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THE BENEFICIAL ACTIONS OF BEPRIDIL IN ACUTE MYOCARDIAL INFARCTION IN ANAESTHETIZED DOGS

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1 When administered intravenously shortly before acute coronary ligation in dogs anaesthetized with chloralose, bepridil (5 mg/kg) produced immediate and transient falls in coronary and systemic vascular resistance which were accompanied by marked decreases in myocardial oxygen extraction. These effects were followed by sustained decreases in heart rate and myocardial oxygen consumption.

2 This dose of bepridil reduced the number of premature ventricular beats and abolished fibrillation induced by coronary artery ligation without modifying the haemodynamic or metabolic consequences (lactate production) of myocardial ischaemia.

3 When administered 1.5–2 h after ligation, bepridil did not compromise the critical perfusion of the acutely ischaemic zone but reduced the lactate production and ST-segment elevation in the ischaemic zone.

4 These results suggest that bepridil may be a useful drug in the chronic treatment of angina pectoris and in this respect may possess advantages over β-adrenoceptor antagonists.

Introduction

Bepridil (1-[3-isobutoxy-2-(benzylphenyl)-amino] propyl pyrrolidine hydrochloride) has been shown to possess a potentially useful anti-anginal profile in both anaesthetized and conscious dogs (Cosnier, Duchene-Marullaz, Rispat & Streichenberger, 1977; Piris, Beaughard, Cosnier & Labrid, 1978). In addition, electrophysiological studies have demonstrated that bepridil is capable of blocking the slow inward current in mammalian and amphibian myocardium (Vogel, Crampton & Sperelakis, 1979; Labrid, Grosset, Dureng, Mironneau & Duchene-Marullaz, 1979). Since there are no data available on the effects of bepridil on the acutely ischaemic myocardium, it was of interest to study the effects of the compound on the electrophysiological, metabolic and haemodynamic consequences of acute myocardial ischaemia in a well-documented experimental model (Marshall, Parratt & Ledingham, 1974; Marshall & Parratt, 1976). Some of the results obtained have been presented to the British and Italian Pharmacological Societies (Marshall & Muir, 1981).

Methods

These experiments were carried out in greyhounds of either sex weighing between 18 and 32 kg. Anaesthesia was induced by intravenous administration of sodium thiopentone (20 mg/kg) and maintained by the intravenous injection of α-chloralose (80–90 mg/kg). After endotracheal intubation, respiration with 100% O_2 was applied from a positive pressure ventilation pump whose rate and stroke were adjusted to maintain arterial P_{CO_2} around 37 mmHg (1 mmHg = 1.33 mbar). Reflex movements were prevented by the intermittent intravenous administration of pancuronium bromide (4 mg). In our hands, this anaesthetic procedure is associated with good haemodynamic and metabolic stability over 6–8 h without the excessive sympathetic activity associated with barbiturates or trichlorethylene.

In all dogs, catheters were placed under fluoroscopic control, in the descending aorta, the pulmonary artery (Swan-Ganz), the coronary sinus, the left ventricle and in a femoral vein as previously described (Marshall & Parratt, 1977). Records of left ventricular pressure at high gain allowed accurate assessments to be made of left ventricular end-diastolic pressure. Myocardial contractility was assessed by the measurement of left ventricular dP/dt divided by the instantaneous pressure (i.e. $(dP/dt)/P$). Cardiac output was measured (in duplicate) by thermodilution as described by Douglas, McDonald, Milligan, Mellon & Ledingham (1975).

After a left thoracotomy, the antero-lateral aspect of the heart was exposed and a calibrated electromagnetic flow probe (1.5–3.0 mm diameter) placed around the left circumflex coronary artery for the measurement of coronary blood flow using a Statham SP2202 flowmeter with non-occlusive zeroing facilities. The anterior descending branch of the left coronary artery (LAD) was prepared for ligation

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at a point distal to the septal branch and a major branch of the main (anterior coronary) vein adjacent to this artery was catheterized with a Longdwel teflon catheter (size 20G). Positive end-expiratory pressure (2 cmH_2O) was initiated in all animals after thoracotomy to minimize alveolar shunting.

Blood samples (1 ml) were taken from the aorta, pulmonary artery, coronary sinus and local coronary vein and were analysed for O_2 and CO_2 tensions, O_2 content and pH, using an I.L. blood gas analyser. Arterial coronary sinus and coronary vein blood samples were also deproteinized (with chilled trichloroacetic acid (TCA), centrifuged (3000 rev/min for 10 min) and analysed for lactate with a standard commercial kit (Boehringer Ingelheim).

After a 30–40 min stabilization period, during which at least two control measurements were taken, 10 of the dogs were given bepridil (5 mg/kg administered over 2 min) and changes in haemodynamics and blood gases monitored. In these dogs and in 20 untreated animals, the ligature on the LAD was tied in one stage and the number of ventricular ectopic beats counted during each 5 min period for a total period of 30 min; no manipulations were carried out during this time.

After the crucial 30 min period immediately after ligation, a catheter was inserted into the peripheral stump of the ligated artery and was used for the measurement of peripheral coronary pressure (PCP) and for the injection of ^{133}Xenon into the infarcting zone. Total myocardial blood flow in this area was assessed from the clearance of ^{133}Xenon using a NaI scintillation counter clamped over the epicardium (Marshall *et al.*, 1974). To record epicardial ECGs, nine silver epicardial electrodes embedded in a triangular piece of rubber were sutured to the surface of the anterior left ventricular wall so that at least six electrodes were situated in the obviously ischaemic zone. Frequent epicardial ECG recordings were taken before and at various times after intravenous administration of bepridil (5 mg/kg, $n=6$) 1.5–2 h after ligation and were compared with epicardial ECGs measured in five untreated animals over the same time period.

At the end of each experiment, diffusible dye (indocyanine green) was infused at a pressure of 50 mmHg into the peripheral stump of the ligated coronary artery. Fibrillation was immediately induced with potassium chloride and the dyed muscle quickly excised and weighed. The mass of dyed myocardium which represents the area perfused by the ligated artery was expressed as a percentage of the free left ventricular wall.

Systemic arterial pressure (pulsatile and mean by electronic integration), pulmonary artery pressure, left ventricular pressure, LV dP/dt, LV $dP/dt/P$, left circumflex coronary blood flow and the electrocardiogram (standard limb lead II) were recorded on a Siemens ink-jet writing recorder (Mingograph 82). Myocardial oxygen extraction and consumption were calculated as outlined by Marshall & Parratt (1973) and cardiac work and vascular resistances as described by Ledingham, Parratt, Smith & Vance (1971).

Results were statistically analysed by Student's t test for paired or unpaired data. Bepridil was moistened with 0.2 ml monopropylene glycol and then dissolved in warm distilled water and infused over 2 min. All doses in the text refer to the hydrochloride salt.

Results

Haemodynamic effects of bepridil when administered intravenously 20 min before coronary artery ligation

Preliminary dose-finding showed that bepridil (1–5 mg/kg) caused an immediate dose-dependent fall in mean arterial blood pressure (range 15–70 mmHg) and a more sustained decrease in heart rate (12–35 beats/min). It was therefore decided to use 5 mg/kg in this study. It has been shown previously that this dose of bepridil reduces the

Table 1 Haemodynamic effects of bepridil (5mg/kg) when administered before coronary artery ligation

	Pre-drug	*Immediately post-drug*	*20 min post-drug*
Mean BP (mmHg)	135±9	77±11**	135±9
Heart rate (beats/min)	159±7	159±8	132±5*
LV(dP/dt)/P(s^{-1})	42±2	44±3	39±1
Stroke volume (ml/beat)	20.0±1.3	29.0±2.3*	19.6±1.1
Coronary blood flow (ml/min)	68±9	108±17*	53±5*
Myocardial oxygen consumption (ml/min)	10.4±1.3	—	8.5±1.0*

*$P<0.05$; **$P<0.005$.

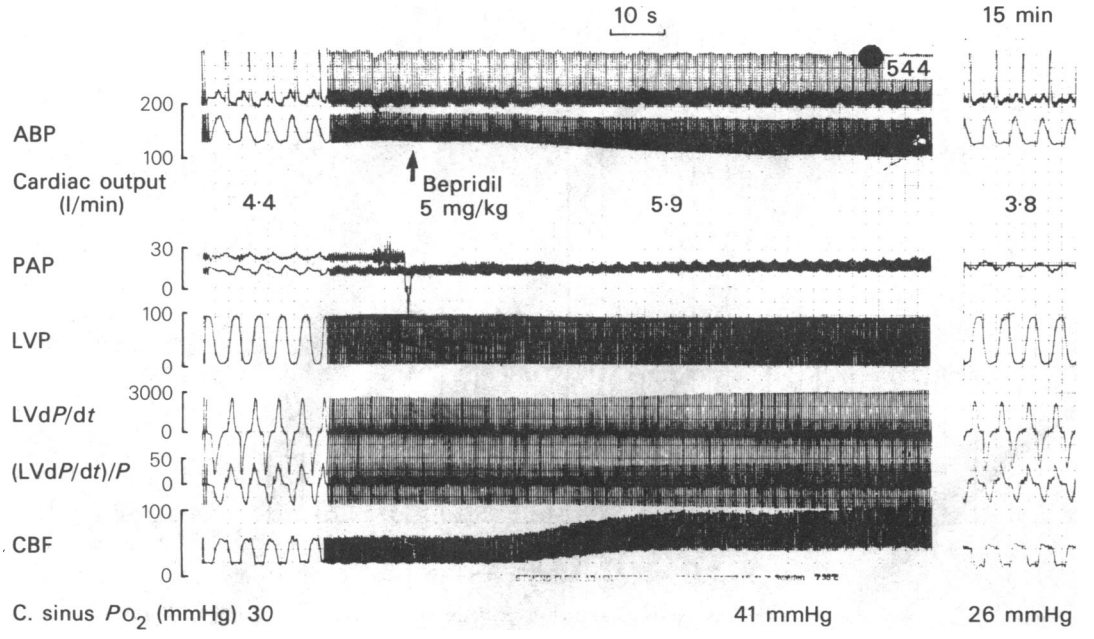

Figure 1 Typical trace showing the immediate and later haemodynamic effects of bepridil 5mg/kg when administered to an anaesthetized dog before coronary artery ligation.

tachycardia and elevation of blood pressure evoked by auditory-induced emotional stress in the conscious dog (Piris *et al.*, 1978).

The haemodynamic effects of bepridil (5 mg/kg) are summarized in Table 1 and a typical trace shown in Figure 1. Clearly the effects of bepridil can be divided temporally into two phases. Immediately on injection, bepridil caused a decrease in arterial blood pressure (with an increased pulse pressure) which was accompanied by increases in both circumflex coronary blood flow and in cardiac output. At this time myocardial oxygen extraction was significantly decreased (from 60 ± 3 to $41 \pm 5\%$, $P < 0.001$) but heart rate and left ventricular contractility (measured as $(dP/dt)/P$) were unchanged. Systolic pulmonary artery pressure (SPAP) was significantly elevated from 24 ± 2 to 32 ± 3 mmHg ($P < 0.01$) at a time when stroke volume was increased but 20 min later SPAP had returned to control levels (25 ± 4 mmHg). Diastolic PAP remained unchanged, the values being 15 ± 2, 18 ± 3 and 15 ± 2 mmHg before, immediately after and 20 min after bepridil administration respectively. These immediate haemodynamic effects were short-lived (3 to 5 min) and 20 min after bepridil administration, heart rate and myocardial oxygen consumption were significantly reduced although stroke volume and contractility were unchanged (Table 1).

The effects of bepridil on the immediate dysrhythmias ensuing after acute coronary ligation

The number of ventricular ectopic beats and the incidence of ventricular fibrillation in the untreated group and in the dogs pretreated with bepridil are compared in Figure 2. In the 20 control animals, ligation of the LAD resulted in marked ventricular ectopics and ventricular tachycardia in all animals in the first 30 min period. In 35% of these animals, the dysrhythmias developed into terminal ventricular fibrillation in the 11 and 20 min period after ligation. In contrast, although the bepridil-treated group also exhibited ventricular dysrhythmias during the first 10 min, they were of a different configuration (usually bigeminy), and ventricular tachycardia and fibrillation were not observed in any of these animals. This marked difference in the type of dysrhythmias observed in the two groups is illustrated in Figure 3. The area of myocardium perfused by the ligated artery was similar in the control ($23 \pm 3\%$) and in the bepridil ($27 \pm 3\%$) groups.

The effects of bepridil on the haemodynamic and metabolic consequences of acute coronary artery ligation

The haemodynamic consequences of acute coronary

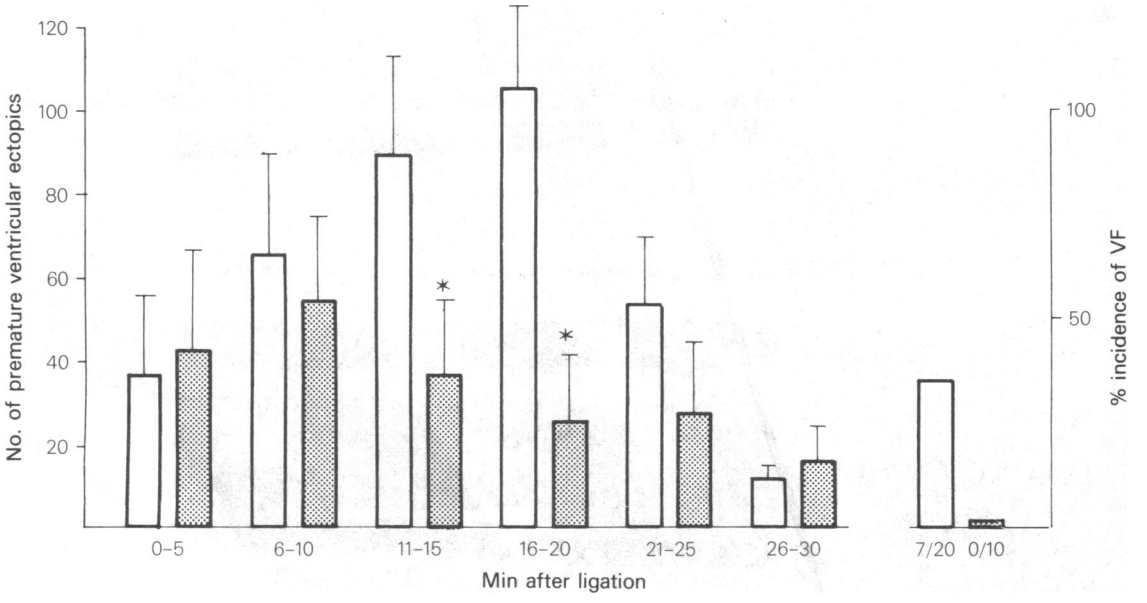

Figure 2 The number of ventricular ectopic beats and the incidence of ventricular fibrillation (VF) in control dogs (open columns) and in animals administered bepridil, 20 min before ligation (stippled columns).
*$P<0.05$

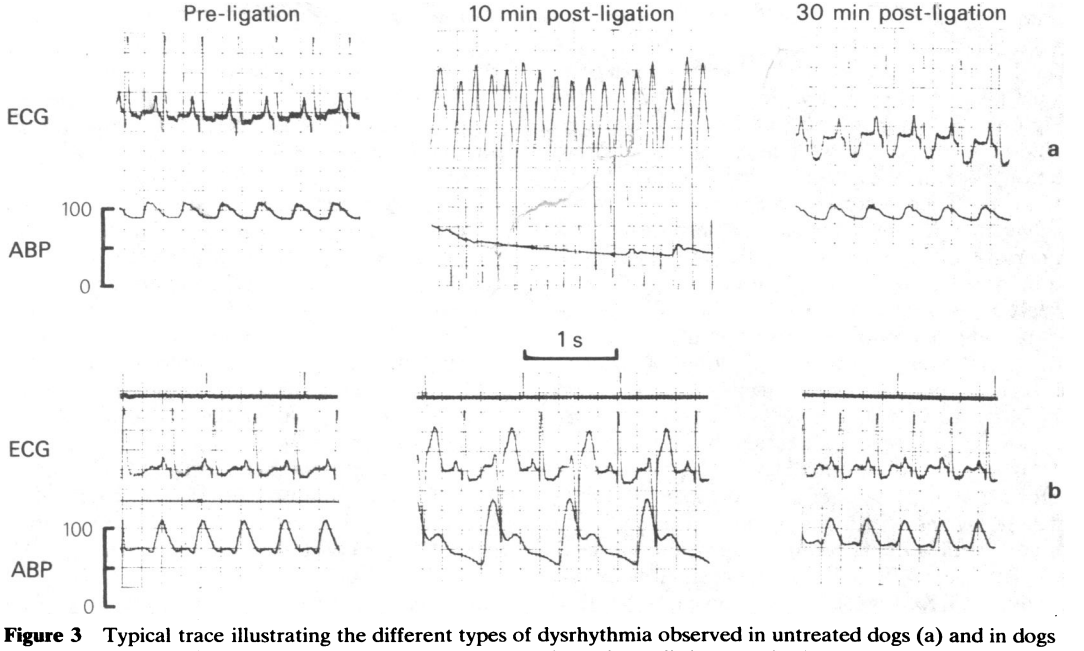

Figure 3 Typical trace illustrating the different types of dysrhythmia observed in untreated dogs (a) and in dogs treated with bepridil (b). Whereas ligation produces ventricular tachycardia in control animals, bigeminy is the major dysrhythmia observed in the bepridil troup. ABP denotes arterial blood pressure trace calibrated in mmHg. Limb lead II of the electrocardiogram is shown.

Table 2 Haemodynamic effects of acute coronary artery ligation in untreated (control) anaesthetized dogs and in animals pretreated with bepridil (5mg/kg, i.v.) 20 min before ligation

	Control (n = 10)		*Bepridil* (n = 10)	
	Pre	*30 min post*	*Pre*	*30 min post*
Heart rate (beats/min)	131 ± 13	138 ± 14	131 ± 6	143 ± 13
Mean blood pressure (mmHg)	126 ± 5	124 ± 4	134 ± 8	136 ± 7
LV d*P*/d*t max.* (mmHg/s)	1650 ± 130	1325 ± 80*	1890 ± 200	1690 ± 160*
LVEDP (mmHg)	8 ± 1	10 ± 2	9 ± 1	11 ± 1*
Stroke volume (ml/beat)	27.4 ± 2.5	21.0 ± 2.8*	20.2 ± 1.1	15.3 ± 1.9*
Pulmonary vascular resistance (units)	6.4 ± 0.6	7.9 ± 0.4*	7.3 ± 0.7	9.1 ± 0.8*
Peripheral vascular resistance (units)	48 ± 2	60 ± 3*	51 ± 3	67 ± 7*
External cardiac work (kgm/min)	6.2 ± 0.9	4.8 ± 0.7*	5.3 ± 0.7	4.2 ± 0.6*

*$P < 0.05$, paired *t* test.

ligation in this experimental model have been described previously (Marshall *et al.*, 1974; Marshall & Parratt, 1976; 1977). The haemodynamic effects of ligation in the bepridil-treated and control animals were essentially similar (Table 2) and included decreases in stroke volume, external cardiac work and left ventricular contractility. Perfusion pressure in both the systemic and pulmonary vascular beds was maintained through an increase in vascular resistance.

We have previously shown (Marshall *et al.*, 1974; Marshall & Parratt, 1976; 1977) that following ligation of the LAD, metabolic changes occur in the ischaemic zone that are reflected in reductions in coronary vein O_2 content and pH and increases in coronary vein P_{CO_2} and lactate. Changes in these parameters induced by coronary artery ligation in dogs pretreated with bepridil are shown in Table 3 and in Table 4. Clearly bepridil when administered before ligation did not significantly modify these metabolic consequences.

The effects of bepridil (5 mg/kg) when administered 1.5–2 h after acute coronary artery ligation

When administered (n=8) 1–2 h after coronary artery ligation, bepridil (5 mg/kg) caused similar haemodynamic effects to those observed before ligation, i.e. initial increases in circumflex coronary flow (69 ± 8 to 100 ± 18 ml/min), in coronary sinus P_{O_2} (24 ± 1 to 40 ± 2 mmHg; $P < 0.01$) and in stroke volume (15.2 ± 1.7 to 24.0 ± 3.4 ml/beat; $P < 0.05$) and a decrease in arterial blood pressure (mean diastolic fall of 59 ± 6 mmHg) which were followed by a long-lasting bradycardia (148 ± 13 to 131 ± 8 beats/min; $P < 0.05$) and a decrease in myocardial oxygen consumption (9.5 ± 2.0 to 6.9 ± 1.1 ml/min). In contrast to its effects before ligation, bepridil decreased myocardial contractility (from 39 ± 1 to 29 ± 2 s^{-1}; $P < 0.01$) but stroke volume was not affected (15.1 ± 1.7 to 14.8 ± 0.8 ml/beat). In contrast to blood flow in the normal myocardium which fell at this time (from 69 ± 8 to 46 ± 6 ml/min), presumably

Table 3 Metabolic changes produced by acute coronary artery ligation in untreated (control) anaesthetized dogs and in animals pretreated with bepridil (5mg/kg, i.v.) 20 min before ligation

	Control (n = 10)		*Bepridil* (n = 10)	
	Pre	*30 min post*	*Pre*	*30 min post*
Coronary sinus				
Oxygen content (ml/100ml)	9.8 ± 0.8	9.3 ± 0.9	10.3 ± 0.5	9.6 ± 0.7
P_{CO_2} (mmHg)	57 ± 2	61 ± 4	56 ± 3	56 ± 3
pH (units	7.31 ± 0.02	7.31 ± 0.03	7.33 ± 0.02	7.34 ± 0.02
Coronary vein				
Oxygen content (ml/100ml)	9.6 ± 0.5	6.2 ± 0.8*	9.3 ± 0.4	6.1 ± 0.6*
P_{CO_2} (mmHg)	54 ± 2	65 ± 4*	56 ± 2	64 ± 3*
pH (units)	7.32 ± 0.02	7.27 ± 0.02*	7.34 ± 0.02	7.26 ± 0.02*

*$P < 0.05$; significantly different from pre-ligation value.

Table 4 The handling of lactate by both normal (coronary sinus) and ischaemic (local coronary venous) myocardium and its modification by coronary artery ligation and the subsequent administration of bepridil 5mg/kg (90 min post-ligation)

Control group (n = 6)

	Pre-ligation	*30*	*60*	*90*	*120*	min after ligation
Coronary sinus	43 ± 4	32 ± 7	37 ± 3	25 ± 4	26 ± 5	
Coronary vein	39 ± 5	−121 ± 30*	−68 ± 21*	−62 ± 18*	−65 ± 15*	

Bepridil group (n = 5)

	Pre-ligation	*30*	*60*	*90*	Bepridil ↓ *105*	*150*	min after ligation
Coronary sinus	43 ± 4	27 ± 5	30 ± 7	26 ± 6	32 ± 7	41 ± 7	
Coronary vein	45 ± 8	−102 ± 40*	−42 ± 22*	−47 ± 9*	−13 ± 8†	− 9 ± 7†	

Values are expressed as % lactate extraction coefficients (A-V/A).
*$P < 0.05$; significantly different from pre-ligation value.
†$P < 0.05$; significantly different from pre-bepridil value.

in response to the decreased oxygen demand, perfusion of the infarcting zone (measured by ^{133}Xe clearance) was not impaired by bepridil (22 ± 4 to 26 ± 5 ml $100\,g^{-1}min^{-1}$). In addition the diastolic retrograde perfusion pressure (PCP) was also unchanged (17 ± 2 to 18 ± 3 mmHg). There was some evidence from the lactate results that bepridil exerted a beneficial action on the ischaemic myocardium (Table 4). Just before the administration of bepridil, all 5 dogs in which lactate was measured showed lactate production by the ischaemic area. However, 15 and 60 min after bepridil, lactate production in the ischaemic zone was reversed to lactate extraction in three of these animals. In contrast all untreated dogs (n=6) continued to produce lactate throughout this same time period (Table 4). Bepridil also reduced the magnitude and severity of myocardial ischaemia as assessed from a reduction in the ST-element elevation in epicardial leads (Figure 4). In control dogs ST-segment elevation was stable over the experimental period. This effect may be explained by the decrease in oxygen extraction by the ischaemic zone which was manifest as a significant increase in local coronary vein P_{O_2} from 21 ± 2 to 32 ± 5 mmHg ($P < 0.01$). The haemodynamic and metabolic effects of bepridil were sustained and were still evident for up to 2 h after administration of the drug, when the experiments were terminated.

Discussion

When administered intravenously shortly before acute coronary artery ligation, bepridil causes haemodynamic effects which can be divided temporally into two distinct phases. Immediately on injection, bepridil caused a marked fall in blood pressure which was accompanied by marked increases in coronary blood flow and in stroke volume. The increased coronary flow is not metabolic in origin, since neither heart rate nor myocardial contractility were significantly increased at this time and the increase in flow was accompanied by a marked fall in myocardial oxygen extraction. Thus it would seem that the coronary dilator actions of bepridil may be due to a direct action on the arterial smooth muscle and indeed we have observed that bepridil, like verapamil, causes relaxation of partially contracted pig coronary artery strips, an effect which can be reversed by increasing the calcium concentration of the bathing medium (Campbell, Marshall & Winslow, unpublished observation). The marked decrease in systemic vascular resistance (i.e. decrease in blood pressure and increase in cardiac output) observed at this time is probably also due to a direct action of bepridil on peripheral arterioles. All these effects of bepridil were transient in nature (2–5 min) and were replaced by sustained (> 60 min) decreases in heart rate and in myocardial oxygen consumption. In contrast to the effects of β-adrenoceptor antagonists (e.g. Marshall & Parratt, 1976) this bradycardia produced by bepridil was not accompanied by any significant decrease in left ventricular contractility or stroke volume. It has previously been shown (Cosnier *et al.*, 1977) that the bradycardia induced by bepridil is not due to either cardiac sympathetic blockade or to an increase in vagal tone. The recent observation that micromolar concentrations of bepridil depress phase 4 depolarization of guinea-pig nodal cells. (Winslow & Kane, 1980) adequately explains the mechanism behind the bradycardia produced by bepridil.

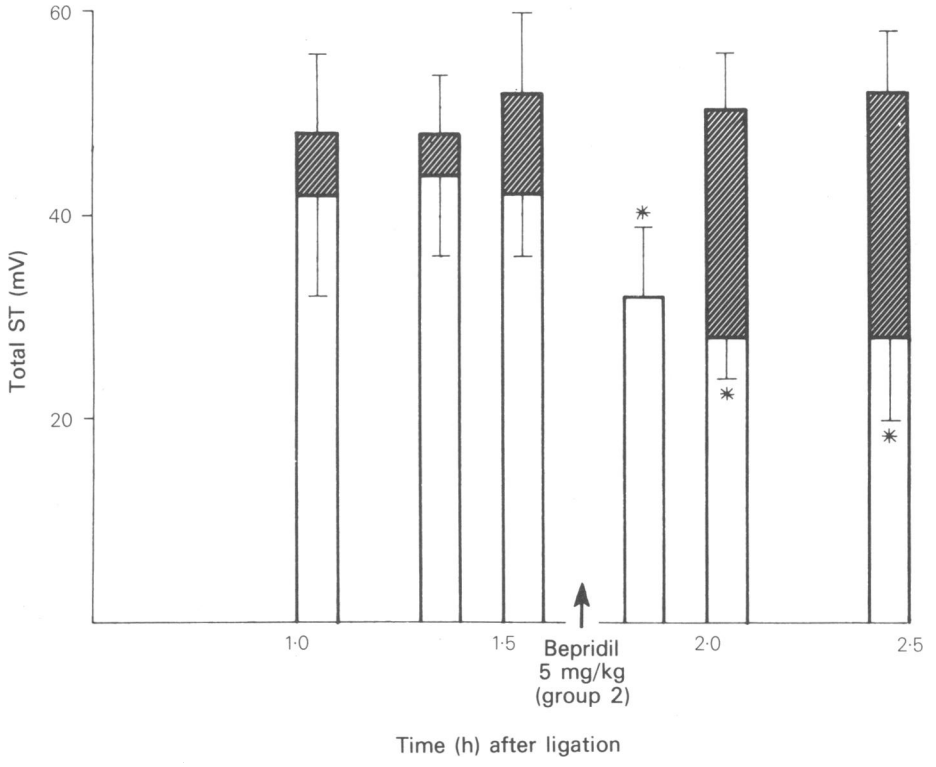

Figure 4 Total ST-segment elevation observed in epicardial ECG leads in control dogs (hatched columns, group 1) and in dogs administered 5mg/kg bepridil (open columns, group 2), 1.5 h post-ligation.
*$P<0.05$ compared with pre-bepridil value (paired t test).

In this study, bepridil significantly protected dogs from the early ventricular tachycardia and fibrillation produced by acute coronary artery ligation, an effect previously demonstrated in this model for drugs like disopyramide, Org 6001 and prenylamine, which all block the fast Na^+ channel (Marshall & Parratt, 1975; 1977; 1979). Bepridil is capable of blocking both the fast Na^+ channel (Class I action) and the slow Na^+/Ca^{2+} channel (Class IV action) in amphibian and mammalian myocardium (Labrid *et al.*, 1979; Vogel *et al.*, 1979; Kane & Winslow, 1980). It is difficult to ascertain which component of bepridil's action plays the major role in preventing these early dysrhythmias, since other workers have shown that the specific slow-channel blocker, verapamil, also suppresses the early dysrhythmias and fibrillation following coronary ligation in anaesthetized dogs (Kaumann & Aramendia, 1968; Elharrar, Guam & Zipes, 1977; Brooks, Verrier & Lown, 1980). Theoretically, impairment of the slow inward current (by verapamil or bepridil) should further retard conduction through the ischaemic myocardium and thus facilitate the production of re-entry dysrhythmias. In fact verapamil has been shown to decrease the delay in conduction in ischaemic canine myocardium (Elharrer *et al.*, 1977), an effect which may be explained by metabolic or autonomic effects of the drug rather than its electrophysiological actions (Brooks *et al.*, 1980). However, in this present study, pretreatment with bepridil did not modify either the haemodynamic (cardiac depression) or the metabolic (lactate production) consequences of coronary artery ligation.

When administered 1.5 h after coronary artery ligation, bepridil (5 mg/kg) caused similar haemodynamic effects to those observed before ligation, except that myocardial contractility was now significantly decreased. This negative inotropic action coupled with the bradycardia was also reflected in a greater reduction in myocardial oxygen consumption (mean of 27%) than seen before ligation (18%).

In contrast to its biphasic effect on coronary flow in the normal myocardium, bepridil did not significantly affect blood flow in the acutely ischaemic area, but decreased the extraction of oxygen in this zone. There was evidence that bepridil favourably influenced the balance between oxygen supply and demand in the ischaemic area and this was also manifest as a reduction in epicardial ST-segment elevation in sites overlying this zone, and by a significant decrease in lactate production. Previous studies have demon-

strated a good correlation between ST-segment elevation and various indices of myocardial ischaemia (see Marshall & Parratt, 1979, for references). These beneficial effects of bepridil are probably related to the reduction in oxygen demand by the normal myocardium but may also be related to changes in the distribution of blood flow in the ischaemic area. Bradycardia and a reduction in extravascular compression (i.e. decreased contractility) on transmural vessels in the ischaemic myocardium would both favour blood flow to the deep subendocardial layers (Gross & Winbury, 1973; Marshall & Parratt, 1974; Stein, Marzillie, Sabbah & Lee, 1980).

In summary, when administered shortly before coronary artery ligation, bepridil (5 mg/kg) reduced the number of premature ventricular ectopic beats and prevented ventricular fibrillation. In contrast to β-adrenoceptor antagonists, bepridil is capable of slowing heart rate without markedly affecting the pumping ability of the heart. In addition unlike many β-adrenoceptor antagonists, bepridil does not impair the already critical blood flow in the acutely ischaemic myocardium. When reviewing anti-anginal agents in 1971, Charlier remarked that the ideal anti-anginal agent should (1) dampen down rather than suppress sympathetic influences on the heart and (2) exert a dilator effect on the coronary bed. Clearly bepridil would appear to possess both these attributes.

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