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COMPARATIVE EFFECTS OF PROPRANOLOL AND PRACTOLOL IN THE EARLY STAGES OF EXPERIMENTAL CANINE MYOCARDIAL INFARCTION

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1 The effects of propranolol and practolol, at equivalent myocardial β-adrenoceptor blocking doses, (as assessed by the degree of shift of isoprenaline dose-response curves) were investigated in anaesthetized greyhounds before and after acute coronary artery ligation.

2 When administered intravenously to the intact closed-chest dog, propranolol (0.1 mg/kg) and practolol (0.5 mg/kg) caused similar decreases in heart rate, left ventricular dP/dt *max*, myocardial blood flow and cardiac output. Only propranolol increased peripheral vascular resistance.

3 When administered 2–3 h after acute coronary artery ligation, propranolol (0.1 mg/kg) significantly decreased blood flow in both normally perfused and ischaemic regions of the heart. There was also electrocardiographic evidence of further deterioration after propranolol; two out of seven animals died following this treatment.

4 Practolol (0.5 mg/kg) when administered after coronary artery ligation also decreased normal myocardial blood flow but flow in the ischaemic area remained unchanged. Evidence was obtained from electrocardiographic, myocardial temperature, myocardial O_2 consumption and lactate measurements that the administration of practolol, in contrast to propranolol, benefited the ischaemic myocardium.

5 Analysis of the results suggests that this beneficial action of practolol may be related to at least two mechanisms. Firstly the ability of practolol to increase the period during diastole when perfusion of the subendocardium is possible, without decreasing the transventricular pressure during this period. Secondly that practolol does not unmask α-adrenoceptor vasoconstriction in the ischaemic region.

Introduction

The suggestion that β-adrenoceptor blockade with propranolol offers some protection against the development of a subsequent experimental myocardial infarct was first made by Grayson, Irvine, Parratt & Cunningham (1968). Their findings in dogs were confirmed and extended by Maroko, Kjekshus, Sobel, Watanabe, Covell, Ross & Braunwald (1971) and by Serrano, Chavez-Lara, Bisteni & Sodi-Pallares (1971) who assessed the degree and extent of ischaemic injury from epicardial electrocardiograms. Similar results have been obtained with the cardio-selective β-adrenoceptor antagonist, practolol (Libby, Maroko, Covell, Malloch, Ross & Braunwald, 1973) and it has also been demonstrated (Pelides, Reid, Thomas & Shillingford, 1972) that this drug is capable of reducing 'infarct size' in patients shortly after the onset of acute myocardial infarction. Although these beneficial effects of β-adrenoceptor antagonists are thought to be related to a more favourable balance between myocardial O_2 supply and demand in the ischaemia area, there have been no studies published in which these parameters have been measured. There also exists some controversy as to whether 'cardio-selective' β-blockers possess any real advantages over propranolol in the treatment of ischaemic heart disease. In this study we have compared the effects of equivalent myocardial β-adrenoceptor blocking doses of propranolol and practolol in an experimental model which allows the simultaneous measurement of blood flow in both normal and acutely ischaemic regions of the canine heart and which, through selective coronary venous blood sampling, allows comparisons to be made of O_2 handling and metabolism in these areas (Marshall, Parratt & Ledingham, 1974). Some of the preliminary results obtained with practolol have been published (Marshall & Parratt, 1974a).

Methods

Twenty-six greyhounds of either sex and weighing between 22 and 31 kg were used in this study. Anaesthesia was induced with sodium thiopentone (20 mg/kg, injected intravenously) and was maintained, after endotracheal intubation, with 0.5–0.8% trichlorethylene vaporized from a Tritec vaporizer (Cyprane Ltd.). The animals were maintained on intermittent positive pressure ventilation with O_2 using a Palmer pump; the stroke volume was adjusted to give an arterial P_{CO_2} of 34–41 mmHg; 1 mmHg = 1.333 mbar. Temperature was measured in the mid-oesophagus using a direct recording thermocouple (Ellab, Copenhagen). Under fluoroscopic control, polyethylene catheters were inserted to lie in the descending aorta (via a femoral artery), the right atrium (via a femoral vein) and in the coronary sinus (via the left jugular vein). These catheters were used for the sampling of blood and for pressure measurements using Elema-Schönander capacitance transducers. Left ventricular pressure was measured with a catheter-tip transducer (Millar Instruments, Houston, Texas) inserted by way of the left carotid artery. The frequency response of this catheter system is flat to at least 200 Hz. Left ventricular pressure was also recorded at high gain for the measurement of end-diastolic pressure (LVEDP) and the rate of change of the full left ventricular pressure curve with time (dP/dt) was continuously monitored by means of an Elema-Schönander differentiating circuit.

All capacitance transducers were calibrated before the experiment with a mercury manometer and were zeroed at the level of the animal's right atrium. Mean pressures were obtained by electronic integration. The catheters were kept filled with normal saline to which was added sodium bicarbonate (100 mEq/l), to prevent any gradual onset of acidosis, and heparin (2500 units/l) to prevent clotting. After the position of the intracardiac catheters had been checked fluoroscopically, heparin (1000 units) was injected into the right atrium. Cardiac output was measured by dye-dilution. Indocyanine green (2.5 mg) was injected into the right atrium and blood was withdrawn at a constant rate from the descending aorta through a densitometer (Waters Co., Rochester, Minnesota). The full details of this method have been outlined elsewhere (Douglas, MacDonald, Milligan, Mellon & Ledingham, 1975).

In 11 of the animals (5 given propranolol, 6 given practolol), myocardial blood flow was measured without thoracotomy by the ^{133}xenon clearance technique (Ross, Ueda, Lichtlen & Rees, 1964; Ledingham, McBride, Parratt & Vance, 1970). A Sones 7F catheter was introduced into the right common carotid artery in the neck and, under fluoroscopic control, manipulated until the tip of the catheter lay a distance of 5–10 mm into either the circumflex or anterior descending branch of the left coronary artery. Injections of ^{133}xenon (40–100 μCi, dissolved in 0.9% w/v NaCl solution (saline)) were flushed into this catheter with 3 ml heparinized saline warmed to 37°C. The clearance of xenon from the myocardium (which is a function of capillary blood flow) was measured by means of a narrowly collimated Ecko scintillation counter clamped over the praecordium, an Ecko ratemeter (operating with a 3 s time constant) and a Servoscribe pen recorder. Myocardial blood flow per 100 g tissue was calculated from the clearance curve as previously described (Ledingham *et al.*, 1970).

The remaining 15 dogs were subjected to thoracotomy, the heart was exposed and the anterior descending branch of the left coronary artery (LAD) was prepared for ligation at a position distal to the main septal branch. Blood draining from the potentially ischaemic portion of the heart was sampled by means of a small catheter inserted into one of the anterior coronary veins which lie parallel to the artery. Blood obtained from the aorta, the right atrium, the coronary sinus and the local coronary vein was analysed for P_{O_2}, P_{CO_2}, pH and O_2 content as previously described (Marshall *et al.*, 1974). Samples were also analysed for lactate by a standard spectrophotometric technique (Hohorst, 1962). Blood flow in the left circumflex coronary artery was measured with a Nycotron 372 electromagnetic flowmeter and an implantable 2.0 or 2.5 mm flow probe.

After a 1–2 h stabilization period, the LAD was ligated in one stage. A Portex catheter (o.d. 1.34 mm) was inserted into the ligated vessel distal to the ligature. The pressure in this ligated vessel (peripheral coronary pressure; PCP) was measured by means of an Elema-Schönander capacitance transducer. This coronary artery catheter was also used for the measurement of retrograde coronary flow (backflow from the open catheter) and for the injection of small amounts (usually 20 μCi) of radioactive ^{133}xenon. Clearance of radioactivity from the clearly demarcated ischaemic region was measured with a collimator having a narrow angle of acceptance. This experimental model thus allows the simultaneous measurement of blood flow in both normal (left circumflex flow) and acutely ischaemic (xenon clearance) regions of the canine heart and also allows comparison to be made of coronary sinus blood, draining essentially normal myocardium, with local coronary vein blood, which drains predominantly from the damaged ischaemic zone.

Local myocardial muscle temperatures were measured with small direct-recording copper-constantan thermocouples (Ellab, Copenhagen), anchored at known depths in the ventricular wall, and were compared with the temperature of the aortic

blood. During temperature recording care was taken to avoid procedures, such as blood sampling, which might influence local muscle temperature. The depth of insertion of each thermocouple was carefully measured at the end of each experiment.

Systemic arterial pressure, right atrial pressure, left ventricular pressure and d*P*/d*t*, peripheral coronary pressure, left circumflex coronary blood flow and the electrocardiogram (standard limb lead II) were recorded on an Elema-Schönander ink-jet writing recorder (Mingograph 81). The heart rate was measured from the electrocardiogram. O_2 consumption, availability and extraction, coronary and peripheral vascular resistances, and external cardiac work were calculated as previously described (Marshall & Parratt, 1973a). Drugs used were (±)-propranolol hydrochloride and (±)-practolol (ICI), dipyridamole (Boehringer) and (±)-isoprenaline hydrochloride (Pharmax). All doses refer to the free base and the drugs were injected into a catheter in a brachial vein. All values quoted in the text are means ± standard error. Statistical analysis of the results was performed using the Student's *t* test for paired data.

Results

The effects of propranolol and practolol in the closed-chest anaesthetized dog

It was of some importance to investigate the effects of propranolol and practolol at equivalent β-adrenoceptor blocking doses. Preliminary experiments showed that propranolol, 0.1 mg/kg intravenously, caused 11, 16 and 19-fold parallel shifts in the mean dose-response curves for the positive chronotropic, positive inotropic and the vasodepressor responses to intravenous isoprenaline. An equivalent degree of myocardial adrenoceptor blockade was produced by practolol in a dose of 0.5 mg/kg intravenously. When administered in this dose, practolol caused a 17-fold shift in the myocardial dose-response curves to isoprenaline (β_1 responses) but had much less effect (four-fold shift) on isoprenaline-induced vasodepression (a β_2 response).

The haemodynamic effects of propranolol (0.1 mg/kg) and practolol (0.5 mg/kg) in anaesthetized greyhounds without thoracotomy are shown in Table 1. Both drugs caused significant and comparable decreases in heart rate, left ventricular d*P*/d*t max*, cardiac output, external cardiac work, myocardial blood flow and myocardial O_2 consumption. Neither drug significantly affected blood pressure or stroke volume. Only propranolol significantly increased LVEDP and coronary and peripheral vascular resistance. The ratio between myocardial O_2 consumption and availability remained unchanged after both propranolol (0.55 ± 0.07 to 0.58 ± 0.07) and practolol (0.60 ± 0.03 to 0.58 ± 0.05).

The effects of coronary ligation

The effects of ligation of the anterior descending branch of the left coronary artery in these experiments were similar to those previously described (Marshall & Parratt, 1973a, Marshall *et al.*, 1974) and included marked decreases in cardiac output and external cardiac work. These changes are secondary to depressed myocardial contractility (manifested by

Table 1 The haemodynamic effects of propranolol (0.1 mg/kg) and practolol (0.5 mg/kg) in the closed-chest greyhound

	Propranolol $n=5$		*Practolol* $n=6$	
	Pre-drug	*15 min Post-drug*	*Pre-drug*	*15 min Post-drug*
Systolic blood pressure (mmHg)	145 ± 13	145 ± 17	180 ± 20	159 ± 23
Diastolic blood pressure (mmHg)	105 ± 8	106 ± 12	126 ± 12	112 ± 19
Heart rate (beats/min)	203 ± 25	149 ± 14*	224 ± 15	162 ± 5*
Cardiac output (litres/min)	4.7 ± 0.5	3.0 ± 0.4*	6.2 ± 1.2	4.5 ± 1.0*
LV d*P*/d*t max* (mmHg/s)	3640 ± 247	2740 ± 317*	4400 ± 601	2500 ± 184*
LVEDP (mmHg)	7.2 ± 0.4	11.0 ± 1.5*	8.1 ± 0.7	9.3 ± 0.4
External cardiac work (kg. m/min)	8.7 ± 0.6	4.9 ± 0.6*	12.5 ± 3.2	8.4 ± 2.7*
Myocardial blood flow (ml 100 g^{-1} min^{-1})	96 ± 23	76 ± 20*	134 ± 20	102 ± 21*
Myocardial O_2 consumption (ml 100 g^{-1} min^{-1})	18.0 ± 2.5	12.3 ± 1.4*	24.0 ± 3.9	15.2 ± 2.1*
Coronary vascular resistance (units)	1.4 ± 0.2	1.8 ± 0.2*	1.1 ± 0.1	1.3 ± 0.2
Peripheral vascular resistance (units)	37 ± 6	59 ± 14*	25 ± 4	28 ± 3

Values are mean ± s.e.
*$P < 0.05$

transient decreases in left ventricular d*P*/d*t max* with more sustained increases in LVEDP). Blood flow through the ischaemic region of the myocardium, as measured by radioactive xenon clearance, was about 25% of that from the same region before ligation of the artery.

Haemodynamic effects of propranolol and practolol after acute coronary artery occlusion.

The haemodynamic effects of both propranolol and practolol, when administered 2–3 h after occlusion, were essentially similar to those seen when the drugs were administered before ligation (Table 2). Both drugs decreased heart rate, cardiac output, left ventricular d*P*/d*t max* and external cardiac work; LVEDP and coronary and peripheral vascular resistance were increased. Only after occlusion did propranolol significantly decrease systemic blood pressure and stroke volume. Blood flow in the normal myocardium was significantly decreased by propranolol (by a mean of 46%) and there was also a reduction in O_2 consumption (Table 3). Although practolol also markedly decreased cardiac output and external cardiac work, the decreases in blood flow (32%) and O_2 consumption in the normal myocardial regions were less than those seen with propranolol.

Effects of propranolol and practolol in the ischaemic myocardium

Blood flow in the ischaemic region of the myocardium was greatly reduced by propranolol (mean of 54%) as was O_2 consumption (Table 3) and O_2 availability.

Table 2 The effects of propranolol (0.1 mg/kg) and practolol (0.5 mg/kg) on haemodynamics when administered 1–3 h after acute coronary artery ligation

	Propranolol $n=7$		*Practolol* $n=8$	
	Pre-drug	*15 min Post-drug*	*Pre-drug*	*15 min Post-drug*
Mean blood pressure (mmHg)	126 ± 7	102 ± 9*	120 ± 7	109 ± 8
Systolic PCP (mmHg)	58 ± 9	48 ± 8	55 ± 7	47 ± 6
Diastolic PCP (mmHg)	20 ± 3	20 ± 3	18 ± 5	17 ± 3
Heart rate (beats/min)	180 ± 14	144 ± 5*	198 ± 13	151 ± 7†
Cardiac output (litres/min)	1.8 ± 0.3	0.8 ± 0.1†	2.0 ± 0.3	1.2 ± 0.2†
Stroke volume (ml/beat)	9.5 ± 1.5	5.7 ± 0.5*	10.1 ± 1.2	7.9 ± 1.2
External cardiac work (kgm/min)	3.3 ± 0.5	1.2 ± 0.7†	3.4 ± 0.6	1.8 ± 0.4†
LV d*P*/d*t max* (mmHg/s)	2130 ± 329	1224 ± 143*	2412 ± 324	1288 ± 172†
LVEDP (mmHg)	13 ± 2	21 ± 3†	12 ± 5	17 ± 5
Peripheral vascular resistance (units)	87 ± 13	131 ± 15*	71 ± 16	105 ± 14*

Values are mean ± s.e.
*$P < 0.05$; †$P < 0.005$.

Table 3 The effects of propranolol (0.1 mg/kg) and practolol (0.5 mg/kg) on blood flow and O_2 consumption in normal and acutely ischaemic regions of the canine myocardium

	Propranolol $n=7$		*Practolol* $n=8$	
	Pre-drug	*15 min Post-drug*	*Pre-drug*	*15 min Post-drug*
Normal region of the left ventricular wall				
Blood flow (ml/min)	68 ± 12	37 ± 8*	49 ± 8	33 ± 4*
O_2 consumption (ml/min)	9.7 ± 2.1	6.5 ± 1.8*	8.7 ± 0.6	6.4 ± 0.9*
Coronary vascular resistance (units)	2.0 ± 0.3	3.4 ± 0.5*	2.6 ± 0.3	3.2 ± 0.4
Ischaemic region of the left ventricular wall				
Blood flow (ml 100 g^{-1} min^{-1})	24 ± 7	11 ± 3*	28 ± 6	28 ± 5
O_2 consumption (ml 100 g^{-1} min^{-1})	3.0 ± 1.1	1.6 ± 0.4*	4.9 ± 1.1	4.6 ± 0.8
Peripheral coronary flow (ml/min)	2.4 ± 0.4	1.6 ± 0.2*	2.2 ± 0.5	2.0 ± 0.5
Infarct vascular resistance (units)	1.1 ± 0.4	2.4 ± 0.7*	0.9 ± 0.3	0.7 ± 0.1

Values are mean ± s.e.
*$P < 0.05$.

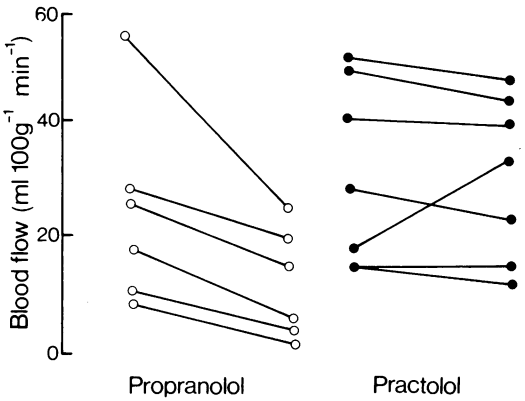


Figure 1 The effects of intravenously administered propranolol (0.1 mg/kg) and practolol (0.5 mg/kg) on blood flow (measured by radioactive xenon clearance) in a region of myocardium made ischaemic by acute coronary ligation, 2 h previously.

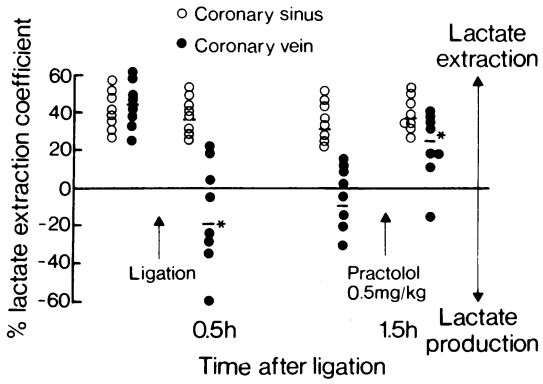


Figure 2 The effects of acute coronary artery ligation and the subsequent administration of practolol on the lactate handling in both normal (O) and acutely ischaemic (●) regions of the canine myocardium. Practolol when administered 2 h after ligation reversed the lactate production to extraction in the ischaemic area. *$P < 0.005$.

The further deterioration in blood flow in this critical region was accompanied by a more markedly ischaemic electrocardiographic pattern. The mean ST-segment depression in limb lead II, 2–3 h after ligation in these animals was 570 ± 80 μV and this changed significantly ($P < 0.05$) to 890 ± 120 μV, 15 min after the administration of propranolol.

In two of the dogs propranolol caused a particularly pronounced bradycardia. This was gradual in onset and progressed to asystole 16 and 23 min respectively after drug administration. As has been previously shown (Marshall *et al.*, 1974), ligation of the LAD results in markedly decreased lactate extraction (or even lactate production) by the region served by that artery with little change in lactate handling by the normal region (Table 4). Propranolol caused no marked changes in lactate handling in either region of the myocardium. (Table 4).

In contrast to propranolol, practolol did not decrease nutritive blood flow in the acutely ischaemic area of myocardium (Figure 1) and O_2 consumption (Table 3) and availability were also unaffected. The back pressure in the ligated artery (PCP) was also unchanged after practolol. There was evidence that practolol improved the situation in the ischaemic myocardium. Thus the ST-segment depression in the electrocardiogram was significantly reduced (from 606 ± 135 μV just before drug administration, to 300 ± 83 μV, 15 min after practolol, $P > 0.02$). More direct evidence of the beneficial effects of practolol was obtained by analysis of blood lactate and lactate extraction coefficients in both the normal and ischaemic myocardium are shown in Figure 2. Coronary artery ligation caused lactate production by the ischaemic area of myocardium but not by the normally perfused areas draining into the coronary sinus. This shift from aerobic to anaerobic metabolism in the ischaemic myocardium was still evident just before administration of practolol and was reversed by practolol in all but one dog. This means that at least some cells in the ischaemic region were apparently capable of resuming extraction of lactate and this continued for at least 2 h after practolol administration.

Table 4 The effects of ligation, and of the subsequent administration of propranolol, on lactate extraction (%) by both normal (sinus sampling) and acutely ischaemic (venous sampling) regions of the canine myocardium.

Pre-ligation		*30 min Post-ligation*		*2 h Post-ligation*		*15 min Post-propranolol*	
Sinus	*Vein*	*Sinus*	*Vein*	*Sinus*	*Vein*	*Sinus*	*Vein*
41.4	31.9	52.2	−55.0	37.5	−12.9	37.9	11.2
40.6	35.8	30.0	7.2	37.2	13.6	22.0	6.6
32.8	30.5	33.4	6.9	43.0	25.8	31.2	22.0
38.2	35.1	33.2	11.7	35.8	10.1	43.0	6.7

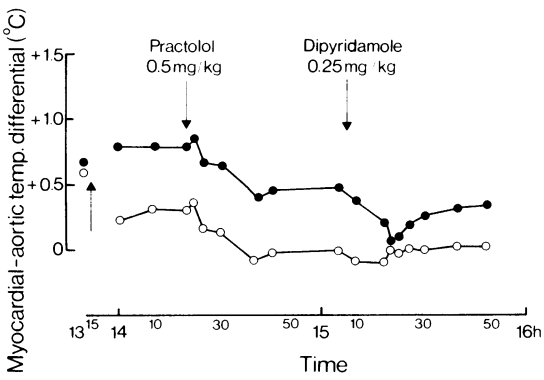


Figure 3 The effects of practolol and the coronary vasodilator drug, dipyridamole, on local myocardial muscle temperature in both normal (●) and ischaemic (○) regions of the canine left ventricle. The arrow indicates time of ligation.

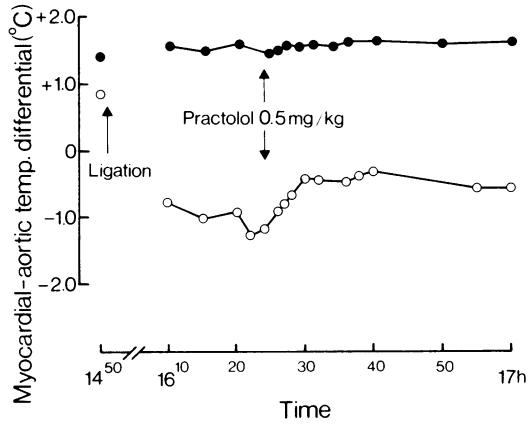


Figure 4 The effects of practolol on both normal (●) and ischaemic (○) myocardial muscle temperature in the deep subendocardial layers of the canine left ventricle.

Effects of propranolol and practolol on local myocardial temperature; comparison with dipyridamole

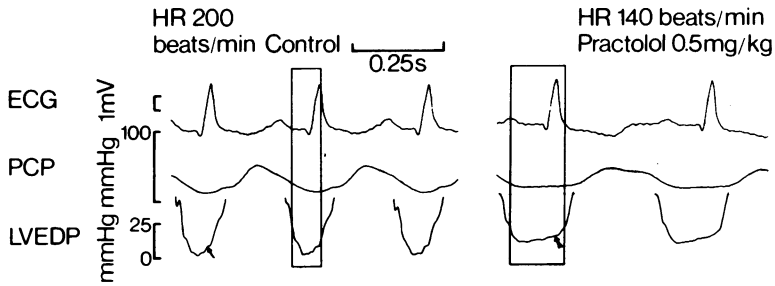
The effects of coronary artery ligation, and of the subsequent administration of practolol, on myocardial temperature are shown in Figure 3. In this particular experiment ligation of the LAD produced a marked fall in temperature in the region (thermocouple depth 6 mm) served by that artery; muscle temperature in a region supplied by the left circumflex branch was slightly increased. Practolol, when administered 1 h after ligation, caused marked decreases in muscle temperature in both the normal and ischaemic zones of myocardium. Similar changes in temperature were obtained in other experiments with both practolol and propranolol. Although these reductions in temperature in the normal myocardium were associated with decreased blood flow and O_2 consumption, only propranolol decreased these parameters in the ischaemic zone (Table 3). The fall in ischaemic muscle temperature produced by practolol cannot therefore be explained by a decrease in O_2 consumption. For comparative purposes, the selective coronary dilator drug dipyridamole was administered. This drug has been shown to increase flow to the normal myocardium considerably and to leave flow in the ischaemic zone unchanged (Marshall & Parratt, 1973b). Dipyridamole also decreased normal muscle temperature, an effect presumably due to increased blood flow. However, in contrast to practolol, dipyridamole did not affect muscle temperature in the ischaemic zone.

Although decreased temperature in both regions of the heart was the usual response to practolol, a different effect was obtained when the thermocouples were placed in the subendocardial region of the ventricle (depth 11–12 mm). The results from one of these experiments are shown in Figure 4. In this particular animal, muscle temperature in the ischaemic region fell markedly on ligation and was 1°C cooler than the aortic blood immediately before the administration of practolol. Muscle temperature in the essentially normal myocardium was relatively unchanged. Practolol did not affect muscle temperature in the normal myocardium but markedly elevated that in the ischaemic region. This increase in muscle temperature could be due to a local increase in subendocardial blood flow, since blood would be a warming factor in this situation.

Discussion

In these experiments, practolol was about 4–5 times less active than propranolol as an antagonist of the positive inotropic and chronotropic actions of intravenous isoprenaline. This agrees well with the results of other workers who, using dogs, have reported ratios of 3–4 (Dunlop & Shanks, 1968), of 2.6 (Boissier, Advenier, Giudicelli & Viars, 1971), and of 4 (Vaughan Williams, Bagwell & Singh, 1973). Our results also confirm previous findings in this species that practolol (in a dose of 0.5 mg/kg) blocks the β_1-adrenoceptor mediated responses to isoprenaline much more effectively than those responses mediated through β_2-adrenoceptors (Dunlop & Shanks, 1968; Ross & Jorgensen, 1970).

The haemodynamic effects of equivalent myocardial β-blocking doses of propranolol and



End-diastolic transventricular pressure (mmHg)	5	7	6	6	6
Effective perfusion period (% cardiac cycle)	26	25	25	32	31
Effective perfusion period / min (s)	32	30	30	41	40

Figure 5 The calculation of end-diastolic transventricular pressure and effective perfusion period in one dog before and 15 min after the intravenous administration of practolol. Although transventricular pressure remains unchanged, the period of effective perfusion is increased by practolol. PCP = peripheral coronary pressure; LVEDP = left ventricular end-diastolic pressure.

practolol in the closed-chest normal dog were very similar except that only propranolol increased peripheral vascular resistance, an effect presumably due to blockade of the β_2-adrenoceptors in peripheral vascular smooth muscle. Certainly the decreases in heart rate, left ventricular dP/dt *max*, cardiac output, external cardiac work, myocardial blood flow and O_2 consumption that resulted from the administration of the two drugs were similar in magnitude. This is in contrast to the results obtained when the drugs were administered after acute coronary artery ligation. Although both drugs caused similar decreases in heart rate, left ventricular dP/dt *max*, cardiac output and external cardiac work, propranolol tended to reduce blood flow to regions of normal myocardium (mean reduction 46%) rather more than did practolol (32%).

However, a more marked difference between the two drugs became apparent when their effects in the ischaemic region were examined. Propranolol consistently decreased blood flow in this region (by a mean of 54%) whereas practolol had no effect on flow. This consistent finding may be one reason why practolol, but not propranolol, was capable of beneficially modifying other indices of ischaemia, e.g. ST-segment depression and lactate production. There are two possible explanations for this marked difference between the effects of practolol and propranolol in equivalent myocardial β-adrenoceptor blocking doses.

(a) We have previously shown (Ledingham, Marshall & Parratt, 1973; Marshall & Parratt, 1974b) that one of the main factors influencing blood flow in the acutely ischaemic myocardium is the transventricular driving pressure, i.e., the difference during diastole between coronary artery pressure distal to the occlusion and left ventricular pressure. It was therefore of interest to see whether the differing effects of propranolol and practolol on infarct flow were related to changes in this parameter. Propranolol consistently reduced transventricular driving pressure (mean decrease 8 mmHg) whereas practolol had more equivocal effects (the mean change being 3 mmHg). Figure 5 illustrates an example of the calculation of transventricular driving pressure before and after practolol in one dog. Although practolol did not affect the transventricular pressure gradient, the period of effective perfusion (i.e., the period during which diastolic PCP exceeds LVEDP) was increased significantly by the drug. Although heart rate was consistently reduced by practolol, the absolute effective perfusion period was increased by practolol from 24 ± 4 to 42 ± 6 s/min, ($P < 0.05$). Propranolol increased the effective perfusion period to a considerably lesser degree (from 19 ± 2 to 28 ± 3 s/min, $P < 0.05$) and, in contrast to practolol, it actually decreased transventricular driving pressure. Practolol thus significantly increases the period, during diastole, when there exists a positive pressure gradient tending to drive blood to the subendocardial regions of the left ventricular wall. Since this effect would tend to favour blood flow to the subendocardium, it is possible that practolol may cause a redistribution of flow from the epicardial to the endocardial layers of the ischaemic ventricular wall without affecting total blood flow (measured by xenon clearance) in this area. Some experimental evidence for such a flow redistribution was obtained in the present studies from an analysis of temperature

records obtained from deeply implanted thermocouples. Practolol markedly elevated temperature in this region (Figure 4), a finding that can be explained on the basis of a local increase in endocardial blood flow. Other experimental evidence for this concept has also been obtained by other workers (Moir & DeBra, 1967; Becker, Fortuin & Pitt, 1971; Fortuin, Kaihara, Becker & Pitt, 1971; Gross & Winbury, 1973). Using either rubidium uptake or radioactive microspheres to measure local regional blood flow, these workers found that β-adrenoceptor antagonists increase the ratio of blood flow between inner and outer layers of the left ventricular wall in both normal and ischaemic regions of the canine myocardium. Such a redistribution of blood flow favouring subendocardial regions would also explain the findings of Winbury, Weiss & Howe (1971) that β-adrenoceptor blockade often produces a selective rise in subendocardial O_2 tension but does not affect, or may even decrease, epicardial O_2 tension.

Possible mechanisms by which β-adrenoceptor antagonists might favour subendocardial perfusion have been recently reviewed by Gross & Winbury (1973) and include decreased heart rate. Of relevance to this problem are the observations that tachycardia *per se* increases 'infarct size' in both anaesthetized (Maroko *et al.*, 1971) and conscious dogs (Shell & Sobel, 1973). In two of the experiments described here in which the dogs were electrically paced, practolol caused a pronounced deterioration of cardiac function. That the bradycardia produced by β-blockers is important to their beneficial effects has also been shown in man (Dwyer, Weiner & Cox, 1967; Balcon, 1971).

(b) The second possible explanation for the difference between the actions of practolol and propanolol on the ischaemic myocardium involves their differential effects on vascular β-adrenoceptors. Most *in vivo* studies indicate either that coronary vascular β-adrenoceptors can be classified as β_2 (Parratt & Wadsworth, 1970; Mark, Abboud, Schmid, Heistad & Mayer, 1972; Adam & Boyles, 1974; Gross & Feigl, 1975) or indicate that they are at least different from myocardial β_1-adrenoceptors (Adam, Boyles & Scholfield, 1970; Ross & Jorgensen, 1970). There is considerable evidence for the release of noradrenaline into the circulation following coronary artery occlusion and, although in the early stages (up to 1 h after occlusion) this amine induces active coronary vasoconstriction in the ischaemic area (for references see Moore & Parratt, 1973), noradrenaline later increases blood flow in the ischaemic region (Marshall & Parratt, 1973a), an effect not solely related to increased perfusion pressure. The administration of propranolol would block vascular β_2-adrenoceptors in the ischaemic region (as it certainly does in the normal coronary circulation; Parratt & Grayson, 1966) and unmask a vasoconstrictor effect of released noradrenaline on vascular α-adrenoceptors present within this region (Parratt, 1967). This would adequately explain the active increase in resistance to flow (from 1.07 ± 0.38 to 2.35 ± 0.48 units; $P < 0.025$) within the developing infarct following propranolol administration. A similar vasoconstriction does not occur after practolol administration (the calculated resistances were 0.86 ± 0.27 units before and 0.68 ± 0.11 units after practolol) presumably because of the relative insensitivity of vascular β-adrenoceptors to this 'cardioselective' blocking agent.

These present studies have shown that at equivalent myocardial β_1-adrenoceptor blocking doses, only practolol benefits an acutely ischaemic area of myocardium; propranolol causes further deterioration which may be fatal. Analysis of the results suggests that the beneficial actions of practolol may be related to at least two mechanisms. Firstly, the ability of practolol to increase the period during diastole when perfusion of the subendocardium is possible without decreasing the transventricular driving pressure during this period. Secondly, the fact that practolol does not unmask α-adrenoceptor vasoconstriction in the ischaemic region. Although practolol also differs from propranolol in that it does not possess direct negative inotropic actions on the heart, it is unlikely that this difference between the drugs is relevant to the results presented here, since 'quinidine-like' properties are only demonstrated with propranolol at considerably higher doses than those used in this study (Harry, Kappagoda, Linden & Snow, 1973). Further evidence excluding this possibility was obtained in this study in the fact that propranolol and practolol decreased left ventricular dP/dt and stroke volume to the same extent.

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