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THE EFFECTS OF DISOPYRAMIDE PHOSPHATE ON EARLY POST-CORONARY ARTERY LIGATION DYSRHYTHMIAS AND ON EPICARDIAL ST-SEGMENT ELEVATION IN ANAESTHETIZED DOGS

R.J. MARSHALL & J.R. PARRATT

Department of Physiology & Pharmacology, University of Strathclyde, Glasgow, and of Surgery, University of Glasgow (Western Infirmary)

1 The antidysrhythmic, haemodynamic and metabolic effects of intravenously administered disopyramide phosphate (1 to 5 mg/kg) have been studied in greyhounds, anaesthetized with trichloroethylene.

2 In doses of 2.5 and 5.0 mg/kg, disopyramide significantly reduced the ventricular dysrhythmias that occur in the initial 30-min period following acute coronary artery ligation. None of the disopyramide-treated animals developed ventricular fibrillation.

3 The metabolic consequences of coronary artery ligation, assessed by local coronary venous sampling from the ischaemic area, were not modified by disopyramide except that K^+ egress was prevented.

4 There was evidence for substantial disopyramide-induced myocardial depression (decreased cardiac output and left ventricular dP/dt_{max} with elevated ventricular filling pressure and pulmonary oedema and shunting) and it is suggested that great care be taken when the drug is administered intravenously in conditions where cardiac function is already compromised. Disopyramide also reduced myocardial blood flow.

5 In chloralose-anaesthetized mongrel dogs, disopyramide (2.5 mg/kg) significantly reduced the ST-segment elevation (assessed from epicardial recordings) that resulted from short (3 min) coronary artery occlusions. This could indicate a reduction in the extent and severity of myocardial injury or simply reflect decreased K^+ efflux (since locally administered K^+ itself increased ST-segment elevation).

Introduction

Although the basic cardiovascular pharmacology of disopyramide was described as long ago as 1962 (Mokler & Van Arman, 1962; Sekiya & Vaughan Williams, 1963) it is only in the last few years that the drug has been extensively used clinically in the treatment of dysrhythmias of various origins. The clinical pharmacology of the compound has been recently reviewed by Danilo & Rosen (1976) and by Ankier, Carmichael & Kidner (1977).

Disopyramide has been reported to be effective against dysrhythmias resulting from myocardial infarction (Croxson, 1977; Sandler, 1977—quoted by Ankier *et al.*, 1977) but there has been only one relevant experimental study (Kus & Sasyniuk, 1976) and in this attention was mainly focused on the late (24 to 48 h) post-infarction ventricular dysrhythmias. However, there is clinical evidence that it is in the early phase (i.e. within 2 h of an acute infaction) that the serious, life-threatening dysrhythmias occur and certainly it is those dysrhythmias that would mainly be relevant to any prophylactic use of the drug. The present studies examine the effectiveness of intravenously administered disopyramide in reducing the ventricular dysrhythmias that result from acute coronary artery ligation in anaesthetized greyhounds (Marshall & Parratt, 1975). In view of the evidence that disopyramide also preserves mitochondrial function and prevents cellular creatine phosphokinase loss (Nayler, quoted by Ankier *et al.*, 1977), we have also examined the effects of the drug on epicardial ST-segment elevation following transient coronary artery occlusion, a technique that has been suggested as useful for assessing possible drug effects on the extent and severity of myocardial ischaemic damage (Maroko, Kjekshus, Sobel, Watanabe, Covell, Ross & Braunwald, 1971).

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Methods

Permanent ligation studies

Anaesthesia was induced in healthy adult greyhound dogs of either sex with sodium thiopentone (15 to 20 mg/kg) administered intravenously. After endotracheal intubation, anaesthesia was maintained by using a gas mixture containing 0.5 to 1% trichloroethylene vaporized from a Tritec vaporizer (Cyprane); the carrier gas was O_2. Ventilation was controlled with a Palmer respiratory pump, the rate and stroke volume of which were adjusted to give an arterial CO_2 tension of about 38 mmHg. Reflex respiratory movements were prevented by the intramuscular administration of suxamethonium (usually 50 mg at intervals of about 90 min). Catheters were inserted into the descending aorta and into the right atrium via the femoral vessels for pressure recording and blood sampling. During flow measurements arterial and right atrial pressures and the electrocardiogram were recorded on a multi-channel ink-jet recorder (Elema–Schönander Minograph 81). Temperature was recorded from the mid-oesophagus with direct recording copper-constantan thermocouples (Ellab, Copenhagen). A catheter-tip transducer (Miller Instruments Inc.) was inserted into the lumen of the left ventricle (via a carotid artery) for the measurement of left ventricular pressure and also dP/dt (using an Elema–Schönander differentiating circuit). The frequency response of this transducer system is flat to 200 Hz. Records of left ventricular pressure at high gain allowed accurate assessment to be made of left ventricular end-diastolic pressure (LVEDP).

The heart was exposed through a left thoracotomy and the pericardium overlying the anterolateral aspect of the heart incised. Blood flow in the circumflex branch of the left coronary artery was measured with a Nycotron 372 electromagnetic flowmeter and a 2 or 2.5 mm probe. The anterior descending branch of the left coronary, at a point approximately halfway between the tip of the atrium and the apex of the heart, was prepared for ligation with limited dissection. A major branch of the main vein adjacent to the artery (the anterior coronary vein) was catheterised by the Seldinger technique with a 4-inch Longdwel teflon catheter (size 20G). This catheter was not tied in position. It will be referred to in the text as the coronary vein catheter and after coronary artery ligation, has been shown to drain blood predominantly from the ischaemic area (Marshall, Parratt & Ledingham, 1974). Simultaneous anaerobic blood samples were taken at regular intervals from this vein and from the coronary sinus, right atrium and descending aorta. Blood was analysed for O_2 and CO_2 tensions, for O_2 content and for pH as outlined by Ledingham, McBride, Parratt & Vance (1970).

After a suitable stabilization period the anterior descending branch of the left coronary artery (LAD) was ligated in one stage just above the bifurcation of the apical branch. This ultimately produces an infarct about 10 to 15% of the weight of the left ventricular wall (Marshall *et al.*, 1974). After ligation at this point, ventricular dysrhythmias are common and unless anti-dysrhythmic agents are administered, ventricular fibrillation occurs in 20 to 25% of the dogs (Marshall & Parratt, 1975). The number of ventricular ectopic beats were counted in each dog over six consecutive 5-min intervals. There are very few dysrhythmias after this critical 30-min period until about 8 to 12 h post-ligation.

Disopyramide was administered (over 2 min) in intravenous doses of 1.0, 2.5 or 5.0 mg/kg (as disopyramide phosphate) 15 min before ligation and the numbers of ventricular ectopic beats occurring after ligation were compared with those in 12 control (untreated) dogs (Marshall & Parratt, 1975). In some of the dogs arterial samples were taken for estimation of plasma drug levels (through the kindness of Dr S. Ankier, Roussel Laboratories).

Thirty min after ligation, samples were taken from the coronary vein (which now drained the ischaemic area), from the coronary sinus and aorta and these were analyzed for potassium, lactate, P_{O_2}, P_{CO_2} and pH.

Systemic arterial pressure, left ventricular pressure and dP/dt, left ventricular end-diastolic pressure (LVEDP), left circumflex coronary flow and the electrocardiogram (standard limb lead II) were recorded on an Elema–Schönander ink-jet writing recorder (Mingograph 81). Heart rate was calculated from the electrocardiogram. Results were treated statistically using Students' paired or unpaired t test as applicable.

Effects of disopyramide on ST-segment elevation following transient coronary artery occlusions

Five mongrel dogs of either sex and weighing between 13 to 20 kg were anaesthetized with sodium thiopentone (30 mg/kg i.v.) followed by α-chloralose 85 mg/kg. The dogs were ventilated with 100% O_2 and catheters were placed in the descending aorta, right atrium and coronary sinus for pressure measurements and for blood sampling. In 3 of the animals catheters were also placed in the pulmonary artery (via a jugular vein) and in the left ventricle (via a carotid artery) for pressure measurements. In these animals cardiac output was measured by thermal dilution using a Devices cardiac output monitor. After a left thoracotomy the heart was slung in a pericardial cradle and a Mersilk thread passed around the LAD about 2 cm from its origin. A triangular sheet of rubber in which were embedded nine silver electrodes (impedance 600 to 1200Ω) was sutured to the anterior

surface of the left ventricle so that at least six of the electrodes lay in areas supplied by the artery to be occluded (Marshall & Parratt, 1977). Care was taken to keep the epicardium moist with 0.9% w/v NaCl solution (saline) throughout the experiment. Aortic blood pressure, left ventricular pressure, left ventricular dP/dt, pulmonary artery pressure and epicardial electrocardiograms (ECGs) were recorded on a Mingograph ink-jet recorder (impedance >1 Megohm). After baseline haemodynamics, blood gases and epicardial ECGs had been obtained, the artery was occluded and epicardial ECGs at each of the nine sites (3 simultaneously) were recorded, by means of a rapid switching circuit, at 1, 2 and 3 min after occlusion and at a paper speed of 50 mm/s. A coronary sinus blood sample was taken after 3 min. Only short (i.e. 3 min) occlusions were used in this study because longer occlusions occasionally resulted in bursts of ventricular dysrhythmias and conduction defects (e.g. QRS widening), both of which mask shifts in the ST-segment. In each animal, two control occlusions were performed and occlusions repeated 10 and 40 min after injection of disopyramide phosphate (2.5 mg/kg) into the right atrium. The results were analysed statistically using the Student's t test for paired data.

In 3 dogs the effects of the local administration of sodium chloride, potassium chloride, or phosphate buffer of pH 6.70 on the epicardial electrocardiograms were investigated by infusing these agents (1 ml/min) into the LAD through an indwelling SW6 28 gauge stainless-steel needle. Introduction of this needle did not itself cause any changes in the epicardial recordings.

Results

The effects of disopyramide on the immediate arrhythmias induced by acute coronary artery ligation

Acute ligation of the anterior descending branch of the left coronary artery (LAD) in anaesthetized greyhounds causes a burst of marked dysrhythmic activity lasting for 30 min. These immediate dysrhythmias are usually ventricular in origin and are in many cases fatal. In this study 4 out of 12 control dogs succumbed within 30 min and the others had many dysrhythmias in the first 30 min after ligation (Table 1). The dogs which received disopyramide (2.5 and 5.0 mg/kg intravenously) 15 min before ligation, had significantly fewer dysrhythmias during the first 30 min after ligation and none of these animals fibrillated within this critical period. The 2 dogs given 1.0 mg/kg disopyramide had frequent runs of ventricular tachycardia and had 1237 and 810 ventricular ectopics respectively over the initial 30-min period. It should be noted that in 5 of the dogs given the higher doses of disopyramide, there were occasional bursts of ventricular tachycardia (defined as a consecutive run of at least 4 premature ventricular ectopics), which occurred in the 6 to 15 min post-ligation period, although in no case did fibrillation develop. In general, the reduction in the number of ventricular dysrhythmias correlated reasonably well with the plasma concentration of disopyramide, 30 min after ligation ($r = 0.686$, $P < 0.005$). For example 2 of the dogs with the lowest ectopic counts (52 and 63 over the 30-min period) had the highest plasma levels (6.5 and 6.0 μg/ml respectively); those with higher counts (435 and 362 ventricular ectopic beats) had lower drug levels (1.7 and 3.3 μg/ml respectively). However, one dog with very few ectopic beats (21) had a relatively low plasma level (2.0 μg/ml).

Haemodynamic effects of disopyramide in the open-chest greyhound

The haemodynamic effects of disopyramide (2.5 mg/kg) in the open-chest anaesthetized dog are summarized in Table 2 and a typical response shown in Figure 1. Immediately on injection, disopyramide caused first a (5 to 15 mmHg) depressor response followed immediately by a (15 to 32 mmHg) pressor

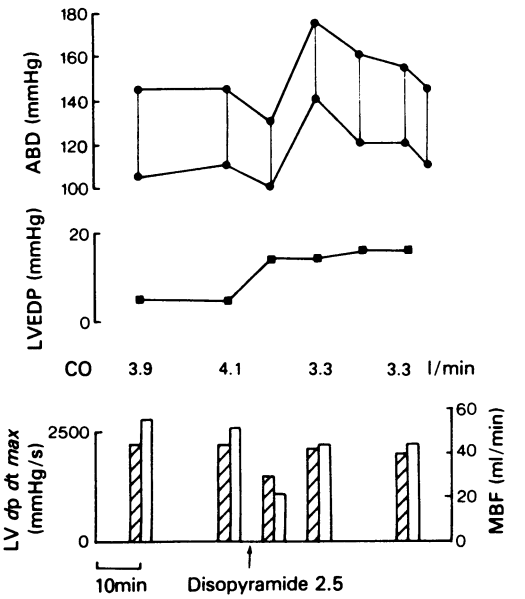

Figure 1 The time-course of the effects of an intravenous injection of disopyramide phosphate (2.5 mg/kg at arrow) on systolic and diastolic blood pressure (ABP), left ventricular end-diastolic pressure (LVEDP), cardiac output (CO), left ventricular dP/dt_{max} (hatched columns) and left circumflex coronary blood flow (open columns), in an anaesthetized greyhound.

Table 1 Mean (+s.e.) number of ventricular ectopic beats at various times after the acute ligation of the anterior descending branch of the left coronary artery in control (untreated) dogs and in dogs pretreated with disopyramide

	Time after ligation							
	0 to 5 min	*6 to 10 min*	*11 to 15 min*	*16 to 20 min*	*21 to 25 min*	*26 to 30 min*	*Total*	*Deaths within 30 min*
Control	120 ± 42	150 ± 60	94 ± 67	286 ± 92	96 ± 38	52 ± 21	904 ± 260 (193–2250)	4/12
Disopyramide 2.5 mg/kg 15 min pre-ligation	7 ± 4*	125 ± 75	71 ± 43	29 ± 22*	3 ± 2*	6 ± 5*	241 ± 140* (2–750)	0/5
Disopyramide 5.0 mg/kg 15 min pre-ligation	19 ± 19	42 ± 42*	9 ± 7*	13 ± 7*	12 ± 6*	64 ± 34	159 ± 102* (52–362)	0/3

* $P < 0.05$.

Table 2 The haemodynamic effects of intravenous disopyramide (2.5 mg/kg) in the open-chest anaesthetized greyhound

	Pre-drug	*10 min post-drug*
Systolic blood pressure (mmHg)	143 ± 7	150 ± 12
Diastolic blood pressure (mmHg)	107 ± 7	120 ± 9
Heart rate (beats/min)	171 ± 10	170 ± 8
Cardiac output (litres/min)	3.7 ± 0.8	2.9 ± 0.4*
Left ventricular dP/dt (mmHg/s)	2660 ± 388	2360 ± 345*
LVEDP (mmHg)	6 ± 1	10 ± 1*
External cardiac work (kgm/min)	3.7 ± 0.3	3.6 ± 0.3
Peripheral vascular resistance (units)	36 ± 3	43 ± 3*
Whole-body oxygen consumption (ml/min)	139 ± 21	146 ± 29
Coronary blood flow (ml/min)	52 ± 7	42 ± 5*
Myocardial O_2 consumption (ml/min)	7.8 ± 1.1	7.5 ± 1.1
Myocardial O_2 extraction (%)	52 ± 4	59 ± 6*

Values are mean ± s.e. mean; $n = 5$. * $P < 0.05$.

response. The depressor responses were extremely transient but the secondary increases in blood pressure were more sustained. However, 10 min after drug administration blood pressure was not significantly different from control (Table 2).

There was clear evidence that at this dose level disopyramide caused myocardial depression, reduced cardiac output and left ventricular dP/dt_{max} and elevated LVEDP (Table 2). Left circumflex coronary blood flow was also significantly decreased but since myocardial oxygen extraction increased, oxygen consumption of the heart remained unchanged (Table 2). Disopyramide significantly increased calculated coronary vascular resistance from 2.5 ± 0.3 to 3.1 ± 0.2 units ($P < 0.05$).

Similar but more marked, haemodynamic effects were seen in the 3 dogs given 5.0 mg/kg disopyramide. The myocardial depression, manifest as decreased cardiac output (from 1.4 to 0.9 litres/min) and dP/dt_{max} (from a mean of 1870 to 1170 mmHg/s), was so marked that in 2 out of the 3 dogs there was evidence of incipient cardiac failure, e.g. pulmonary oedema, high left ventricular filling pressure (>20 mmHg) and pulmonary shunting. Pulmonary shunting, calculated by the method of Hyde (1970) was increased by disopyramide from 7 to 18% of the cardiac output, and a constant finding was a reduction in arterial Po_2 (from 327 ± 10 to 268 ± 15 mmHg) and an increase in Pco_2 (from 36 ± 2 to 39 ± 1 mmHg). These changes were clearly due to disopyramide itself, since in 2 animals the phosphoric acid solvent alone did not affect haemodynamics or blood gases.

The effects of ligation on regional myocardial metabolism in control dogs and in dogs administered disopyramide

When the LAD is acutely ligated, metabolic changes occur in coronary venous blood (draining the ischaemic myocardium) which are not seen in coronary sinus blood draining essentially normal areas of myocardium. These changes, which have been previously described in detail (Marshall *et al.*, 1974), are increases in oxygen extraction and in Pco_2, decrease in pH and a change from lactate extraction to production. Values obtained in some of the control dogs are presented in Table 3 and compared with results obtained in dogs pretreated with disopyramide (2.5 or 5.0 mg/kg). It is clear that disopyramide did not modify the metabolic changes observed in coronary venous blood, induced by ligation, although disopyramide itself increased coronary venous Pco_2 and decreased pH. Another metabolic change induced by ligation is potassium egress from ischaemic cardiac cells (Marshall & Parratt, 1975). In control dogs, coronary vein potassium rose from 3.5 ± 0.3 pre-ligation to 4.4 ± 0.2 mEq/30 min after ligation, although arterial and coronary sinus levels remained unchanged. Disopyramide successfully prevented this increase in potassium in coronary venous blood, levels being 3.5 ± 0.3 mEq/l before ligation and 3.8 ± 0.4 mEq/l 30 min later ($P > 0.05$).

The effect of disopyramide on the epicardial ST-segment elevation resulting from short periods of coronary artery occlusion

Coronary artery occlusion resulted in a time-related elevation of the ST-segment in the epicardial leads overlying the ischaemic area (Figure 2); the ST-segment in leads lying outside the affected area remained unchanged. Two or three leads showed small (<3 mV) *depression* of the ST-segment after occlusion but these were not included in the analysis since it has been shown that areas showing ST-segment depression are not depleted of creatine phosphokinase 24 h later (Kjekshus, Maroko & Sobel, 1972). Heart rate and pulmonary artery pressure remained unchanged

Table 3 The metabolic consequences of coronary artery ligation in control dogs and in dogs treated previously with disopyramide (2.5 or 5.0 mg/kg)

	Pre-ligation				*30 min post-ligation*			
Dose of disopyramide (mg/kg)	*Coronary sinus*		*Coronary vein*		*Coronary sinus*		*Coronary vein*	
	Pco_2 *(mmHg)*	*pH (units)*	Pco_2 *(mmHg)*	*pH (units)*	Pco_2 *(mmHg)*	*pH (units)*	Pco_2 *(mmHg)*	*pH (units)*
Control	49 ± 3	7.390 ±0.017	49 ± 3	7.379 ±0.014	51 ± 4	7.345 ±0.019	60 ± 3*	7.265* ±0.023
2.5	68 ± 4†	7.260† ±0.030	67 ± 5†	7.254† ±0.027	65 ± 3	7.248 ±0.026	77 ± 5*	7.202* ±0.022
5.0	66 ± 4†	7.240† ±0.040	68 ± 4†	7.251† ±0.031	67 ± 5	7.160 ±0.068	78 ± 6*	7.164* ±0.062

Values are mean ± s.e. mean; $n = 3$ to 8. Significantly different from pre-ligation coronary venous values. * $P < 0.05$. † Significantly different from values obtained in untreated (i.e. control) greyhounds.

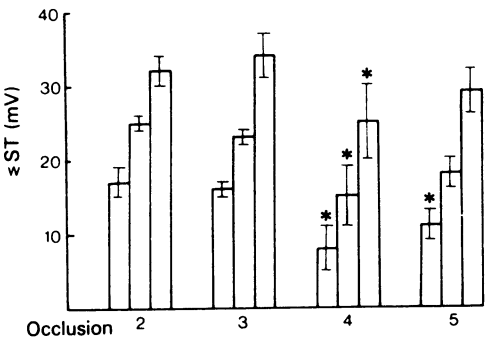

Figure 2 Total ST-segment elevation (ΣST) produced at 1, 2 and 3 min after acute occlusions of the left anterior descending coronary artery in anaesthetized dogs. Disopyramide phosphate (2.5 mg/kg) was administered intravenously 15 min after occlusion 3 and occlusions 4 and 5 were carried out 10 and 40 min after drug administration respectively. Values are mean of five experiments; vertical lines show s.e. mean. * Significantly different from control occlusion 3 ($P < 0.05$).

throughout all occlusions but there was always a small (5 to 15 mmHg) fall in blood pressure, which immediately returned to control levels on releasing the occlusion. Blood pressure and heart rate remained constant in every animal throughout the period of study. For reasons outlined in a previous publication the results of the first LAD occlusion were disregarded but we have shown that the *total* ST-segment elevations produced by subsequent occlusions (up to 5) are very similar in untreated animals (Marshall & Parratt, 1977).

Administration of disopyramide phosphate (2.5 mg/kg) caused similar transient haemodynamic changes to those reported above, i.e. transient falls in blood pressure (7 to 40 mmHg) and more prolonged decreases in cardiac output (11 to 20%) and left ventricular dP/dt_{max} (5 to 12%). Heart rate and pulmonary artery pressure remained unchanged. As in the ligation studies (Table 3) disopyramide lowered Po_2 and pH and increased CO_2 tension in coronary sinus blood (Table 4). Since content was also reduced, these effects are consistent with disopyramide-induced decreases in myocardial blood flow. These parameters had not returned to control levels 10 min after drug administration and before the next coronary occlusion. Disopyramide did not itself produce any change in the ST-segment of control epicardial ECGs but did cause T-wave inversion. However, the drug significantly reduced ST-segment elevation throughout the occlusion (Figure 2) and in addition reduced the mean number of leads showing >2 mV elevation (Maroko *et al.*, 1971) from 6.8 ± 0.3 to 4.3 ± 0.2 ($P < 0.01$). These effects of disopyramide were relatively short-lasting and the ST-segment elevation induced by occlusion tended to return towards control values 40 min after drug administration (Figure 2).

Although it was not possible to use coronary vein sampling in this study (local sampling can itself cause changes in the ST-segment and induce dysrhythmias), interesting changes in coronary sinus blood were apparent after 3-min occlusion. These changes are shown in Table 4 and consisted of significant reductions in O_2 content and pH. These changes were not apparent in simultaneous arterial blood samples and undoubtedly reflect the consequences of myocardial ischaemia. It was of some interest to observe that after treatment with disopyramide these changes did not occur (Table 4).

The effects of local coronary infusions of Na^+, K^+, or H^+ on epicardial ST-segment elevation

Local coronary infusion of either 0.9 M sodium chloride or phosphate buffer (pH 6.70) into a branch of the LAD did not affect the waveform of epicardial electrocardiograms overlying areas of myocardium served by that artery (Figure 3). In contrast, infusions of KCl (10 to 200 μM) caused concentration-dependent increases in ST-segment elevation without affecting either the magnitude or duration of the QRS complex. The ST-segment elevation produced by K^+ was reversible in that it slowly disappeared when the artery was perfused with sodium chloride.

Discussion

Although several clinical studies have demonstrated the effectiveness of orally and intravenously administered disopyramide in suppressing both atrial dysrhythmias and ventricular premature beats of multiple etiology (reviewed by Danilo & Rosen, 1976 and by Anker *et al.*, 1977), there is little information available on the efficacy of intravenously administered disopyramide in suppressing early dysrhythmias which occur in the acute phase of myocardial infarction. This information is of some importance since it is known that 61% of electrical deaths arising from myocardial infarction among patients younger than 65 occur within 1 h of onset (Gordon & Kannel, 1971).

The results obtained in this study have shown that disopyramide when given intravenously in a dose of 2.5 or 5.0 mg/kg, 15 min before, protects anaesthetized greyhounds from the initial (30 min) burst of ventricular dysrhythmias induced by acute ligation of the LAD. In addition, none of the animals given either of these doses of disopyramide succumbed to ventricular fibrillation in this crucial 30 min period. Ventricular fibrillation is commonly observed in un-

Table 4 Changes in coronary sinus blood produced by short 3 min occlusions of the left anterior descending coronary artery

	Pre-occlusion				*3 min post-occlusion*			
	Po_2 (*mmHg*)	Pco_2 (*mmHg*)	*pH*	O_2 *content* (*ml/100 ml*)	Po_2 (*mmHg*)	Pco_2 (*mmHg*)	*pH*	O_2 *content* (*ml/100 ml*)
Occlusion 2	30 ± 1	58 ± 2	7.300 ± 0.015	9.2 ± 0.6	26 ± 1*	61 ± 2	7.260 ± 0.020*	7.4 ± 0.5*
Occlusion 3	30 ± 1	62 ± 4	7.286 ± 0.030	8.8 ± 0.4	27 ± 1	63 ± 5	7.226 ± 0.035*	7.3 ± 0.4*
Disopyramide (2.5 mg/kg)	29 ± 1	60 ± 4	7.252 ± 0.021	8.4 ± 0.3	23 ± 3*	64 ± 5	7.231 ± 0.012	5.7 ± 1.4*
Occlusion 4	26 ± 1	66 ± 6	7.214 ± 0.028	6.6 ± 0.8	27 ± 1	66 ± 7	7.200 ± 0.030	7.0 ± 0.4
Occlusion 5	27 ± 1	66 ± 5	7.189 ± 0.027	6.8 ± 0.6	24 ± 1	70 ± 6	7.194 ± 0.030	5.5 ± 0.5*

Values are mean ± s.e. mean, $n = 5$. * Significantly different from pre-occlusion, $P < 0.05$.

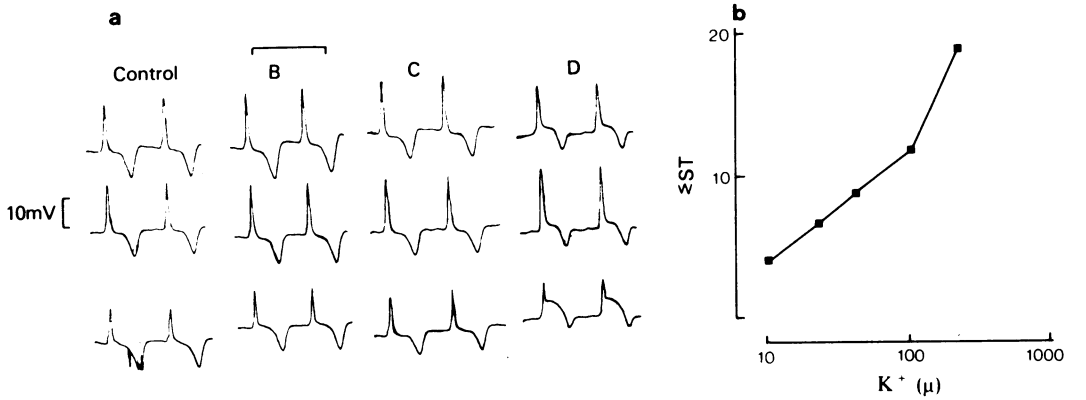

Figure 3 (a) The effects of local coronary infusions of 0.9 M sodium chloride (B), phosphate-bicarbonate buffer pH 6.70 (C) and 2×10^{-5} M potassium chloride (D) on the epicardial electrocardiograms from three sites overlying myocardium served by the artery. Only potassium solutions produced ST-segment elevation and the relation between potassium concentration and ST-segment elevation (in the three leads) in one dog is shown in (b).

treated dogs and in this study 4/12 control dogs succumbed within the first half-hour. The antidysrhythmic effects of disopyramide were observed with plasma levels between 1.8 and 6.5 μg/ml and in general there was a reasonable negative correlation between the total number of arrhythmias in the first half-hour in each animal and the plasma concentration of disopyramide at this time ($r = 0.686$). One worrying observation, however, was the occurrence in 5 animals of sustained runs of ventricular tachycardia. This suggests that disopyramide may be more effective against dysrhythmias which are due to enhanced automaticity than against those which are probably reentrant in nature. In 2 animals pretreated with 1 mg/kg disopyramide, there was marked dysrhythmic activity (including sustained runs of ventricular tachycardia), and it would seem that this dose did not produce a plasma concentration which is significantly antidysrhythmic.

At dose levels which were clearly antidysrhythmic (2.5 and 5.0 mg/kg) disopyramide produced haemodynamic changes, indicative of myocardial depression. Cardiac output and myocardial contractility were reduced in a dose-dependent manner and filling pressure (LVEDP) was significantly elevated. Blood pressure was maintained through an increased peripheral vascular resistance. Myocardial blood flow was also depressed by disopyramide (2.5 and 5.0 mg/kg) but since myocardial oxygen extraction was increased, oxygen consumption by the heart was unchanged. Thus the heart had to increase its extraction of available oxygen (and presumably its metabolism) to perform its external work and this may be disadvantageous in cardiac patients whose hearts are already compromised by local ischaemia. Myocardial depression is not peculiar to disopyramide and indeed is probably the major drawback in the use of quinidine and procaineamide in the therapy of dysrhythmias associated with myocardial infarction (Jewitt, 1971; Mason, de Maria, Amsterdam, Zelias & Massuin, 1973). The problem with intravenous disopyramide will be to choose a dose which possesses the maximum antidysrhythmic activity but which causes minimal depression of the myocardium. Our results would suggest that this optimal dose of disopyramide might lie in the range 1.5 to 2.5 mg/kg.

It should be borne in mind that in these experiments disopyramide was always given *prior* to coronary artery ligation and at a time when myocardial function was essentially normal. It might be expected that disopyramide-induced myocardial depression would be even more pronounced if it were administered under conditions (e.g. after infarction) when the myocardium was already compromised. This is clear from the clinical studies of Jensen, Sigurd & Uhrenholt (1975) who found that, in a dose (2 mg/kg) similar to those used in the present study, disopyramide very markedly depressed cardiac function in patients with imminent or clinically apparent heart failure. This effect was manifested by increases in both left and right ventricular filling pressures, by a reduction in cardiac output and by a downward shift of the Frank–Starling curve. Significant cardiac depression was observed in the present study in normal but thoracotomised dogs administered a dose of 5.0 mg kg of disopyramide; this resulted in pulmonary oedema and shunting.

Immediately after acute ligation of the LAD, marked metabolic changes occur in coronary venous blood draining the ischaemic myocardium which do

not occur in coronary sinus blood draining from the remaining essentially normal regions of the heart. These changes have been described in full elsewhere (Marshall *et al.*, 1974) and in the present study the values have been summarized for control dogs in Table 3. These changes take the form of decreases in coronary vein oxygen content and pH and increases in P_{CO_2} and in lactate production and potassium efflux. In doses which significantly suppressed dysrhythmias, disopyramide did not modify the metabolic consequences of acute coronary artery ligation, and there were decreases in coronary vein pH and increases in P_{CO_2} (Table 3). However, the drug did prevent the efflux of potassium (as measured 30 min after ligation) into coronary venous blood. The relevance of the potassium ion to the occurrence of lethal ventricular arrhythmias soon after the production of acute myocardial ischaemia has been the subject of a number of experimental studies. Some authors have deduced a causal relationship between cumulative potassium loss and the incidence of these early arrhythmias (Harris, Bisteni, Russell, Brigham & Firestone, 1954; Regan, Harman, Lehan, Burke & Oldewurtel, 1967) while others have failed to show any such relationship (Wexler & Patt, 1960; Thomas, Schulman & Opie, 1970). Although our results would seem to suggest a causal role for potassium ions, there was in fact no significant correlation in individual animals between the number of arrhythmias and potassium efflux ($r = 0.316$; $P > 0.05$).

Although the mechanisms underlying ST-segment changes are still incompletely understood, many experimental studies have demonstrated that epicardial ECG mapping can be used to assess the degree and extent of myocardial ischaemia. Changes in the ST-segment correlate well with the degree of change in coronary blood flow (Wegria, Segers, Keating & Ward, 1949), with changes in membrane potential (Toyoshima, Prinzmetal, Horiba, Kobayashi, Mizuno, Nakayama & Yamada, 1965) and with the extent of anaerobic metabolism (Karlsson, Templeton & Willerson, 1973).

This present study has shown that disopyramide in a dose (2.5 mg/kg) which reduces the number of post-infarction dysrhythmias in experimental animals (Table 1) and which is also effective in man (Hillis, Tweddel, Lorimer & Lawrie, 1976; Mizgala & Huvelle, 1976) is capable of reducing ST-segment elevation produced by short coronary occlusions. Previous studies (Maroko *et al.*, 1971; Wendt, Canavan & Michalak, 1974; Smith, Singh, Nisbet & Norris, 1975) have demonstrated that β-adrenoceptor antagonists and verapamil, both of which decrease myocardial O_2 requirements, decrease ST segment elevation produced by coronary artery occlusion. It is unlikely that disopyramide shares this mechanism of action since the drug is devoid of β-blocking activity (Mathur, 1972; Grant, Marshall & Ankier, 1978) and since this dose of disopyramide does not reduce myocardial O_2 consumption (Table 2).

One explanation for this decrease in ST-segment elevation is the observation in the present study that disopyramide prevents K^+ efflux from ischaemic myocardial cells into coronary venous blood. Potassium efflux *per se* would be expected to elevate the ST-segment (Fozzard & Das Gupta, 1976) and indeed Figure 3 shows a good relationship between local K^+ concentration and ST-segment elevation. Also of possible relevance are the findings that disopyramide prevents the decreases in O_2 content and pH in coronary sinus blood produced by coronary occlusion (Table 4) although local coronary vein sampling would be needed to verify the relevance of these observations. It is possible that disopyramide may beneficially modify the acute effects of ischaemia on cardiac metabolism and/or membrane integrity. This suggestion is supported by unpublished data that the drug preserves myocardial ATP formation and storage and mitochondrial function (Nayler, quoted by Ankier *et al.*, 1977). A decrease in ST-segment elevation has also been described for the antidysrhythmic aminosteroid ORG 6001 (Marshall & Parratt, 1977) and it has also been demonstrated that intravenous infusions of lignocaine reduce the area of myocardial damage (assessed histologically) resulting from coronary occlusion in dogs (Schaub, Stewart, Strong, Ruotola & Lemole, 1977). The ability of disopyramide to reduce ST-segment elevation may have clinical relevance to its antidysrhythmic properties since a good correlation has been shown between infarct size and the incidence of ventricular ectopics in patients with recent myocardial infarcts (Roberts, Husain, Armbos, Oliver, Cox & Sobel, 1975).

In summary, we have demonstrated that disopyramide (2.5 and 5.0 mg/kg) significantly suppresses the early ventricular dysrhythmias induced by coronary artery ligation in anaesthetized greyhounds. However, at these doses, disopyramide causes substantial myocardial depression and should clearly be administered with care under conditions (e.g. acute myocardial infarction) when the myocardium is already compromised.

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