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The effect of exaprolol (MG 8823) on epicardial ST-segment changes in a feline model of acute myocardial ischaemia

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1 A model is described (anaesthetized, open-chest cats subjected to acute coronary artery occlusion) which allows the effects of drug interventions to be determined on one major electrocardiographic index of myocardial ischaemia. Epicardial ST-segment changes were continuously recorded from five individual sites on the surface of the left ventricle.

2 Coronary artery occlusion (left anterior descending branch) resulted in marked and consistent elevations of the ST-segment in all sites in nearly all experiments. These changes started within 1 min of the onset of ischaemia and reached a peak at between 30 and 60 min; thereafter there was a gradual reduction over the next 4 h. The one significant haemodynamic effect of coronary artery occlusion was an increase in left ventricular (LV) end-diastolic pressure (LVEDP). Ventricular ectopic activity was not pronounced in this model (about 50 ectopic beats over the initial 30 min post-occlusion period).

3 Exaprolol (1.0 mg kg^{-1}, intravenously) a potent β-adrenoceptor blocking agent with 'membrane stabilising activity', when given 1 h after the onset of ischaemia, reduced heart rate and LV dP/dt_{max} and increased LVEDP. These effects were prolonged (i.e. little recovery in heart rate 3 h after administration).

4 Exaprolol decreased total ST-segment elevation immediately after administration; this was significantly different from the effect of intravenous saline and lasted for at least 3 h. The effects appeared to be greater at sites of less pronounced ischaemia.

5 Intramyocardial temperature records were taken to indicate a reduction in blood flow to the ischaemic region; however the alleviation of epicardial ST-segment elevation suggests an improved myocardial oxygen demand:supply ratio.

6 Reperfusion was unsuccessfully attempted after a 4 h occlusion period; reperfusion after a shorter period (30 min) resulted in ventricular ectopic activity but no fibrillation.

Introduction

There is a good deal of experimental evidence that β-adrenoceptor blocking agents, when administered before acute coronary occlusion, reduce both the extent (area) and degree (intensity) of myocardial ischaemic injury. This was first demonstrated in dogs by Grayson, Irvine, Parratt & Cunningham in 1968 and has been confirmed on many subsequent occasions (e.g. Reimer, Rasmussen & Jennings, 1973; Jennings & Reimer, 1979). Such histological evidence remains the 'reference standard' by which other, less laborious, techniques for the assessment of infarct size should be evaluated. One of the most often used of these is epicardial ST-segment mapping in dogs (Maroko, Kjekshus, Sobel, Watanabe, Covell, Ross & Braunwald, 1971). This method has two particular disadvantages. Firstly, coronary occlusion in this species results in the occurrence of ventricular arrhythmias, often fatal, both during ischaemia (e.g. Marshall & Parratt, 1975) and during subsequent reperfusion (Coker & Parratt, 1983). Secondly, this method, as well as the 'short occlusions' technique in this species (Marshall & Parratt, 1977a) relates only to drug administration before the onset of acute myocardial ischaemia.

The above mentioned experimental studies may

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well have relevance to 'primary prophylaxis' and to secondary prevention trials with β-adrenoceptor blocking drugs (a subject recently reviewed by Fitzgerald, 1982) but not to the possibility of giving β-blocking drugs as soon as possible after the onset of myocardial infarction in the clinical situation. Although recent evidence in patients suggests that these drugs can reduce 'infarct size' (as assessed by enzyme leakage or by R wave and ST-segment analysis) even when given several hours after the onset of chest pain (Hjalmarson, 1981; Sleight, Yusuf, Peto, Rossi, Ramsdale, Bennett, Bray & Furse, 1981), there are surprisingly few experimental studies in which intervention with β-blocking drugs has been attempted after the onset of myocardial ischaemia. This present study summarises the results of intervention with the cyclohexylphenol exaprolol (Carissimi, Gentili, Grumelli, Milla, Picciola & Ravenna, 1976) in an experimental cat model in which ischaemic, life-threatening arrhythmias present no serious problem. A preliminary account of this work was given to a meeting of the British Pharmacological Society (Parratt & Udvary, 1980).

Methods

Fourteen cats of either sex weighing between 1.9 and 3.5 kg (mean weight 2.6 ± 0.1 kg) were anaesthetized with sodium pentobarbitone (40 mg kg^{-1} by intraperitoneal injection). Temperature was measured from the rectum and mid-oesophagus using direct recording thermocouples (Ellab, Copenhagen). Body (mid-oesophageal) core temperature was maintained between 36.5 and 38°C. After tracheotomy the animals were artificially respired with room air delivered by a Palmer positive pressure ventilation pump (stroke volume 45–75 ml; rate 20 min^{-1}). The stroke volume was adjusted so that the arterial P_{O_2}, measured with a micro-electrode system (Radiometer, Copenhagen), was between 70 and 100 mmHg (1 mmHg = 1.333 mbar). At a pH of 7.350–7.400 this indicates an arterial blood oxygen saturation of between 85 and 100%.

Systemic arterial pressure was recorded from a femoral artery by means of a capacitance transducer (Elema-Schönander EMT 35). Right atrial pressure was recorded with a second capacitance transducer (Elema-Schönander EMT 33) from a catheter inserted via the right external jugular vein. Left ventricular pressure was measured by a third transducer (Elema-Schönander EMT 34) and (usually) a stiff catheter inserted by way of the right carotid artery. The left ventricular pressure pulse was continuously differentiated to provide an index of myocardial contractility and end-diastolic pressure (LVEDP) was measured by cutting off the intraventricular pressure pulse above 20 mmHg. Left ventricular pressure, LVEDP, left ventricular dP/dt, systemic arterial pressure, right atrial pressure and the electrocardiogram (leads I or II) were recorded on an eight-channel ink jet writing recorder (Mingograph 81). Heart rate was calculated from the electrocardiogram.

A blood sample (2.0 ml) was taken anaerobically from the arterial catheter and analysed for O_2 and CO_2 tensions, and pH, using appropriate electrode systems (Radiometer, Copenhagen). The pH electrode was calibrated with standard buffers and O_2 and CO_2 electrodes with gas mixtures, the O_2 and CO_2 concentrations of which had been measured with a modified Lloyd-Haldane apparatus. O_2 and CO_2 tensions (mmHg) and pH were corrected for any temperature difference between the electrode systems (usually 37.3°C) and the animal's mid-oesophageal temperature. After a stabilization period a left thoracotomy was performed and a silk suture placed around the anterior descending coronary artery. This suture thread was brought out of the thoracic cavity through a smooth piece of polythene tubing such that pulling on the ligature occluded the artery against the lower end of the tubing. This also allowed the ligature to be released such that the effects of reperfusion could be examined.

Three additional intramyocardial sutures then allowed a modification of the device, described by Marshall & Parratt (1977a) for the measurement of surface epicardiograms in the dog, to be sutured to the surface of the left ventricular wall, in the region supplied by the anterior descending coronary artery. This was obviously much smaller than that used in the dog; it consisted of a piece of rubber, measuring 20 by 15 mm, in which were embedded five silver epicardial electrodes. The details of construction will form the subject of a separate communication but, in the meantime, can be obtained from the authors. Using this technique there was no evidence of ST-segment elevation from any lead before acute coronary artery occlusion. In addition, a small thermocouple was inserted in the apical region of the anterior surface for the measurement of intramyocardial temperature; this method has been used before in this laboratory (Kane, McDonald & Parratt, 1979). The object was to see whether post-coronary artery occlusion arrhythmias could be correlated with reductions in intramyocardial temperature (see Marshall & Parratt, 1980).

Before occlusion of the coronary artery a second arterial sample was taken and analysed for blood gases and pH. The artery was then occluded, initially for periods of 30 min but in subsequent experiments for periods of 4–5 h. This resulted in marked, time-dependent, increases in ST-segment elevation which were recorded 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 40, 50 and 60 min after occlusion from each of the five

epicardial sites. Thereafter the animals were divided into two groups: (1) Control group (7 cats); these were given saline (1 ml) and left for a further 4–5 h, recording the epicardiograms 65, 70, 75, 80, 85, 90, 100, 110 and 120 min after occlusion and thereafter every 30 min. (2) Treated group (7 cats); these were given exaprolol (MG 8823; 1.0 mg kg^{-1} intravenously) and the epicardiograms recorded as in the control group. Records were made in both groups of systemic arterial and left ventricular pressure, of LVEDP and LV dP/dt and of a limb lead electrocardiogram (usually lead I) at each of these times. After 4–5 h the occlusion of the artery was stopped and attempts were made to reperfuse the myocardium.

The assessment of the ST-segment changes resulting from ischaemia was examined both with regard to the changes that took place *at each individual epicardial site* and by meaning or summing ST-segment changes from all five sites. ST-elevation was measured at each individual site and at chart speeds of 25 or 50 mm/s, usually from the take-off point on the QRS complex. The results from the exaprolol treated cats were compared with those of the control group at different times after drug administration.

Results

Effects of coronary artery occlusion

The haemodynamic effects of acute coronary artery occlusion in anaesthetized cats are summarized in Table 1 and in Figure 1. There was an immediate but slight reduction in arterial blood pressure of about 10 mmHg; this was more marked the higher the initial resting blood pressure and very little recovery took place over the next 60 min period (Figure 1). There was also a transient reduction in LV dP/dt_{max} (Table 1; Figure 1) with, in most cases, partial recovery over the next 60 min. Since LVEDP was always increased (Table 1) this decrease in LV dP/dt_{max} (at an almost unchanged afterload) indicates a decrease in myocardial contractility. This is what one would expect with a substantial area of the left ventricular wall rendered ischaemic. Changes in heart rate were inconsistent (Figure 1). In two cats there were substantial increases (of 48 and 44 beats min^{-1}); in two others there was a significant bradycardia (of 12 and 20 beats min^{-1}). These alterations in heart rate, resulting from autonomic nervous activity, are rather like those seen in patients immediately after an acute infarction (Pantridge, Adgey, Geddes & Webb, 1975).

In all 14 cats there was ventricular ectopic activity soon after coronary artery occlusion. This, however, was not pronounced (mean of 52 ± 26 ventricular ectopic beats in the initial 30 min post-occlusion

Table 1 Haemodynamic changes resulting from acute coronary artery occlusion and, 1 h later, from the intravenous injection of exaprolol (1.0 mg kg^{-1})

	Pre-ligation	*Post-ligation* (min)			*Post-MG 8823* (min)		
	5	10	30	60	5	10	30	60
Arterial blood pressure (systolic; mmHg)	125 ± 9	121 ± 6	126 ± 6	126 ± 9	119 ± 6	119 ± 6	114 ± 6	117 ± 8
(diastolic; mmHg)	96 ± 6	89 ± 6	92 ± 3	89 ± 6	81 ± 6	81 ± 7	78 ± 5	77 ± 4
Heart rate (beats min^{-1})	203 ± 15	210 ± 14	217 ± 13	212 ± 14	168 ± 7*	164 ± 6*	167 ± 9**	178 ± 10*
LV dP/dt_{max} ($mmHg\ s^{-1}$)	3760 ± 540	3050 ± 333	3210 ± 400	3223 ± 430	1880 ± 260*	1950 ± 250	2120 ± 230*	2330 ± 280*
LVEDP (mmHg)	4.3 ± 0.5	6.5 ± 0.6*	6.9 ± 1.0*	5.9 ± 0.6	7.8 ± 1.0*	7.6 ± 1.0*	7.8 ± 1.2	5.8 ± 1.1

*$P < 0.01$; **$P < 0.05$

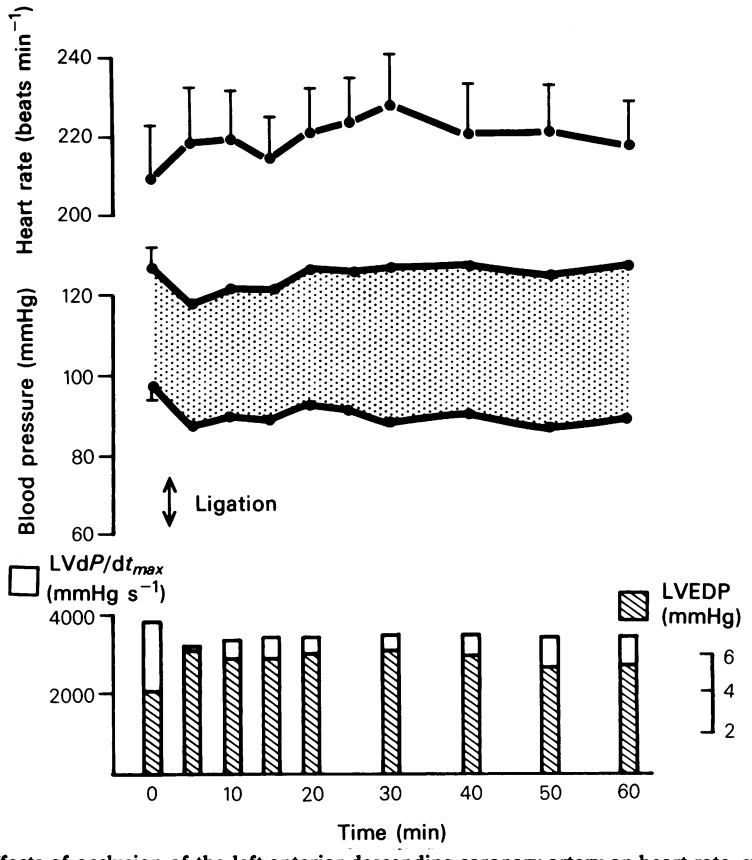

Figure 1 The effects of occlusion of the left anterior descending coronary artery on heart rate, systemic arterial blood pressure, left ventricular dP/dt_{max} and left ventricular end-diastolic pressure in anaesthetized cats. The more pronounced effects are a reduction in LV dP/dt_{max} with an increase in filling pressure, a transient hypotension and a slight increase in heart rate. The values are the mean of 14 experiments; standard errors have been omitted for clarity but are given (at some of the times) in Table 1.

period) and is in marked contrast to what happens in dogs (greyhounds) when this coronary artery is ligated. In nearly all the animals there appeared to be two distinct populations of arrhythmias; an initial burst (within 1–2 min of the onset of ischaemia; phase 1a) and often a later, more severe period of ectopic activity between 10 and 20 min. In 6 of the animals there were more than 50 (i.e. 52 to 329) ventricular ectopic beats during this phase (1b). In only 2 animals was there ventricular tachycardia and no cat fibrillated during this early period. Except in 2 animals ventricular ectopic activity was rare after 30 min. One cat fibrillated 120 min after coronary artery occlusion; this cat is not included in the Results section.

Attempts were made to re-open the occlusion at the end of the 4 h occlusion period. This was possible in only a small number of animals and did not result either in reversal of the ST-ischaemic changes or in the occurrence of reperfusion arrhythmias. In a separate series of four experiments coronary artery occlusion was maintained for only 30 min and the ischaemic area was then reperfused. This resulted in the appearance of ventricular ectopic beats (10, 20, 30 and 38 respectively) but not in fibrillation.

Coronary artery ligation resulted in pronounced increases in ST-segment elevation, assessed from epicardial electrodes, commencing within 20 beats of the onset of ischaemia. In no animal was there ST-segment elevation before occlusion. This ST-segment elevation recorded from epicardial sites increased with time (Figure 2) and tended to reach a peak 30 min – 2 h after occlusion. These alterations in ST-segment elevation were similar in the 7 control cats (in which the coronary artery was ligated and the animals followed for a further 3–4 h) to those in which exaprolol was given 1 h post-occlusion. Thus, at 60 min, ST-segment elevation was 13.5 ± 1.8 mV

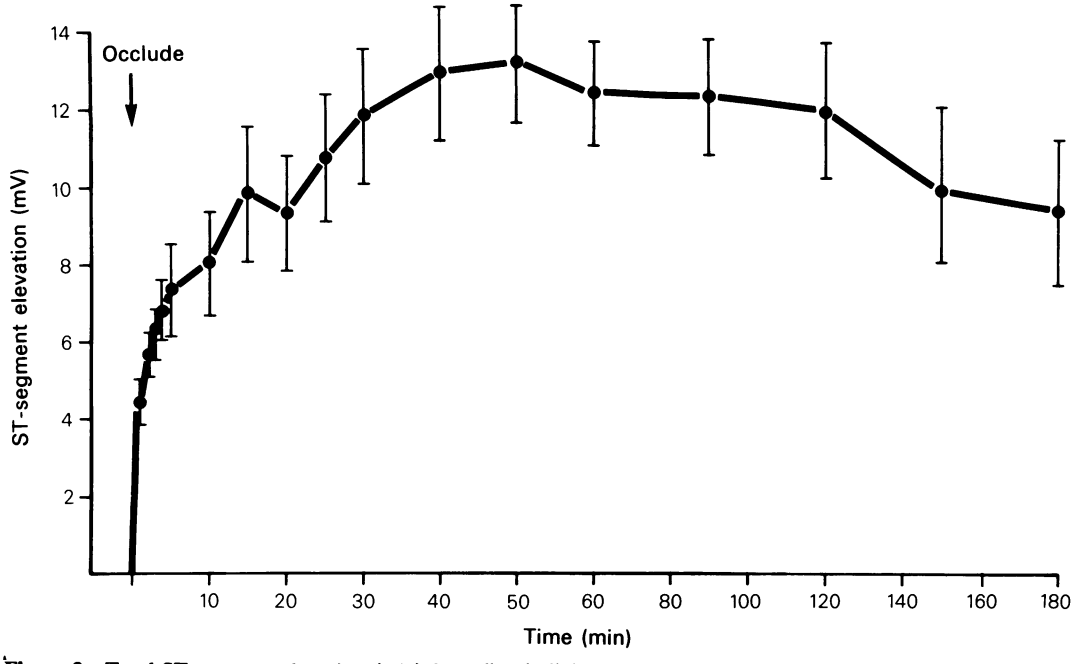

Figure 2 Total ST-segment elevation (mV) from five individual epicardial leads in 7 anaesthetized cats which were not given exaprolol (control series).

(total) and 2.71 ± 0.37 mV (mean) in the control series and 11.2 ± 2.0 mV (total) and 2.25 ± 0.40 mV (mean) in the cats that were then given exaprolol. Figure 3 illustrates records obtained in a cat that received saline 60 min after coronary artery occlusion.

Coronary artery ligation resulted in a gradually increasing difference between local intramyocardial temperature and mid-oesophageal temperature. Previous, unpublished studies from this laboratory have demonstrated that, in anaesthetized cats, oesophageal temperature accurately reflects temperature simultaneously recorded from the aortic arch. Under resting conditions (open-chest, but before coronary occlusion) myocardial temperature exceeded oesophageal temperature by 0.66 ± 0.23°C; this had increased to 1.00 ± 0.32°C at 1 h.

The haemodynamic effects of exaprolol 1 h after acute coronary artery occlusion

The results are given in Table 1 and are summarised in Figure 4. They may be compared with the results of a separate (unpublished) study in which exaprolol was given intravenously, in the same dose, to normal (closed-chest) anaesthetized cats. Changes in systemic arterial pressure were not particularly marked following the injection of exaprolol; in 2 animals there were distinct increases in mean pressure of 10 and 16 mmHg respectively. In 3 animals there were reductions in pressure of 24,20 and 10 mmHg and in the remaining 2 cats there was no change (i.e. < 5 mmHg). These changes are significantly less than those seen in intact, closed-chest cats (Table 2). There was, as one might expect, a significant reduction in heart rate (Table 1; Figure 4) of between 18 and 78 beats min^{-1}; this bradycardia was often very long-lasting (Figure 4). Exaprolol also markedly decreased LV dP/dt_{max} and (usually) increased LVEDP (Table 1; Figure 4). Again these are the effects one would expect following the administration of a potent β-adrenoceptor blocking agent after acute myocardial infarction and were only slightly more pronounced than those observed in normal cats given this dose of exaprolol (similar reduction in LV dP/dt_{max} but at a slightly decreased LV filling pressure; Table 2).

The effects of exaprolol on epicardial ST-segment changes

The effects of exaprolol on epicardial ST-segment elevation were profound and consistent (Figure 5). For example, total ST-segment elevation was reduced from 11.2 ± 2.0 mV (mean for each lead 2.25 ± 0.4 mV) to 7.4 ± 1.7 mV ($P < 0.01$) and 1.48 ± 0.34 mV respectively at 120 min, i.e. 60 min after MG 8823 administration. In the cats given

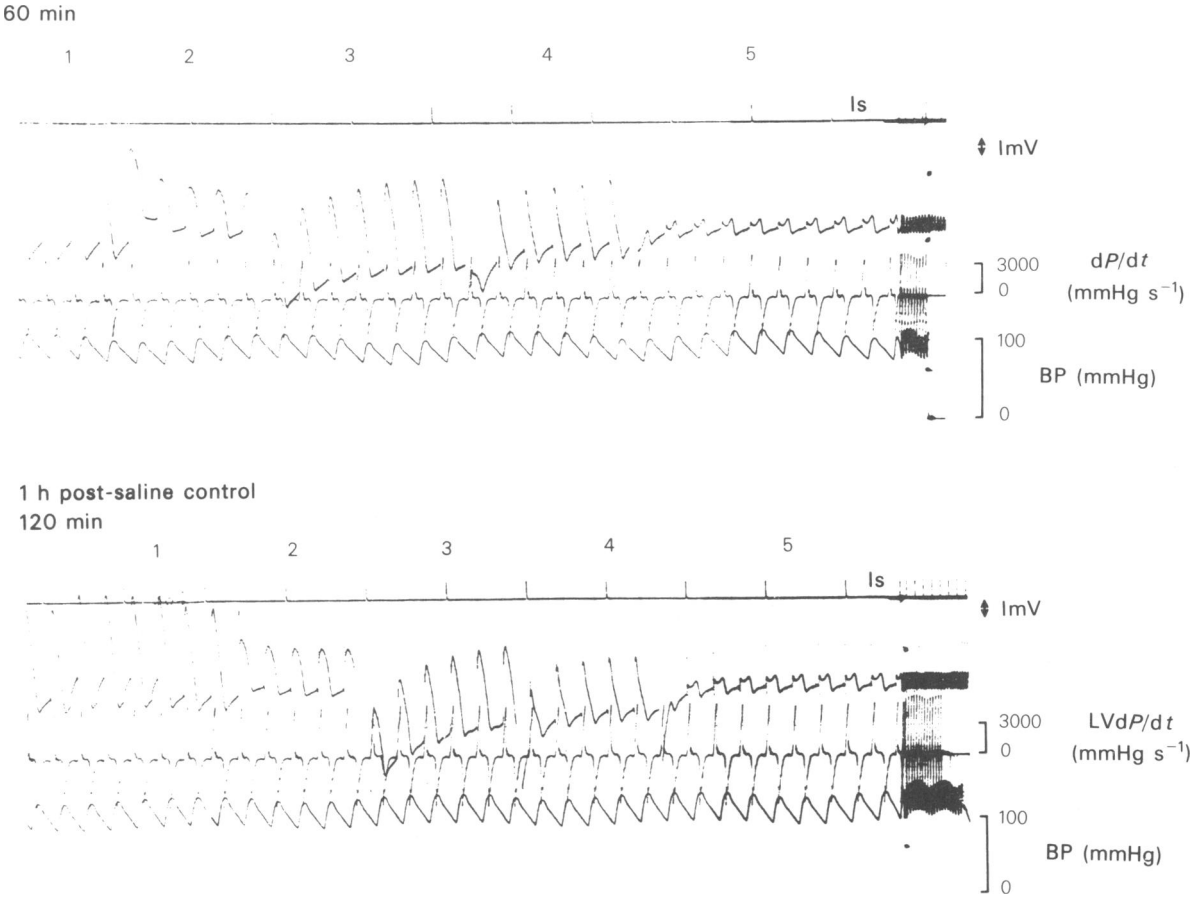

Figure 3 Electrocardiographic recordings from five epicardial sites one and two hours after acute coronary occlusion. Also shown are LV d*P*/d*t* and systemic arterial blood pressure.

saline (controls), ST-segment elevation was insignificantly reduced over this 1 h period (i.e. from 13.5 ± 1.6 mV (mean for individual leads of 2.7 ± 0.37 mV) to 12.1 ± 1.8 mV and 2.42 ± 0.36 mV (Figure 5). There was a highly significant difference ($P < 0.001$) between the reduction in the mean ST-segment elevation in the saline controls (0.32 ± 0.08 mV between 1 and 2 h) and those administered exaprolol (0.77 ± 0.10 mV).

There is clearly a gradual reduction in epicardial ST-segment elevation with time even in untreated cats but this is much less than that observed when exaprolol is administered; this difference is still pronounced at 3 and 4 h (Table 3).

Some attempt was made, by looking at ST-segment changes recorded from individual leads, to determine whether there was any evidence that exaprolol reduced ST-segment elevation more in those regions of more severe ischaemia. This involved the analysis of ST-segment elevation at 35 different sites in 7 individual cats before, and at 13 separate times after, exaprolol administration (i.e. over 400 individual records). However, the effect at one particular time (15 min after drug administration) will suffice. At this time the change in individual leads varied from 0 to 1.56 mV (from a mean of $+2.25 \pm 0.21$ mV); as one might expect, the greatest change (arbitrarily chosen as greater than 0.4 mV) took place in those leads where ST-segment elevation was initially more pronounced (ST-segment elevation greater than 2.0 mV). However, if the percentage reduction in ST-segment elevation was calculated at each site, the greatest effect of exaprolol was on those sites where ST-segment elevation was less than 2 mV i.e. in those areas of less pronounced ischaemia.

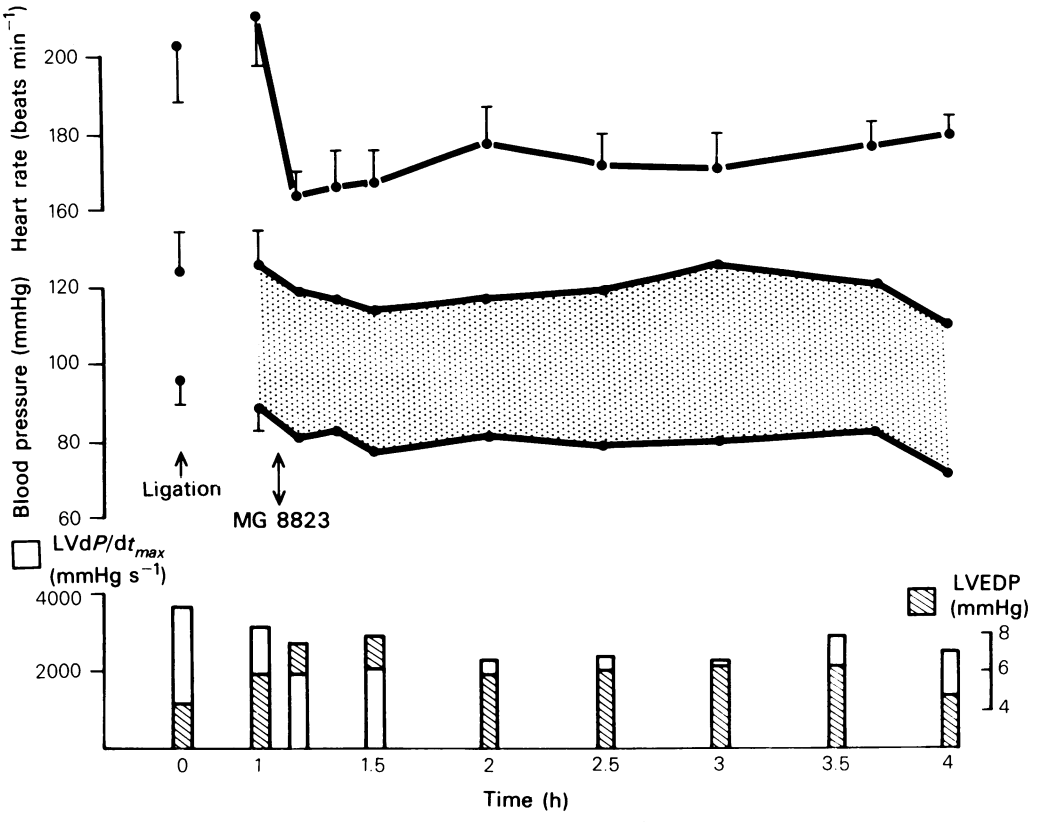

Figure 4 Haemodynamic effects of exaprolol (MG8823), 1.0 mg kg^{-1} intravenously, when given after the onset of myocardial ischaemia. There is a pronounced bradycardia and a depression of myocardial contractility (decreased LV dP/dt with increased LVEDP). Note the duration of these effects.

Effects of exaprolol on myocardial temperature

Exaprolol administration increased the temperature differential between the myocardium and mid-oesophagus e.g. from 0.76±0.21°C (myocardium hotter than aortic blood) before drug administration to +0.94±0.20°C, +1.01±0.21°C and +1.09±0.27°C 5,15 and 30 min after administration respectively. In the control group (given saline rather than exaprolol) the corresponding myocardial-oesophageal temperature gradients were +0.80±0.15°C (before) and +0.80±0.22°C and +0.72±0.22°C, 15 min and 30 min later. Exaprolol therefore increases the myocardial-aortic (coronary) blood temperature differential whereas saline does not ($P<0.01$ at both 15 and 30 min).

Table 2 The immediate haemodynamic effects of exaprolol (1 mg kg^{-1}) in normal anaesthetized cats and in cats that had been subjected to coronary artery occlusion 1 h previously (Values are changes from those given in Table 1)

	Normal	*Coronary occlusion*
Systolic arterial pressure (mmHg)	−23±6	−7±2*
Diastolic arterial pressure (mmHg)	−24±6	−8±4*
Mean arterial pressure (mmHg)	−23±6	−7±5*
Heart rate (beats min^{-1})	−44±8	−44±9
LV dP/dt_{max} (mmHg s^{-1})	−1080±440	−1345±320
LVEDP (mmHg)	−0.8±0.6	+1.7±0.6*

*Significantly different from effects in normal anaesthetized cats: $P<0.01$.

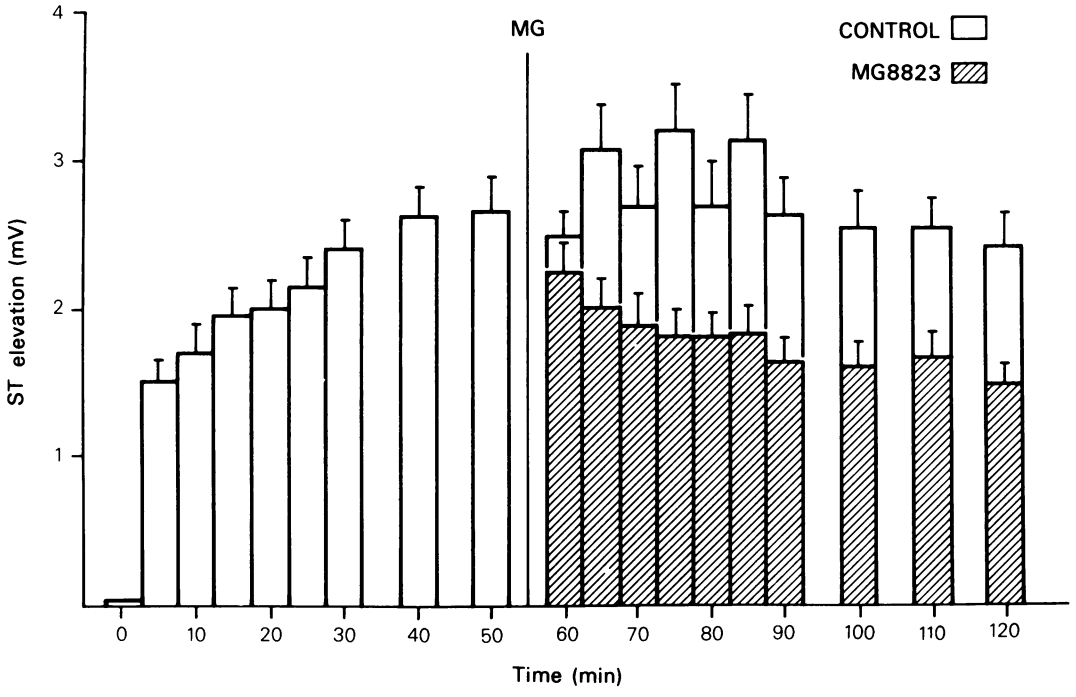

Figure 5 Change in mean epicardial ST-segment elevation in cats subjected to acute coronary artery occlusion. At 1 h the cats were divided into two groups; one (open columns) received saline, the rest received exaprolol (MG8823). Notice the immediate and prolonged reduction in ST-segment elevation in those cats that received exaprolol.

Discussion

One of the most often used indirect techniques for assessing myocardial ischaemic damage is that of ST-segment mapping over the area supplied by the occluded artery. This method, for example, has been extensively used by Braunwald's group in the United States (e.g. reviewed by Braunwald & Maroko, 1974). Although the relationship between acute ST-segment changes and the ultimate size of the infarcting area is still controversial, a number of studies have shown that such changes correlate well with the degree of reduction in myocardial blood flow, with changes in membrane potential and with the extent of anaerobic metabolism and creatine phosphokinase depletion at sites below the epicardial electrodes. This evidence has been reviewed (Marshall & Parratt, 1979). One possible reason for the apparent efficacy of β-adrenoceptor blocking agents when given before coronary artery occlusion is the consequent reduction in the number and severity of post-coronary artery occlusion arrhythmias (Fitzgerald, 1982). Ventricular arrhythmias, by reducing blood pressure and coronary blood flow, would further reduce myocardial perfusion and jeopardise the developing ischaemic area. This would explain, for example, the efficacy of lignocaine in reducing ischaemic injury resulting from acute coronary artery

Table 3 Total ST-segment elevation (mV) recorded by an epicardial 'mapping' technique in anaesthetized cats subjected to acute occlusion of the left anterior descending coronary artery

	Time after coronary artery occlusion (h)						
	1	1.5	2	2.5	3	3.5	4
Control	13.51±1.9	12.3±1.5	11.9±1.8	10.9±1.9	9.3±1.9	9.0±1.8	8.3±1.1
Exaprolol	11.06±2.09	8.1±1.7*	7.4±1.7*	6.9±1.4*	5.9±1.2*	5.3±1.2*	4.6±1.0*

Exaprolol or saline (control) was given 1 h after the onset of ischaemia.
*$P<0.001$ compared with control (saline) group.

occlusion. One way round this problem is to use a model in which post-occlusion arrhythmias are rare or non-existent. The most common method is to occlude a major coronary artery for short periods (e.g. 5–15 min) since such a short period of occlusion rarely gives rise to severe ventricular arrhythmias except perhaps on reperfusion. Such occlusions can be repeated at intervals in the same preparation and the effect of the agent under examination studied by administering it before such a short occlusion. In the greyhound model we have previously used such short (3–5 min) periods of occlusion to examine the effects of β-adrenoceptor blocking drugs and of prenylamine derivatives (Marshall & Parratt, 1977b). The obvious disadvantages of the technique as outlined above is that it bears little relevance to the possibility of acute pharmacological interventions in the early stages of infarction (i.e. treatment rather than prophylaxis). Much less is known about the effects of β-adrenoceptor blocking drugs administered once the ischaemic injury processes have already started (i.e. after coronary artery occlusion), at least in the experimental situation.

The feline model we have developed is one in which ventricular ectopic activity during the ischaemic period is not pronounced. For example, the mean ventricular ectopic count during the initial 30 min post-occlusion period was about 50 compared with more than 700 when the anterior descending coronary artery is occluded in dogs (Marshall & Parratt, 1980) and more than 1000 following coronary artery occlusion in anaesthetized rats (Clark, Foreman, Kane, McDonald & Parratt, 1980). In addition, no cat fibrillated early in ischaemia; this contrasts with a 20–30% incidence in the greyhound model and a 50–75% incidence (and 10–20% mortality) in the rat model.

The incidence and severity of ventricular arrhythmias following coronary artery occlusion in the present studies were similar to those described in our original paper involving coronary occlusion in the cat (Moore & Parratt, 1973). The severity is much less than that reported more recently by Corr, Witkowski & Sobel (1978) and by Sheridan, Penkoske, Sobel & Corr (1980) who quote values of 1205 ± 97 and 908 ± 120 ventricular ectopic beats, with an incidence of fibrillation of 20 and 28% respectively. These authors however ligated the anterior descending coronary artery (LAD) at its bifurcation from the main left trunk (i.e. considerably higher than in our studies) and used α-chloralose as their anaesthetic. The site of occlusion and anaesthetic used are two major factors determining the severity of early ischaemic arrhythmias (Marshall & Parratt, 1980). The other groups using a pentobarbitone-anaesthetized cat model similar to our own (Lefer, Cohn & Osman, 1977; Kisin, 1978) do not mention ventricular arrhythmias occurring after LAD occlusion; presumably these were not serious.

The cat model described in this paper is one in which compounds can be given after the processes concerned with ischaemic injury have started. We assessed ST-segment changes continuously by mapping electrodes from five different points on the surface of the myocardium and administered the drug under discussion 1 h after occlusion (when ST-segment changes were maximal; Figure 5). Exaprolol reduced ST-segment elevation to a greater extent than saline and this reduction was present up to 3 h after drug administration (Table 2). There is no doubt that this compound greatly reduces this particular index of myocardial ischaemia. We were interested in determining whether this reduction depends upon the initial level of ST-segment elevation (i.e. the initial degree of myocardial ischaemia). Is there, for example, a more marked effect at 'border zones' of limited ischaemia than at the centre (core) of the infarcting region? This appeared to be so since the percentage reduction in ST-segment elevation following exaprolol administration was greater in those areas where ST-segment elevation was less than 2 mV. This might suggest, as one might perhaps expect, that it is in those areas of less pronounced ischaemia that the benefits of β-blockade are most clearly seen. Certainly in this model there is histological evidence of irreversible injury, leading to cell necrosis, at the time (1 h) after occlusion when, in these experiments, exaprolol was given (Krug, 1972). It could be therefore that earlier intervention would have been even more effective.

There are a number of possible explanations for the effect of exaprolol on ST-segment elevation. Firstly, it could be the consequence of the reductions in heart rate and myocardial contractility (Table 1). These would reduce myocardial oxygen demand and thus improve the imbalance between the limited myocardial oxygen supply (resulting from decreased myocardial perfusion) and continued cellular oxygen demands. We do not know whether blood flow to the ischaemic area is reduced by exaprolol or is maintained by it. Our studies in anaesthetized greyhounds indicate that those β-adrenoceptor blocking agents with intrinsic sympathomimetic activity maintain blood flow within the ischaemic area (and may indeed improve endocardial perfusion) whereas those without this property reduce ischaemic muscle blood flow and may even accentuate the metabolic consequences of myocardial ischaemia (e.g. lactate production; Marshall & Parratt, 1976; 1977c). Although it is difficult to interpret accurately myocardial temperature data (since it represents the balance between heat production as a consequence of myocardial metabolism, and heat loss as a result of blood flow) the administration of exaprolol 1 h after the onset of

ischaemia increased the myocardial-blood temperature differential. The most likely explanation for this is a reduction in blood flow (which is a cooling factor for the ischaemic region). This, of course, does not allow us to determine whether the myocardial oxygen demand: supply ratio in this area is reduced; presumably, on the evidence of the ischaemic electrocardiographic results, it is.

Another possible explanation for the observed effect of exaprolol is a 'membrane-stabilizing effect' similar to that of lignocaine; certainly this β-blocker has marked effects in reducing the rapid Na^+ current in Purkinje fibres (Hughes, Kane, McDonald & Parratt, unpublished). Whatever the explanation, exaprolol clearly limits the consequences of acute myocardial ischaemia in this model. However, the crux of the matter is the question whether ischaemic damage (assessed histochemically or, preferably, histologically) is ultimately reduced, say several days after infarction. Certainly the combination of: (a) effectiveness against early post-infarction arrhythmias (Hughes, Kane, McDonald & Parratt, unpublished), (b) β-adrenoceptor blockade without significant myocardial depression even in the presence of myocardial ischaemia and (c) the ability to reduce at least one index of myocardial ischaemia, indicate that exaprolol is a compound with possible potential in the early therapy of acute myocardial infarction.

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