)	*LV*dP/dt max $mmHgs^{-1}$	*LCx blood flow* (ml min^{-1})
Before LCx stenosis						
Prenalterol	136 ± 9	134 ± 4	168 ± 5	5.7 ± 1.5	3593 ± 412	48 ± 6
AP	131 ± 10	139 ± 10	159 ± 13	6.6 ± 1.7	3333 ± 220	41 ± 8
10 min after LCx stenosis						
Prenalterol	134 ± 8	128 ± 3	162 ± 4	5.8 ± 1.3	3550 ± 352	24 ± 3**
AP	133 ± 9	134 ± 9	152 ± 12	7.7 ± 2.4	2813 ± 120	25 ± 6**
20 min after LCx stenosis						
Prenalterol (5 $\mu g\,kg^{-1}$)	151 ± 10*†	134 ± 4	170 ± 4	3.8 ± 1.1*†	4586 ± 475*†	24 ± 3**
AP (150 beats min^{-1})	150	129 ± 8	146 ± 11	11.2 ± 1.6*	3083 ± 279	19 ± 4**
30 min after LCx stenosis						
Prenalterol (20 $\mu g\,kg^{-1}$)	176 ± 13**†‡	110 ± 7*	147 ± 7*	2.2 ± 1.3*†‡	4835 ± 383**†‡	15 ± 3**†‡
AP (175 beats min^{-1})	175	115 ± 5*	134 ± 8**	12.8 ± 1.8*†‡	3350 ± 150	11 ± 3**†‡

Values are means ± s.e.mean ($n = 8$ in prenalterol and AP groups).
Significantly different from pre-LCx stenosis value: $*P < 0.05$; $**P < 0.01$.
Significantly different from 10 min-LCx stenosis value: $\dagger P < 0.05$.
Significantly different from prenalterol (5 $\mu g\,kg^{-1}$) or AP (150 beats min^{-1}) corresponding value: $\ddagger P < 0.05$.

Results

Effects of coronary artery stenosis

As shown in Table 1, mean circumflex coronary blood flow was significantly reduced by approximately 40–50% after 10 min of stenosis ($P<0.01$) whereas heart rate, mean arterial pressure, LV systolic pressure, LVEDP and dP/dt_{max} remained unchanged as compared to their corresponding pre-stenosis values in both groups of dogs.

In the ischaemic zone (Figure 1), both RMBF and endo/epi ratio were significantly reduced after coronary stenosis and to the same extent in both groups of dogs. Simultaneously, EDL increased significantly ($P<0.05$) and systolic shortening was severely depressed ($P<0.001$).

In the nonischaemic zone, RMBF and endo/epi ratio were not affected by coronary stenosis (Figure 2). In reaction to the loss of shortening in the ischaemic zone and as previously observed in this model (Théroux *et al.*, 1974), active systolic shorten-

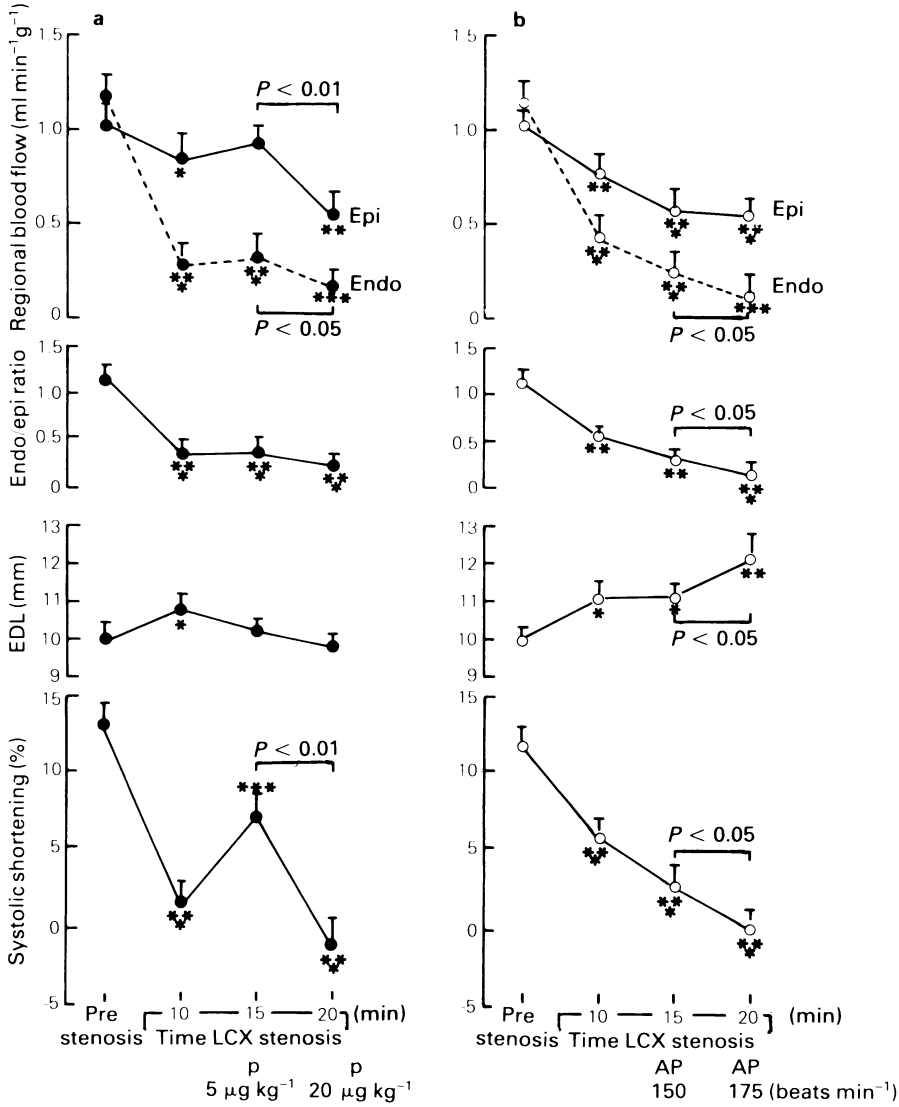

Figure 1 Effects of prenalterol (p) (●) (a) and atrial pacing (AP) (○) (b) on regional myocardial blood flow (Endo = endocardial; Epi = epicardial), endo/epi ratio, end-diastolic length (EDL) and % systolic shortening in the ischaemic zone during left circumflex (LCx) coronary stenosis in dogs. Values are means, vertical lines show s.e.mean. Significantly different from pre-stenosis values: $^{*}P<0.05$; $^{**}P<0.01$.

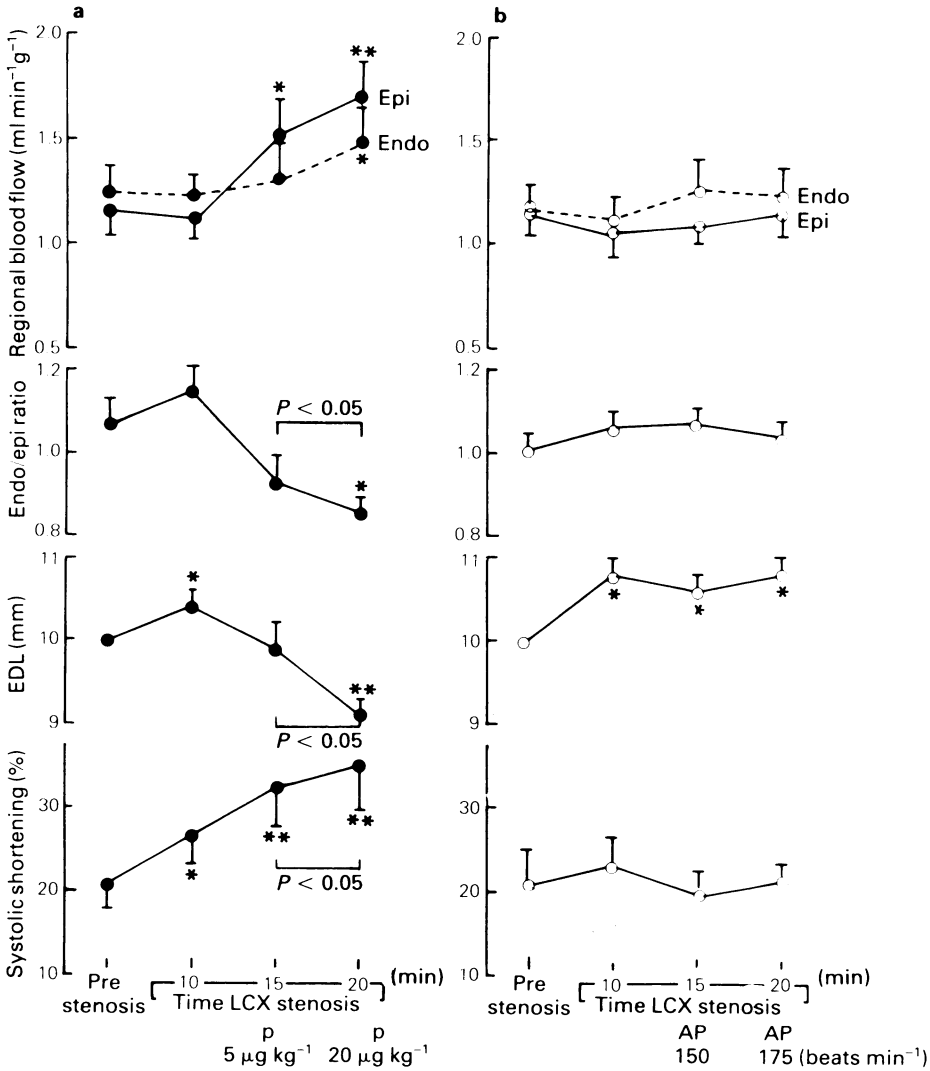

Figure 2 Effects of prenalterol (p) (●) (a) and atrial pacing (AP) (○) (b) on regional myocardial blood flow (Endo = endocardial; Epi = epicardial), endo/epi ratio, end-diastolic length (EDL) and % systolic shortening in the nonischaemic zone during left circumflex (LCx) coronary stenosis in dogs. Values are means, vertical lines show s.e.mean. Significantly different from pre-stenosis values: $*P<0.05$; $**P<0.01$; $***P<0.001$.

ing increased in both groups of dogs. However, this increase was significant only in the prenalterol group, in which the coronary stenosis was slightly more severe, as evidenced by more marked reductions in circumflex coronary blood flow and ischaemic systolic shortening.

These haemodynamic, RMBF and functional modifications were qualitatively and quantitatively similar to those observed with the same experimental protocol in previous studies (Gross *et al.*, 1978; Thuillez *et al.*, 1983a, b).

Effects of prenalterol (5 and 20 μg kg⁻¹) in the presence of coronary artery stenosis

As compared to the corresponding 10 min coronary stenosis values, prenalterol, 5 and 20 μg kg⁻¹, significantly and dose-dependently increased dP/dt_{max} (by respectively 29 and 35%) and heart rate (by respectively 12 and 31%) but significantly decreased LVEDP (by respectively 34 and 62%). Mean aortic pressure and LV systolic pressure decreased, although not significantly, and circumflex coronary

blood flow was significantly reduced only at $20\,\mu g\,kg^{-1}$ (Table 1).

As shown in Figure 2, in the nonischaemic zone, prenalterol significantly and dose-dependently increased both endocardial RMBF (respectively by $6\pm2\%$ and $21\pm6\%$ from $1.23\pm0.09\,ml\,min^{-1}\,g^{-1}$) and epicardial RMBF (respectively by $37\pm7\%$ and $54\pm9\%$ from $1.11\pm0.13\,ml\,min^{-1}\,g^{-1}$). Endo/epi ratio remained unchanged at $5\,\mu g\,kg^{-1}$ of prenalterol but was significantly decreased at $20\,\mu g\,kg^{-1}$ (from 1.15 ± 0.07 to 0.88 ± 0.02, $P<0.05$). Simultaneously, EDL decreased (by $12.5\pm2\%$ from 10.4 ± 0.2 mm at $20\,\mu g\,kg^{-1}$, $P<0.05$) and systolic shortening increased dose-dependently (from $26.5\pm3.3\%$ to respectively $32.4\pm4.9\%$, $P<0.05$ and $37.4\pm4.8\%$, $P<0.01$). The changes in nonischaemic myocardial function between prenalterol 5 and $20\,\mu g\,kg^{-1}$ were significant ($P<0.05$).

In the ischaemic zone (Figure 1), prenalterol, $5\,\mu g\,kg^{-1}$, did not modify RMBF and endo/epi ratio as compared to the corresponding 10 min coronary stenosis values. However at $20\,\mu g\,kg^{-1}$, prenalterol significantly decreased, and in the same proportions, both endocardial (by $39\pm7\%$ from $0.28\pm0.05\,ml\,min^{-1}\,g^{-1}$, $P<0.05$) and epicardial RMBF (by $35\pm11\%$ from $0.84\pm0.09\,ml\,min^{-1}\,g^{-1}$, $P<0.05$) and thus endo/epi ratio remained unchanged. The difference in RMBF values between prenalterol 5 and $20\,\mu g\,kg^{-1}$ was significant. Prenalterol had different effects on regional myocardial function since at $5\,\mu g\,kg^{-1}$ systolic shortening was increased (from $2.2\pm1.4\%$ to $6.6\pm2.5\%$, $P<0.05$) whereas it was decreased at $20\,\mu g\,kg^{-1}$ and the segments became either akinetic or slightly dyskinetic ($-1.1\pm1.7\%$, $P<0.01$ as compared to the corresponding value at $5\,\mu g\,kg^{-1}$).

Effects of atrial pacing in the presence of coronary artery stenosis

As shown in Table 1, atrial pacing at 150 beats min^{-1} did not change significantly the haemodynamic parameters as compared to 10 min coronary stenosis values. However, at 175 beats min^{-1} LVEDP increased ($P<0.05$) and circumflex coronary blood flow decreased ($P<0.05$) whereas LV systolic pressure, mean arterial pressure and dP/dt_{max} remained unchanged. Finally, LV systolic pressure and mean arterial pressure decreased but not significantly.

In the nonischaemic zone, atrial pacing did not change significantly RMBF, endo/epi ratios and functional parameters values, no matter the level of the imposed heart rate (Figure 2). However, in the ischaemic zone, atrial pacing significantly and rate-dependently decreased both endocardial (respectively by $42\pm10\%$ at 150 beats min^{-1} and by $74\pm13\%$ at 175 beats min^{-1}, from $0.43\pm0.06\,ml\,min^{-1}\,g^{-1}$) and epicardial RMBF (respectively by $26\pm9\%$ at 150 beats min^{-1} and by $30\pm8\%$ at 175 beats min^{-1}, from $0.77\pm0.11\,ml\,min^{-1}\,g^{-1}$). Only the decrease in endocardial RMBF between atrial pacing at 150 and 175 beats min^{-1} was significant ($P<0.05$). Since the atrial pacing-induced decrease in RMBF was more marked in the endocardium than in the epicardium at both heart rate levels, the endo/epi ratios were significantly decreased ($P<0.05$ between 150 and 175 beats min^{-1}). Simultaneously, whereas EDL was significantly increased only at 175 beats min^{-1} as compared to the corresponding 10 min coronary stenosis value, systolic shortening was significantly and rate-dependently decreased (from $5.9\pm2.1\%$ at 10 min coronary stenosis to $3.4\pm1.7\%$, $P<0.01$, at 150 beats min^{-1} and $1.1\pm0.9\%$, $P<0.01$, at 175 beats min^{-1}), the difference between the two atrial pacing levels being also significant ($P<0.05$) (Figure 1).

Discussion

Previous studies from our laboratory have shown that in our experimental model of severe circumflex coronary artery stenosis, all haemodynamic, regional flow and contractility parameters in the nonischaemic and ischaemic zones remain perfectly stable from the 10th up to at least the 30th minute following the stenosis (Thuillez *et al.*, 1983b). Thus, all modifications of these parameters observed during this time period in our two experimental groups can be accounted for either by prenalterol administration or atrial pacing.

Prenalterol is a potent and relatively long-acting cardioselective β_1-adrenoceptor agonist which differs from other natural or synthetic sympathomimetic agents in that it lacks concomitant β_2 or α-adrenoceptor stimulating properties in animals and man (Ariniego *et al.*, 1979; Scott *et al.*, 1979; Manders *et al.*, 1980). Moreover, despite the fact that prenalterol does induce positive chronotropic as well as inotropic actions, the latter predominate at low dosages as shown in the present study at $5\,\mu g\,kg^{-1}$. Although the mechanism of this relative selectivity of prenalterol for inotropic vs chronotropic function remains unknown, it clearly appears that the dose-dependent decrease in end-diastolic length and increase in active systolic shortening observed in the nonischaemic zone is only due to the prenalterol-induced increase in myocardial contractile force since at the same heart rate levels, atrial pacing does not modify these functional parameters. Similarly, the dose-dependent decrease in left ventricular end-diastolic pressure induced by prenalterol is probably also linked to the drug's positive inotropic effects since prenalterol *per se* does not affect preload (Manders *et al.*, 1980).

In doses ranging from 5 to 20 $\mu g\,kg^{-1}$, prenalterol has been shown not to affect arterial blood pressure in conscious dogs (Manders *et al.*, 1980). However, in our open-chest anaesthetized dogs with coronary stenosis, arterial blood presure tended to decrease with prenalterol, 5 and 20 $\mu g\,kg^{-1}$, an effect also previously observed with dobutamine (Liang *et al.*, 1981). This result could be due to the fact that both drugs, by improving myocardial performance, reduce the coronary stenosis-induced enhancement of sympathetic tone. However, it must be pointed out that in our experiments, atrial pacing at 150 and 175 beats min^{-1} decreased arterial blood pressure to the same extent as respectively prenalterol 5 and 20 $\mu g\,kg^{-1}$, so that the effect of prenalterol and pacing on RMBF and regional function were investigated at identical coronary perfusion pressure and heart rate values.

In the nonischaemic zone, RMBF increased in a dose-dependent manner with prenalterol, but at the same heart rate levels with atrial pacing RMBF remained unchanged. Although direct myocardial oxygen consumption was not measured in our study, it is clear that the cardiac oxygen demand during prenalterol infusion, with both β_1-adrenoceptor-mediated inotropic and chronotropic effects, is higher than during atrial pacing, leading thus to a greater myocardial vasodilatation in the nonischaemic zone through metabolic autoregulation. However, direct vasodilator effects of prenalterol cannot be excluded since the presence of both β_1 and β_2-adrenoceptors has been demonstrated on coronary vessels (Vatner & Hintze, 1983). Finally, nonischaemic regional function was improved by prenalterol at both doses and there was a close relationship between RMBF increase, especially in the endocardium, and subendocardial functional improvement.

In the ischaemic zone, prenalterol, depending upon the dose used, exerted two different patterns of effects on RMBF distribution and regional contractility. Thus, at 5 $\mu g\,kg^{-1}$, prenalterol maintained RMBF and improved ischaemic systolic shortening, contrasting with the effects of atrial pacing at 150 beats min^{-1} which worsened both RMBF and regional function. With prenalterol, 20 $\mu g\,kg^{-1}$, both RMBF and regional contractility were decreased, a picture similar to that observed with atrial pacing at 175 beats min^{-1}. These results must be considered in the light of those previously reported in anaesthetized (Marshall & Parratt, 1976; Willerson *et al.*, 1976; Warltier *et al.*, 1981; Rude *et al.*, 1982, 1983) or in conscious dogs (Vatner & Baig, 1979; Liang *et al.*, 1981) treated with dobutamine or dopamine during coronary artery occlusion or stenosis. Despite some differences, all these studies concluded that β-adrenoceptor agonists that induce coronary vasodilatation do not always cause a 'coronary steal phenomenon' nor necessarily enhance myocardial injury providing that coronary perfusion pressure is maintained and above all that tachycardia remains limited. Moreover our data with prenalterol, 5 $\mu g\,kg^{-1}$, demonstrate that these drugs can even exert beneficial effects on ischaemic contractile function because of their positive inotropic properties. This conclusion can be drawn from the comparison of the effects on ischaemic RMBF and contractile function of prenalterol infusion, 5 $\mu g\,kg^{-1}$, which are beneficial, and of atrial pacing at 150 beats min^{-1} which are deleterious. Since heart rate and coronary perfusion pressure are identical in both procedures, the difference must be ascribed to the fact that prenalterol significantly increases dP/dt and reduces left ventricular end-diastolic pressure whereas atrial pacing has no effect on dP/dt and significantly increases left ventricular end-diastolic pressure. Since subendocardial RMBF and contractility are closely related in the ischaemic heart (Vatner, 1980), it can be assumed that since prenalterol, 5 $\mu g\,kg^{-1}$, maintains ischaemic flow, systolic shortening can improve in response to the drug's positive inotropic effects, while the contrary occurs during atrial pacing at 150 beats min^{-1}. Furthermore, prenalterol, 5 $\mu g\,kg^{-1}$, by reducing left ventricular volume and hence wall tension (a property not shared by atrial pacing at 150 beats min^{-1}), tends to decrease myocardial oxygen demand, which probably neutralizes the moderate tachycardia-induced increase in oxygen consumption and reduction in diastolic coronary perfusion time. In contrast, when prenalterol is infused at 20 $\mu g\,kg^{-1}$, and despite the positive inotropic effect and the reduction in wall tension it still induces, the strong tachycardia, the reduction in diastolic coronary perfusion time and the abolished metabolic autoregulation no longer allow maintenance of ischaemic RMBF, and hence regional function worsens, as is also the case with atrial pacing at 175 beats min^{-1}.

Finally, it should be stressed that two factors linked to the experimental model used, may have influenced the results obtained with prenalterol. First, it is known that sympathomimetic amines like dobutamine and dopamine cause, for a given positive inotropic effect, a greater increase in heart rate in open-chest anaesthetized dogs (Tuttle & Mills, 1975; Willerson *et al.*, 1976; Tuttle *et al.*, 1977; Rude *et al.*, 1983) than in conscious dogs (Vatner & Baig, 1979; Liang *et al.*, 1981). This phenomenon probably also occurred in our experiments with prenalterol and may have limited its beneficial effects. Second, it has been shown that dobutamine does not affect left ventricular end-diastolic pressure in conscious dogs (Vatner & Baig, 1979; Liang *et al.*, 1981) while it reduces this parameter in anaesthetized dogs (Tuttle *et al.*, 1977). Similarly, prenalterol does not affect left

ventricular end-diastolic pressure in conscious dogs (Manders *et al.*, 1980) but reduced it in our experiments, which may have enhanced the drug's beneficial effects on ischaemic flow and function.

In conclusion, the present data demonstrate once again that ischaemic damage is not always worsened by inotropic stimulation inasmuch as coronary perfusion pressure is kept constant and above all that tachycardia remains moderate. Thus, the development of more selective inotropic agents, such as prenalterol or amrinone (Jentzer *et al.*, 1981) may prove to be of major importance in the treatment of patients with heart failure due to myocardial ischaemic disease.

References

ARINIEGO, R., WAAGSTEIN, F., MOMBAY, B. & HJALMARSON, A. (1979). Haemodynamic effects of a new β_1-receptor agonist in acute myocardial infarction, a useful antidote to unwanted cardiac effects of β-blocking agents. *Br. Heart J.*, **42,** 139–146.

BERDEAUX, A., PERES DA COSTA, C., GARNIER, M., BOISSIER, J.R. & GIUDICELLI, J.F. (1978). Beta adrenergic blockade, regional left ventricular blood flow and ST-segment elevation in canine experimental myocardial ischamia. *J. Pharmac. exp. Ther.*, **205,** 646–656.

GROSS, G.J., WARLTIER, D.C. & HARDMAN, H.F. (1978). Beneficial actions of N-dimethyl propranolol on myocardial oxygen balance and transmural perfusion gradients distal to a severe coronary artery stenosis in the canine heart. *Circulation,* **58,** 663–669.

JENTZER, J.M., LE JEMTEL, T.H., SONNENBLICK, E.H. & KIRK, E.S. (1981). Beneficial effect of amrinone on myocardial oxygen consumption during acute left ventricular failure in dogs. *Am. J. Cardiol.*, **48,** 75–83.

LIANG, C., MARK, Y.J., SHERMAN, L.G., BLACK, J., GAVRAS, H. & HOOD, W.B.Jr. (1981). Dobutamine infusion in conscious dogs with and without acute myocardial infarction. Effects on systemic hemodynamics, myocardial blood flow and infarct size. *Circ. Res.*, **49,** 170–180.

MANDERS, W.T., VATNER, S.F. & BRAUNWALD, E. (1980). Cardio-selective beta adrenergic stimulation with prenalterol in the conscious dog. *J. Pharmac. exp. Ther.*, **215,** 266–270.

MARSHALL, R.J. & PARRATT, J.R. (1976). The effects of dobutamine in the early stages of acute experimental myocardial infarction in dog. *Br. J. Pharmac.*, **58,** 407P.

RUDE, R.E., IZQUIERDO, C., BUJA, M. & WILLERSON, J.T. (1982). Effects of inotropic and chronotropic stimuli on acute myocardial ischemic injury. I. Studies with dobutamine in the anesthetized dog. *Circulation,* **65,** 1321–1328.

RUDE, R.E., IZQUIERDO, C., BUSH, L.R., BUJA, L.M. & WILLERSON, J.T. (1983). Effects of inotropic and chronotropic stimuli on acute myocardial ischemic injury. II. Studies with dopamine and ouabain in the barbiturate-anesthetized dog. *J. cardiovasc. Pharmac.*, **5,** 717–724.

SCOTT, D.H., ARTHUR, G., BOYES, R. & SCOTT, D.B. (1979). Cardiovascular effects of prenalterol (H 133/22) in normal man. *Br. J. clin. Pharmac.*, **7,** 365–370.

THEROUX, P., FRANKLIN, D., ROSS, J.Jr. & KEMPER, W.S. (1974). Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. *Circ. Res.*, **35,** 896–908.

THUILLEZ, C., BERDEAUX, A., BONHENRY, C., DUHAZE, P. & GIUDICELLI, J.F. (1983a) Effects of propranolol on regional myocardial blood flow and function during severe coronary stenosis in dogs. *Eur. J. Pharmac.*, **92,** 171–179.

THUILLEZ, C., MAURY, M. & GIUDICELLI, J.F. (1983b). Differential effects of verapamil and diltiazem on regional blood flow and function in the canine normal and ischemic myocardium. *J. cardiovasc. Pharmac.*, **5,** 19–27.

TUTTLE, R.R. & MILLS, J. (1975). Dobutamine: development of a new catecholamine to selectively increase cardiac contractility. *Circ. Res.*, **36,** 185–196.

TUTTLE, R.R., POLLOCK, G.D., TODD, G., MAC DONALD, B., TUST, R. & DUSENBERRY, W. (1977). The effect of dobutamine on cardiac oxygen balance, regional blood flow, and infarction severity after coronary artery narrowing in dogs. *Circ. Res.*, **41,** 357–364.

VATNER, S.F. (1980). Correlation between acute reductions in myocardial blood flow and function in conscious dogs. *Circ. Res.*, **47,** 201–207.

VATNER, S.F. & BAIG, H. (1979). Importance of heart rate in determining the effects of sympathomimetic amines on regional myocardial function and blood flow in conscious dogs with acute myocardial ischemia. *Circ. Res.*, **45,** 793–803.

VATNER, S.F. & HINTZE, T.H. (1983). Mechanism of constriction of large coronary arteries by β-adrenergic receptor blockade. *Circ. Res.*, **53,** 389–400.

WARLTIER, D.C., ZYVOLOSKI, M., GROSS, G.J., HARDMAN, H.F. & BROOKS, H.L. (1981). Redistribution of myocardial blood flow distal to a dynamic coronary arterial stenosis by sympathomimetic amines. Comparison of dopamine, dobutamine and isoproterenol. *Am. J. Cardiol.*, **48,** 269–279.

WILLERSON, J.T., HUTTON, I., WATSON, J.T., PLATT, M.R. & TEMPLETON, G.H. (1976). Influence of dobutamine on regional myocardial blood flow and ventricular performance during acute and chronic myocardial ischemia in dogs. *Circulation,* **53,** 828–833.

(Received February 13, 1984. Revised May 9, 1984.)