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THE EFFECTS OF PROPRANOLOL AND ACEBUTOLOL ON LEFT VENTRICULAR FUNCTION AND CORONARY HAEMODYNAMICS IN THE CONSCIOUS DOG WITH MYOCARDIAL ISCHAEMIA

W.S. HILLIS, I. HUTTON & T.D.V. LAWRIE

University of Glasgow Department of Medical Cardiology, The Royal Infirmary, Glasgow

1 The cardiovascular effects of the β-adrenoceptor blocking drugs, propranolol and acebutolol, on regional coronary blood flow and left ventricular function have been investigated in the conscious dog with developing myocardial infarction.

2 Propranolol (1 to 1.5 mg/kg) or acebutolol (4 to 5 mg/kg) were administered intravenously 2 to 3 h after occlusion of the left anterior descending coronary artery.

3 Propranolol or acebutolol administration resulted in a relative increase in flow to the ischaemic area of the myocardium, particularly to the subendocardium.

4 Propranolol produced a greater reduction in heart rate and myocardial contractility than acebutolol.

5 These results demonstrate that β-adrenoceptor blocking drugs reduce myocardial oxygen consumption and increase coronary flow to the ischaemic area of the myocardium after coronary artery occlusion in the conscious dog.

Introduction

Braunwald, and his colleagues (1971) in a series of experiments have demonstrated that pharmacological agents which reduce myocardial oxygen consumption can exert a protective effect on the ischaemic myocardium.

β-Adrenoceptor blocking agents were first reported to reduce myocardial ischaemic damage in the anaesthetized dog model of myocardial ischaemia (Maroko, Kjekhus, Sobel, Watanabe, Covell, Ross & Braunwald, 1971). Reimer, Rasmussen & Jennings (1973; 1976) demonstrated that propranolol significantly reduced the amount of myocardial necrosis produced by either temporary or permanent circumflex coronary artery occlusion. Kloner, Reimer & Jennings (1976) concluded that the reduction in infarct size was not related to an increase in collateral coronary flow. Becker, Fortuin & Pitt (1971), Becker, Ferreira & Thomas (1975) and Pitt & Craven (1970) showed that although flow to the ischaemic areas of the myocardium is reduced, there is a lesser reduction in flow to the ischaemic area than to the non-ischaemic area of the myocardium. These studies have all been done in the anaesthetized dog and the purpose of the present study was to compare and evaluate the effects of propranolol, a non-cardioselective β-blocking drug, with no intrinsic sympathomimetic activity and acebutolol which is both cardioselective and has intrinsic sympathomimetic activity, on regional myocardial blood flow and ventricular performance in the conscious, unsedated dog with myocardial ischaemia.

Methods

Twenty-two adult fox hounds weighing 18 to 25 kg were anaesthetized with sodium pentobarbitone 20 mg/kg body weight, intubated and ventilated with a Palmer pump. Anaesthesia was maintained with halothane and a mixture of oxygen and nitrous oxide. Sterile thoracotomies were performed through a left lateral incision. A high fidelity calibrated solid state pressure transducer (Konigsberg P-22) was inserted into the left ventricle through a stab incision into the apex. A 15 gauge polyvinyl catheter was introduced into the left atrial appendage. The anterior descending branch of the left coronary artery (LAD) was mobilised usually within 1 to 2 cm of its origin proximal to the first diagonal branch of the LAD and an inflatable balloon cuff device (Massachusetts Instrument Co.) was sutured around this artery. This occlusive device has been satisfactorily used to produce coronary artery occlusion in the conscious dog by Chimoskey, Szentivanyi, Zakheim & Barger (1967) and Hutton, Curry, Templeton & Willerson (1975). The pericar-

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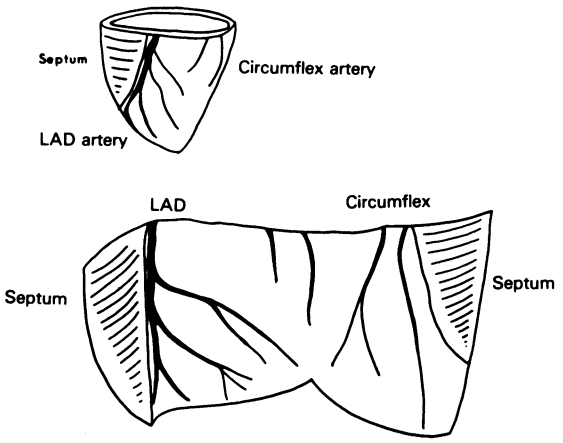

Figure 1 A diagramatic representation of the left ventricle. The upper drawing shows the left ventricle following excision of the right ventricle, atria and great vessels. The lower drawing shows the ventricle divided through the intraventricular septum and laid open to demonstrate the distribution of the left anterior descending (LAD) and circumflex arteries.

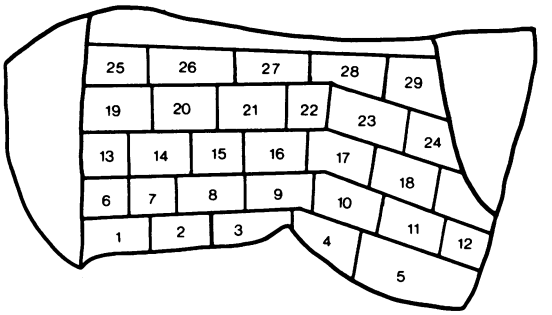

Figure 2 Map of the left ventricle with a superimposed grid. Each tissue block was further divided into endocardial and epicardial portions.

dium was loosely resutured and the catheters and silastic tubing from the balloon device were exteriorised at the back of the dog's neck. The dogs were then allowed two weeks to recover before again being anaesthetized, as described previously, and 15 gauge polyvinyl catheters were introduced into the superior vena cava and the thoracic aorta via the external carotid artery. All catheters were kept patent by intermittent flushing with heparin. The dogs were infection-free and fully mobile with the catheters *in situ*, 48 h after the insertion of the venous and arterial catheters.

The dogs were studied in the fully conscious, unsedated state. Left atrial and systemic arterial pressures were measured with Capacitance Transducers (EMT 34 and EMT 35) and recorded on an Elema-Schönander recorder (Mingograf 81). The zero reference point was mid-thorax with the dog free-standing, supported by a sling. The left ventricular end-diastolic pressure (LVEDP) obtained from the solid-state transducer was calibrated to equal the mean left atrial pressure at the beginning of each study. Cardiac output was determined by the dye dilution technique, the dye being injected into the superior vena cava and arterial blood withdrawn at a constant rate from the thoracic aorta with a Harvard withdrawal pump. All measurements were done in duplicate and the mean of the results was taken. The left ventricular pressure was obtained with the Konigsberg transducer (P-22) which has a flat frequency response >1000 Hz. The LV pressure wave forms were recorded on a frequency modulated instrumentation tape recorder and subsequently analysed on a PDP8 computer. The computer digitised 8 s of recorded signal at a rate of 250 samples/s and then calculated the pressure gradient dP/dt between successive samples from end-diastole to peak systole. The peak dP/dt and $dP/dt/$ developed pressure ($dP/dt/P$) were determined from each beat analysed. The values presented are the means of all beats within an 8 s sample. The electrocardiogram was monitored continuously. Total and regional coronary blood flow was measured by serial injection of 7 to 10 μm microspheres labelled with the gamma emitting nuclides ^{51}Cr, ^{85}Sr and ^{141}Cs. Approximately 1 to 2 million microspheres were injected for each measurement of coronary blood flow.

Prior to injection the microspheres were thoroughly mixed by means of a vortex agitator. The microspheres suspended in warm 0.9% w/v NaCl solution (saline) were injected into the left atrium. During each injection a reference blood sample was collected from the thoracic aorta in 30 s fractions over a 2 min period with a Holter withdrawal pump at a rate of 12 ml/min. At the conclusion of the study the heart was removed and placed in 10% formalin to facilitate sectioning. Only the left ventricle was retained and maps were then made of left ventricular myocardial blood flow (Becker, Ferreira & Thomas, 1973) (Figures 1 and 2). Each area was divided into an inner or endocardial layer and an outer or epicardial layer. The different sections of the heart and reference blood samples were placed in separate scintillation vials and counted in a gamma spectrometer at optimum window settings to correspond to the peak energies of each nuclide (Gamma-Guard 510). The sections of heart weighed approximately 1 to 2 g. Regional coronary blood flow could then be determined from the equation:

$$\text{Regional myocardial blood flow (ml min}^{-1}\text{ g}^{-1}) = \frac{\text{Reference sample flow} \times \text{myocardial nuclide activity}}{\text{Reference sample nuclide activity}}.$$

The data were analysed by Student's t test and the results considered significant when $P < 0.05$.

Experimental protocol

Baseline measurements of heart rate, systemic arterial pressure, cardiac output, left atrial pressure and left ventricular pressure were taken and regional coronary blood flow was measured with one batch of microspheres. Coronary artery occlusion was then produced over a 15 min period by gradually inflating the balloon cuff which had been placed around the proximal LAD. All of the dogs tolerated the procedure well and were not in apparent discomfort. Ventricular ectopic beats were noted during the period of coronary artery occlusion but significant dysrhythmias were not observed. The balloon remained inflated for the remainder of the experiment. At the conclusion of the experiment the balloon was noted to be fully inflated and LAD occlusion was confirmed radiologically by injecting barium sulphate down the coronary artery. The dogs were trained to stand supported by slings on the table and the heart rate was usually in the range of 90 to 120 beats/min.

After 2 h of coronary artery occlusion isotonic saline was infused intravenously in the same volume as the β-blocking drugs, thus similar effects on the filling pressure of the left ventricle were produced, and the haemodynamic and coronary flow measurements using a different batch of microspheres were repeated. Either propranolol 1 to 1.5 mg/kg body weight or acebutolol 4 to 5 mg/kg body weight were infused intravenously, the dose being adjusted to produce a reduction in heart rate. Basil, Jordan, Loveless & Maxwell (1973) have reported that these doses are equivalent in antagonizing isoprenaline-induced tachycardia in the dog. A final set of haemodynamic and coronary blood flow measurements were made.

Results

Propranolol group

The haemodynamic changes following the administration of 1.0 to 1.5 mg/kg of propranolol intravenously are summarised in Table 1.

Heart rate increased after LAD occlusion from 98 ± 8 to 105 ± 8 beats/min and was significantly reduced by propranolol to 85 ± 5 beats/min ($P < 0.005$). Cardiac output was reduced from 3.2 ± 0.1 to 2.9 ± 0.4 l/min ($P < 0.01$) and to 2.4 ± 0.2 ($P < 0.005$). Stroke volume was reduced after LAD occlusion from 33 ± 3 to 28 ± 2 ml ($P < 0.01$) but was unchanged after propranolol (28 ± 3 ml). Mean aortic pressure was not significantly altered: 95 ± 6 mmHg, 88 ± 5 mmHg; 91 ± 6 mmHg. LVEDP was similarly unchanged. dP/dt_{max} was reduced after LAD occlusion but not significantly, but there was a significant fall after propranolol of 25% ($P < 0.005$). $dP/dt/P$ showed a similar trend with a reduction of 20% after propranolol ($P < 0.005$).

The detailed coronary blood flow results are shown in Table 2. After LAD occlusion coronary flow fell by 50% from 0.73 ± 0.09 to 0.36 ± 0.06 ml min^{-1} g^{-1} ($P < 0.005$). When the flows to the LAD and circumflex areas are expressed as a ratio there was a significant reduction in the ratio from 1.0 ± 0.06 to 0.44 ± 0.08 ($P < 0.005$). After propranolol there was an increase in flow to the ischaemic area of 28% from 0.36 ± 0.06 to 0.48 ± 0.07 ml min^{-1} g^{-1} ($P < 0.05$), and in the ratio of the ischaemic to the non-ischaemic area of 0.44 ± 0.08 to 0.62 ± 0.09 ($P < 0.05$).

In the ischaemic area there was a differential reduction in flow to the endocardium, the endocardial/epicardial ratio being reduced after LAD occlusion from 1.24 ± 0.21 to 0.64 ± 0.15 ($P < 0.005$). Propranolol

Table 1 Haemodynamic effects of propranolol in animals with acute cardiac ischaemia

	Control	*Post infarct + saline*	*Post infarct + propranolol*
Heart rate (beats/min)	98 ± 8	105 ± 8	85 ± 5***
Cardiac output (l/min)	3.2 ± 0.1	2.9 ± 0.4*	2.4 ± 0.2***
Stroke volume (ml)	33 ± 3	28 ± 2*	28 ± 3
Aortic pressure (mm/Hg)	95 ± 6	88 ± 5	91 ± 6
Left ventricular end diastolic pressure (mmHg)	5.5 ± 1	5 ± 1	5 ± 1
dP/dt_{max} (mm Hg/s)	2828 ± 409	2622 ± 367	2008 ± 242***
$dP/dt/P$ (s^{-1})	49 ± 9	51 ± 9	42 ± 6***

Results are mean $\pm$ standard error of the mean (s.e. mean) in 12 animals.
* $P < 0.01$; ** $P < 0.001$; *** $P < 0.005$.

increased the endocardial/epicardial ratio to 1.0 ± 0.35 ($P < 0.05$).

In the non-ischaemic, circumflex area after coronary artery occlusion coronary flow tended to increase, but after propranolol there was a reduction of 12%. The endocardial/epicardial ratio was unchanged after LAD occlusion and propranolol.

Acebutolol group

The haemodynamic changes after the intravenous administration of acebutolol, 4–5 mg/kg body weight, are summarized in Table 3.

Heart rate increased after LAD occlusion from 103 ± 5 to 121 ± 4 beats/min ($P < 0.001$) but was significantly reduced by acebutolol to 110 ± 4 beats/min ($P < 0.001$). Cardiac output was reduced from 2.9 ± 0.1 to 2.6 ± 0.1 l/min ($P < 0.02$) and was further reduced by acebutolol to 2.5 ± 0.1 l/min. Stroke volume was reduced after LAD occlusion from 29 ± 2 to 21 ± 1 ml ($P < 0.02$) but was unchanged after acebutolol (22 ± 1 ml). Mean aortic pressure was unchanged as was left ventricular end-diastolic pressure. dP/dt_{max} was reduced after LAD occlusion but not significantly, but there was a significant fall after acebutolol of 10% ($P < 0.02$).

The detailed coronary blood flow results are shown in Table 4. After LAD occlusion, coronary flow fell by 40% in the ischaemic area from 1.18 ± 0.09 to 0.71 ± 0.1 ml min^{-1} g^{-1} ($P < 0.005$). LAD/circumflex ratio was also altered from 1.1 ± 0.06 to 0.6 ± 0.09 ($P < 0.005$). After acebutolol there was a slight but non-significant increase in flow to the ischaemic area from 0.71 ± 0.11 to 0.74 ± 0.12 ml min^{-1} g^{-1}. LAD/circumflex ratio increased from 0.6 ± 0.09 to 0.7 ± 0.11 ($P < 0.05$).

In the non-ischaemic area after LAD occlusion, coronary flow tended to increase but after acebutolol, the effects were similar to propranolol with a reduction in flow of 10%.

Discussion

In theory β-adrenoceptor blocking drugs would appear to be the most promising of agents which protect the ischaemic myocardium. Oxygen demand is decreased in as much as two of the major deter-

Table 2 Effects of propranolol on myocardial blood flow in animals with acute cardiac ischaemia

Full thickness flow (ml g^{-1} min^{-1})	*Control*	*Post infarct – saline*	*Post infarct – propranolol*
Left anterior descending	0.73 ± 0.09	0.36 ± 0.06***	0.48 ± 0.07*
Circumflex	0.73 ± 0.08	0.83 ± 0.09	0.75 ± 0.08
Left anterior descending/ circumflex flow ratio	1 ± 0.06	0.44 ± 0.08***	0.62 ± 0.09*
Endocardial/epicardial flow ratio			
Left anterior descending	1.24 ± 0.21	0.64 ± 0.15***	1.0 ± 0.45*
Circumflex	1.17 ± 0.11	1.2 ± 0.14	1.35 ± 0.23

Results shown as mean ± s.e. mean in 14 animals.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$.

Table 3 Haemodynamic effects of acebutolol in animals with acute cardiac ischaemia

	Control	*Post infarct after saline*	*Post infarct after acebutolol*
Heart rate (beats/min)	103 ± 5	121 ± 4****	110 ± 4****
Mean arterial pressure (mm_2Hg)	90 ± 5	94 ± 7	96 ± 6
Cardiac output (l/min)	2.9 ± 0.1	2.6 ± 0.1**	2.5 ± 0.1
Stroke volume (ml/min)	29 ± 2	21.3 ± 1**	22.1 ± 1
dP/dt_{max} mmHg/s	2706 ± 261	2641 ± 275	2398 ± 244***

Results shown as mean ± s.e. mean in 10 animals.
* $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$; **** $P < 0.001$.

minants of myocardial oxygen consumption are reduced, heart rate and myocardial contractility (Braunwald, 1971; Sonnenblick & Skelton, 1971). Circulatory catecholamines on the other hand appear to increase infarct size (Maroko *et al.*, 1971; Herbacynska-Cedro, 1972). Thus reduction in oxygen demand and slowing of the heart rate should limit the extent of myocardial necrosis. This hypothesis has been tested in anaesthetized models of myocardial ischaemia. Jennings and his colleagues have shown, using histological techniques, that propranolol can reduce infarct size after either temporary or permanent coronary artery occlusion (Jennings & Reimer, 1974; Reimer *et al.*, 1973; 1976). Similar results have been reported for the cardioselective β-adrenoceptor blocking drug, practolol (Libby, Maroko, Covell, Malloch, Ross & Braunwald, 1973; Marshall & Parratt, 1974). Other workers using radioactive microspheres to increase regional coronary flow, have reported that propranolol can produce relative increase in flow to the ischaemic myocardium particularly to the subendocardium (Becker *et al.*, 1971; Becker *et al.*, 1975). Vatner, Baig, Manders, Ochs, & Pagani (1977) in the conscious animal, reported an increase in flow to the ischaemic area of the myocardium after the intravenous administration of propranolol. In this study flow fell in the normal area of the myocardium but after propranolol there was a significant increase in flow to the ischaemic area of the myocardium. In addition to the transmural increase in flow there was a proportionate increase in flow to the endocardium with an increase in the endocardium/epicardium ratio.

Although overall blood flow was reduced there would appear to be a redistribution of coronary blood flow to the ischaemic area. Kloner *et al.* (1976) found no increase in collateral blood flow after the administration of propranolol but this study was performed 3 h after coronary artery occlusion and it has been reported that flow to the ischaemic area of the myocardium does not change up to 6 h after occlusion in the conscious dog (Bishop, White & Bloor, 1976). Tachycardia has been demonstrated to be deleterious to the ischaemic myocardium in both the anaesthetized and the conscious dog by Maroko *et al.* (1971) and Shell & Sobel (1973). Hutton, Curry, Templeton and Willerson (1976) in the conscious dog with established myocardial infarction have shown that myocardial oxygen consumption is increased with the tachycardia of atrial pacing and that flow to the subendocardial part of the infarcted left ventricle was reduced. Buckberg, Fixler, Archie & Hoffman (1972) and Hess & Bache (1976) have demonstrated that subendocardial flow was more dependent on diastolic perfusion pressure and the duration of diastole than subepicardial flow. Thus subendocardial perfusion would be enhanced by both the bradycardia and the unaltered diastolic pressure produced by β-adrenoceptor blockade.

In this study the resting heart rate was reduced by both β-adrenoceptor blocking compounds, the quantitative change being greater with propranolol. This is consistent with the property of intrinsic sympathomimetic activity possessed by acebutolol (Basil *et al.*, 1973).

The contractile state of the heart was assessed by determining the maximal rate of left ventricular pressure rise dP/dt_{max} and the quotient of dP/dt and developed left ventricular pressure, $dP/dt/P$ during isovolumic contraction (Mason *et al.*, 1971; Vatner, Higgins, Patrick, Franklin & Braunwald, 1971). In this study there was an overall moderate depression of left ventricular function, which would result in a reduction of oxygen requirement. The intrinsic sympathomimetic activity of acebutolol resulted in less depression of the myocardium than that produced by propranolol. Theroux, Ross, Franklin, Kemp & Sasayama (1976) have demonstrated in the conscious dog pretreated with propranolol, that there was an improvement in regional myocardial function in the ischaemic area of the myocardium.

The tracer microsphere technique is particularly suitable for measurement of coronary blood blow in the conscious animal. We have found no haemodyna-

Table 4 Effects of acebutolol on myocardial blood flow in animals with acute cardiac ischaemia

Full thickness flow ($ml\ min^{-1}g^{-1}$)	*Control*	*Post infarct – saline*	*Post infarct – acebutolol*
Left anterior descending	1.18 ± 0.09	0.71 ± 0.11**	0.74 ± 0.12
Circumflex	1.13 ± 0.07	1.17 ± 0.65	1.05 ± 0.68
Left anterior descending/ circumflex flow ratio	1.1 ± 0.06	0.6 ± 0.09**	0.7 ± 0.11*

Results shown as mean ± s.e. mean in 8 animals.
* $P < 0.05$; ** $P < 0.005$.

mic disturbance after injection of the spheres which distribute in proportion to regional blood flow. Adequate mixing is ensured by the injection into the left atrium and provided each sample of myocardium contains more than 400 microspheres then the accuracy of this method compares favourably with direct measurements of coronary blood flow (Domenech, Hoffman, Noble, Saunders, Henson & Subijanto, 1969; Buckberg, Luck, Payne, Hoffman, Archie & Fixler, 1971; Cobb, Bache & Greenfield, 1974).

In conclusion this study has demonstrated that β-adrenoceptor blocking drugs produce a relative increase in coronary blood flow to the ischaemic area of the left ventricle after coronary artery occlusion. This increase in flow extended to the subendocardium which is the area most sensitive to myocardial ischaemia (Griggs, Tchokoev & Chen, 1972; Karlsson, Templeton & Willerson, 1973). Overall left ventricular function was slightly depressed. These decreases in heart rate and myocardial contractility should have an oxygen sparing effect on the ischaemic myocardium in the absence of cardiac failure. Qualitatively the changes produced by both propranolol and acebutolol were similar, but quantitatively the effect of propranolol on both haemodynamics and myocardial blood flow was greater. Thus intrinsic sympathomimetic activity of β-adrenoceptor blocking agents appears to bestow no advantage in this conscious dog model of experimental myocardial ischaemia where coronary arterial occlusion produced only modest left ventricular dysfunction.

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