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Anti-arrhythmic effects of prazosin and propranolol during coronary artery occlusion and re-perfusion in dogs and pigs

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1 Open-chest dogs and pigs anaesthetized with pentobarbitone were used to evaluate the anti-arrhythmic effect of prazosin and propranolol during a 30 min period of occlusion of the left anterior descending coronary artery followed by 15 min of re-perfusion.

2 In dogs, both prazosin and propranolol reduced the incidence of ventricular premature depolarizations and ventricular tachycardia during the occlusion period. During the 45 min period of occlusion and re-perfusion, the incidence of ventricular fibrillation was significantly reduced in the prazosin-treated and propranolol-treated dogs.

3 In pigs prazosin reduced the incidence of ventricular premature depolarizations during occlusion and propranolol reduced the incidence of both ventricular premature depolarizations and ventricular tachycardia during occlusion, but the incidence of ventricular fibrillation was not significantly reduced in the prazosin- and propranolol-treated pigs.

4 Prazosin reduced arterial pressure and propranolol lowered heart rate in both dogs and pigs, but a comparison of mean arterial pressure and heart rate in animals surviving and those not surviving the 30 min of coronary artery occlusion and 15 min of re-perfusion showed no significant difference.

Introduction

Most deaths associated with coronary heart disease are sudden and caused by ventricular fibrillation (VF; Armstrong *et al.*, 1972). The precise mechanism responsible for this lethal arrhythmia is not known. Sudden marked impairment of coronary blood flow may be a primary cause. However, many *post mortem* examinations in patients who died suddenly do not demonstrate complete coronary occlusion (Bashe *et al.*, 1975). Re-perfusion arrhythmia which results from spasm or restoring blood flow in a previously occluded coronary artery has recently been suspected to contribute to sudden death (Hellstrom, 1979). The efficacy of prophylactic anti-arrhythmic drugs including β-adrenoceptor blocking agents in preventing sudden death in man is not high (Chamberlain, 1983).

The dog is the most widely used experimental model for studying sudden death resulting from coronary artery disease. Many anti-arrhythmic drugs are ineffective against re-perfusion induced VF (Sommers & Jennings, 1972; Reimer *et al.*, 1977; Naito *et al.*, 1981; Sheehan & Epstein, 1982). Recently Sheridan *et al.*, (1980) found that the α-adrenoceptor blocking drugs prazosin and phentolamine reduced the incidence of VF during coronary artery occlusion and re-perfusion in the cat. However, Corbalan *et al.*, (1976) showed earlier that in the dog phentolamine increased the VF threshold during occlusion but not during re-perfusion.

We decided to study the effect of prazosin and propranolol on the development of VF during coronary artery occlusion and re-perfusion in the dog and the pig. The pig was chosen because it has a different anatomy of the coronary circulation with less collateral flow than that of the dog (Schaper, 1971).

Methods

We used 41 adult mongrel dogs weighing between 10 and 30.5 kg and 48 young male pigs weighing between 18 and 27 kg. The animals were anaesthetized

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by intravenous administration of sodium pentobarbitone, 30 mg kg^{-1} for dogs and 25 mg kg^{-1} for pigs, followed by maintenance doses of 2 mg kg^{-1} each h. Room air ventilation via a cuffed endotracheal tube was maintained mechanically with a Harvard volume cycled respirator against an end-expiratory pressure of 5 cmH_2O.

In dogs a left thoracotomy was performed through the fourth intercostal space and the heart exposed and suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was isolated at a distance of approximately 1 cm from the left main trunk, distal to the septal artery but proximal to all major diagonal branches. In pigs a midsternal thoracotomy was performed and the LAD isolated distal to its first 2 or 3 diagonal branches. A size O suture was placed under the artery and a polyethylene sleeve threaded around the suture. One-step complete occlusion was produced by applying tension on the suture and clamping immediately above the sleeve. Thirty min later re-perfusion was accomplished by the release of the clamped sleeve and gentle massage of the vessel. Re-perfusion was verified by observing pulsatile blood flow through the distal branches of the previously occluded vessel.

The femoral artery was cannulated for recording blood pressure and the femoral vein for the administration of drugs. Lead II of the ECG was continuously recorded. Body temperature was maintained at 38°C, respiratory rate and volume and acid-base balance were monitored by repeated determination of arterial pH, P_{O_2} and P_{CO_2}, and acidaemia was corrected by intermittent administration of $NaHCO_3$.

The following arrhythmias were tabulated: ≥ 60 ventricular premature depolarizations (VPD) during the 30 min occlusion period or ≥ 30 VPD during the re-perfusion period, ventricular tachycardia (VT,

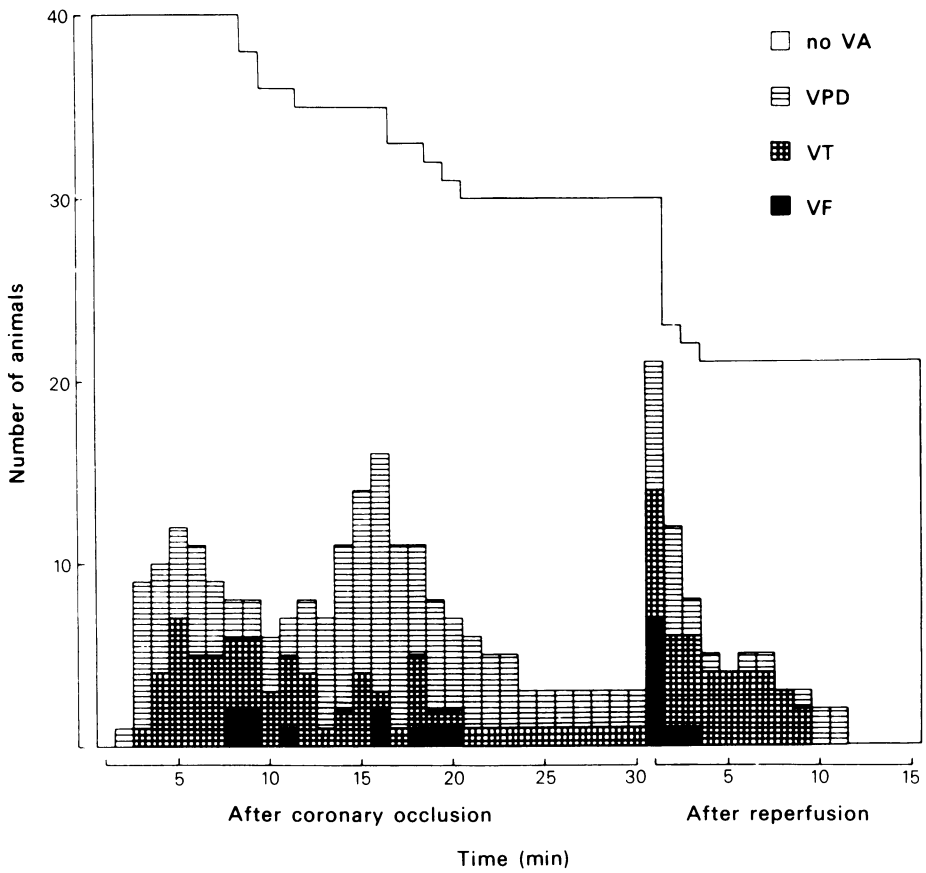

Figure 1 Incidence of ventricular premature depolarizations (≥ 2 VPD min^{-1}), ventricular tachycardia (VT, ≥ 3 consecutive VPD) and ventricular fibrillation (VF), during 30 min of left anterior descending coronary artery (LAD) occlusion followed by 15 min of re-perfusion, in 40 pentobarbitone-anaesthetized dogs.

>3 consecutive VPD), and ventricular fibrillation (VF). Individual animals were categorized with respect to their most severe arrhythmia.

Prazosin HCl (0.5 mg kg^{-1}; Pfizer; dissolved in water) was injected 30 min before occlusion and (±)-propranolol HCl (3 mg kg^{-1}; Aldrich), 60 min before occlusion.

The data were subjected to chi-square (2×4) analysis and statistical significance was determined using Student's t test (for blood pressure and heart rate).

Results

The incidence of ventricular arrhythmias in 40 experiments on dogs is shown in Figure 1. During the 30 min occlusion period there were 2 peak times for arrhythmias, the first at 5 min and the second at 16 min. During re-perfusion the incidence of arrhythmias was highest for the first min. Twelve minutes after re-perfusion the arrhythmias had disappeared.

The occurence of ventricular arrhythmias in 48 experiments on pigs is shown in Figure 2. During the occlusion period there were 2 peaks at 5 min and 18 min, although these were not as clearly delineated as in the dogs. In contrast to the dogs in which VF occurred between 8 and 20 min after occlusion, VF occurred in the pigs as early as 3 min and as late as 29 min following occlusion.

In both species the animals which fibrillated following re-perfusion had a higher incidence of arrhythmias during the occlusion period than the animals which survived the re-perfusion period (Figures 3 and 4).

The incidence of ventricular arrhythmias in both species is shown in Table 1. In the dogs prazosin or

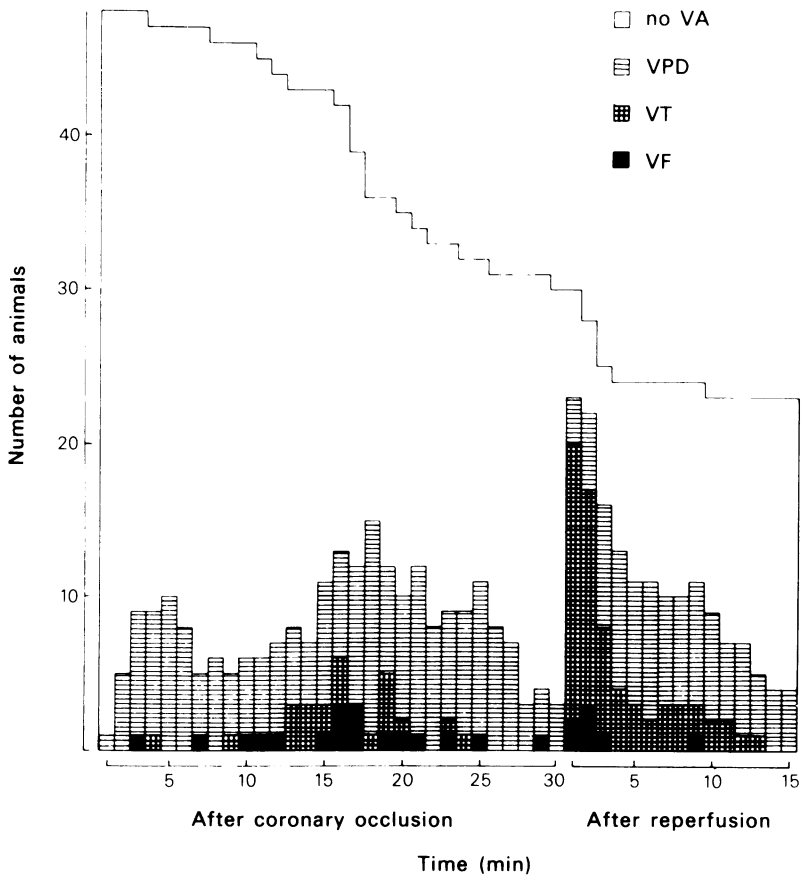

Figure 2 Incidence of ventricular premature depolarizations (>2 VPD min^{-1}), ventricular tachycardia (VT, >3 consecutive VPD) and ventricular fibrillation (VF) during 30 min of LAD occlusion followed by 15 min of re-perfusion in 48 pentobarbitone-anaesthetized pigs.

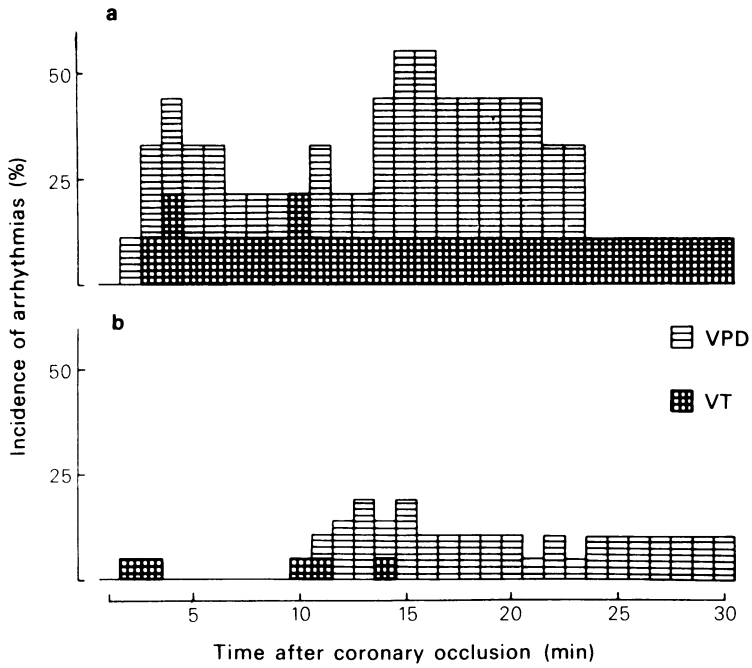

Figure 3 Incidence of ventricular premature depolarizations (>2VPD min^{-1}) and ventricular tachycardia (VT, >3 consecutive VPD) during 30 min of LAD occlusion in (a) 9 dogs which fibrillated during re-perfusion and (b) 21 dogs which did not fibrillate during re-perfusion.

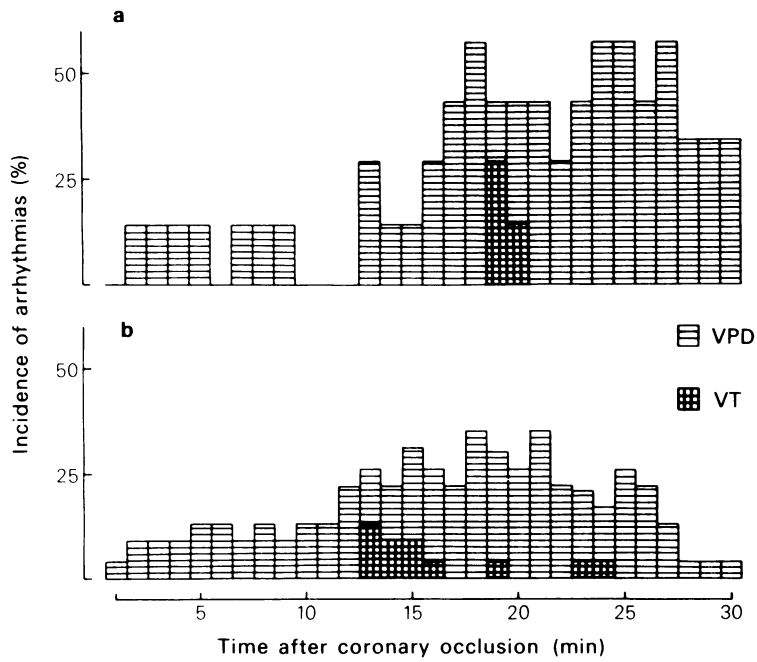

Figure 4 Incidence of ventricular premature depolarizations (>2VPD min^{-1}) and ventricular tachycardia (VT, >3 consecutive VPD) during 30 min of LAD occlusion in (a) 7 pigs which fibrillated during re-perfusion and (b) 23 pigs which did not fibrillate during re-perfusion.

Table 1 Incidence of ventricular premature depolarizations (>2 VPD min^{-1}), ventricular tachycardia (VT>3 consecutive VPD) and ventricular fibrillation (VF) during coronary artery occlusion and re-perfusion

	Occlusion			*Reperfusion*			*Total*
	VPD	*VT*	*VF*	*VPD*	*VT*	*VF*	*VF*
Dogs							
Control	9/11 (82%)	9/11 (82%)	6/12 (50%)	4/5 (80%)	4/5 (80%)	4/6 (67%)	10/12 (83%)
Prazosin	4/11*(36%)	5/11*(45%)	2/11*(18%)	4/9 (44%)	4/9 (44%)	1/9*(11%)	3/11*(27%)
Propranolol	4/8*(50%)	4/8*(50%)	1/8*(13%)	5/7 (71%)	5/7 (71%)	2/7*(29%)	3/8*(38%)
Prazosin + propranolol	2/10*(20%)	1/10*(10%)	1/10*(10%)	3/9 (33%)	2/9 (22%)	3/9*(33%)	4/10*(40%)
Pigs							
Control	11/12 (92%)	11/12 (92%)	4/12 (33%)	8/8 (100%)	5/8 (63%)	3/8 (38%)	7/12 (58%)
Prazosin	4/14*(29%)	9/14 (64%)	8/14 (57%)	5/6 (83%)	5/6 (83%)	2/6 (33%)	10/14 (71%)
Propranolol	1/11* (9%)	1/11* (9%)	2/11 (18%)	8/9 (89%)	6/9 (67%)	1/9 (11%)	3/11 (27%)
Prazosin + propranolol	2/11*(18%)	2/11*(18%)	4/11 (36%)	3/7*(43%)	3/7 (43%)	1/7 (14%)	5/11 (45%)

*$P<0.05$, compared to control.

Table 2 Blood pressure and heart rate before coronary artery occlusion and re-perfusion

	Occlusion				*Reperfusion*			
	Blood pressure		*Heart rate*		*Blood pressure*		*Heart rate*	
Dogs								
Control	150±8	100±6	161±8	(11)	147±6	107±9	150±11	(5)
Prazosin	123±6*	81±5*	167±7	(11)	104±11*	71±9*	181±11	(9)
Propranolol	136±8	89±7	136±8*	(8)	127±13	89±11	143±9	(7)
Prazosin + propranolol	120±6*	82±4*	131±4*	(10)	113±6*	79±5*	136±6	(9)
Pigs								
Control	117±4	73±3	146±8	(12)	116±7	68±4	144±12	(8)
Prazosin	95±4*	52±3*	174±14	(14)	93±8	49±6*	152±24	(6)
Propranolol	131±2*	85±3*	103±4*	(11)	133±5	85±4*	100±5*	(9)
Prazosin + propranolol	103±3*	61±2*	103±4*	(11)	93±5*	55±5	106±5*	(7)

Values are means ± s.e.mean. The number of experiments is in parentheses. *$P<0.05$, compared to control.

Table 3 Mean arterial pressure (MAP) and heart rate (HR) before coronary artery occlusion

	Non-survivors			*Survivors*		
	MAP	*HR*		*MAP*	*HR*	
Dogs						
Control	116±6	157±10	(10)	115±2	165±5	(2)
Prazosin	100±12	163±19	(3)	93±7	169±8	(8)
Propranolol	90±9	120±10	(3)	114±8	146±8	(5)
Prazosin + propranolol	87±9	135±9	(4)	100±4	128±5	(6)
Pigs						
Control	90±5	139±11	(7)	85±4	135±19	(5)
Prazosin	67±2	179±16	(10)	64±10	163±27	(4)
Propranolol	101±6	97±9	(3)	100±3	106±4	(8)
Prazosin + propranolol	78±3	102±8	(5)	73±3	104±4	(6)

Values are means ± s.e.mean. The number of experiments is in parentheses.

propranolol alone and in combination reduced the incidence of VPD and VT during occlusion and the incidence of VF during occlusion and re-perfusion ($P<0.05$). In pigs prazosin reduced the incidence of VPD during occlusion but not the indicence of VF. Propranolol reduced the incidence of VPD and VT during occlusion; it lowered the total incidence of VF from 58% to 27%, but this was not a statistically significant effect for the number of experiments performed.

Blood pressure (BP) and heart rate (HR) immediately before coronary artery occlusion and re-perfusion are shown in Table 2. No significant changes occurred during the occlusion period. Prazo-

sin significantly lowered BP and propranolol lowered HR in both species. These effects remained when the drugs were combined.

A comparison of mean arterial pressure and HR between animals surviving and those not surviving the 30 min of coronary artery occlusion and 15 min of reperfusion revealed no significant difference between these two groups of animals (Table 3).

Discussion

Methodology

In dogs pentobarbitone anaesthesia increases sympathetic tone, inducing an increase in BP and HR as shown in Table 2 (Priano *et al.*, 1969). As increased sympathetic influences are commonly found in patients with arrhythmias in acute myocardial infarction (Jewitt *et al.*, 1969; Pantridge *et al.*, 1981), the present study may be relevant to the properties of ischaemic myocardium responsible for arrhythmias.

In dogs the incidence of VF was 50% during occlusion and 67% during re-perfusion (Table 1). Other authors have obtained similar results using a similar dog model with the incidence of VF ranging between 30% and 57% during LAD occlusion and between 44% and 67% during re-perfusion (Kaplinsky *et al.*, 1979; 1981; Balke *et al.*, 1981; Naito *et al.*, 1981; Kabell *et al.*,1982).

When we performed the same proximal LAD occlusion in pigs that we had used in dogs, all animals died within a few min. Ligation of the LAD below the first 2 or 3 diagonal branches produced VF rates of 33% during occlusion and 38% during re-perfusion (Table 1). Brooks *et al.*, (1975) used the same technique in chloralose-anaesthetized pigs and obtained a 35% incidence of VF during occlusion.

Patterson & Kirk (1983) discourage the use of pigs for the study of ischaemic heart disease. Collateral structure and function in the pig after acute coronary artery occlusion are much less prominent than in human beings with chronic coronary artery disease and probably lower than in human beings without coronary disease. The very low collateral flow in pigs causes virtually complete infarction of the ischaemic region and makes it unlikely that interventions could salvage myocardium. Pigs differ from dogs, but no data support the idea that the pig's collateral function is closer than that of the dog to collateral function in human beings (Gregg & Patterson, 1980).

The present study demonstrates 2 peaks of ventricular arrhythmias during occlusion with the rate of VF being highest following re-perfusion. The factors responsible for arrhythmias in myocardial infaction are poorly understood. During the first 10 min of coronary artery occlusion ectopic activity probably results from re-entrant circuits in the ischaemic zone caused by abnormalities in metabolic activity, accumulation of toxic metabolites, variation in extracellular H^+ or K^+ concentration or adrenergic influences; all such effects are modulated by the degree of reduction in blood flow and hence oxygen and substrate supply to the ischaemic myocardium (Russell *et al.*, 1982). The following quiescent period could be due to further conduction suppression so that re-entrant pathways become blocked (Murdock *et al.*, 1980). Delayed ventricular arrhythmias occuring 12–30 min after ligation could also be re-entrant, with the re-entry pathway located in deep myocardial structures or involving microscopic pathways at the Purkinje muscle junction (Kaplinsky *et al.*, 1979). Recovery of electrical activity occurs immediately after re-perfusion, but it is not homogeneous; such inhomogeneity could provide the appropriate milieau for re-entrant arrhythmias (Murdock *et al.*, 1980; Kaplinsky *et al.*, 1981).

Prazosin

We found that the α-adrenoceptor blocking agent prazosin reduced the incidence of VF during coronary artery occlusion and reperfusion in the dog model. Our results are similar to those obtained in the cat by Sheridan *et al.*, (1980).

Phentolamine has been shown to reduce the incidence of VF induced by coronary re-perfusion but not during 30 min of occlusion in pentobarbitone-anaesthetized dogs (Stephenson *et al.*, 1960), but Corbalan *et al.*, (1976) showed that although phentolamine increased the VF threshold during occlusion, it did not affect the threshold during reperfusion. Unlike prazosin, phentolamine is a non-selective blocker of both α_1- and α_2-adrenoceptors and can increase HR, cardiac output and LAD blood flow as a result of increased noradrenaline release (Gorman & Sparks, 1982; Saeed *et al.*, 1982).

A number of mechanisms might explain the efficacy of prazosin in reducing the incidence of VF during occlusion and re-perfusion including reduction of myocardial oxygen demand, increase in collateral blood flow and/or reduction of electrophysiological derangements. Prazosin blocks α_1-adrenoceptors and causes sustained arteriolar and venous dilation (Miller *et al.*, 1982). This is a beneficial effect in pentobarbitone-anaesthetized dogs with their high peripheral vascular resistance and low stroke volume and cardiac output (Priano *et al.*, 1969). In conscious dogs prazosin reduces myocardial oxygen demand without reducing coronary blood flow. Arterial and left ventricular (LV) pressure, LV end-diastolic diameter and LV dp/dt were reduced, but flow in the

left circumflex coronary artery did not change (Macho & Vatner, 1982; Macho *et al.*, 1982).

The effect of prazosin on collateral and regional myocardial blood flow has not been studied. Lowering LV end-diastolic pressure could increase collateral and endocardial blood flow in the ischaemic area (Kirk & Sonnenblick, 1981). In the present study, although other haemodynamic parameters were not measured, reduction in BP *per se* does not explain the anti-fibrillatory effect of prazosin in the dogs (Table 3).

Sheridan *et al.*, (1980) proposed that prazosin exerts its anti-arrhythmic effect in anaesthetized cats by blocking α-adrenoceptor mediated electrophysiological derangements, and Corr *et al.*, (1981) found an increased α-adrenoceptor concentration in ischaemic cat myocardium. Prolongation of the refractory period and action potential duration is an effect of myocardial α-adrenoceptor stimulation (Benfey, 1982).

In the pigs there was no significant difference in BP between animals which survived and those which developed VF in the prazosin-treated group (Table 3). However, an excessive reduction in diastolic BP to below 60 mmHg by prazosin (Table 2) may reduce coronary perfusion pressure, thus reducing oxygen supply. In addition, other factors such as the absence of or limited collateral vessels (Patterson & Kirk, 1983) and the unknown function and type of α-adrenoceptors in the pig heart may contribute to the failure of prazosin in preventing VF.

Propranolol

In the present study propranolol had anti-fibrillatory effects both during LAD occlusion and re-perfusion in dogs. These results are in accordance with most other investigations which demonstrate that β-adrenoceptor blocking drugs reduce lethal arrhythmias in experimental animals during coronary artery occlusion (Pentecost & Austen, 1966; Fearon, 1967; Reynolds *et al.*, 1978; Kanayama *et al.*, 1982) and in man with coronary heart disease (Chamberlain, 1983).

Sheridan *et al.*, (1980) found that propranolol reduced the incidence of VF during coronary artery occlusion but not during re-perfusion, in the cat. In our dog model, animals protected against arrhythmias in the occlusion period had a better chance of surviving the re-perfusion period. Dogs which survived the re-perfusion period had a lower incidence of arrhythmias during the occlusion period than dogs which died (Figure 2). Similarly, Balke *et al.*, (1981) and Naito *et al.*, (1981) observed that dogs without arrhythmias during occlusion had a significantly lower incidence of arrhythmias during re-perfusion than those with arrhythmias during occlusion. Therefore, the anti-fibrillatory effect of propranolol during re-perfusion may be related to the anti-arrhythmic effect of the drug during the previous occlusion period.

The efficacy of propranolol may result from its effect on myocardial oxygen supply and demand and through electrophysiological mechanisms. Propranolol can exert a beneficial effect on myocardial oxygen supply and demand by reducing HR which increases the duration of the diastolic time interval allowing longer coronary perfusion in the ischaemic zone. A reduction in both HR and contractility reduces myocardial oxygen demand. However, in the present study there was no difference between the HR of animals which survived the LAD occlusion and re-perfusion and those animals which did not survive (Table 3). Other investigators also found a poor correlation between the reduction in HR induced by β-blockade and the decrease in the extent of necrosis or incidence of VF in pentobarbitone-anaesthetized dogs subjected to a 40 min period of occlusion of the circumflex branch of the left coronary artery (Reimer *et al.*, 1976; Abendroth *et al.*, 1977). In addition, dogs free of re-perfusion arrhythmias were not distinguishable on the basis of their HR or BP measured before re-perfusion (Naito *et al.*, 1981; Fujimoto *et al.*, 1983). Thus reduction in HR alone does not explain the anti-fibrillatory effect of propranolol in our dog model.

Beneficial effects of propranolol on regional myocardial blood flow in ischaemia have been described in conscious dogs (Vatner *et al.*, 1977) and anaesthetized dogs (Berdeaux *et al.*, 1978; Gross *et al.*, 1982).

Propranolol could exert a beneficial effect through electrophysiological mechanisms. Myocardial β-adrenoceptor stimulation shortens refractory period and action potential duration (Benfey, 1982). In pentobarbitone-anaesthetized dogs LAD occlusion reduced, and re-perfusion increased the refractory period in the ischaemic zone, but not in the non-ischaemic area, causing dispersion of refractoriness (Levites *et al.*, 1975; Russell & Oliver, 1978). Propranolol may act to make refractoriness more homogeneous. The concentration of β-adrenoceptors has been found to be increased in the ischaemic zone in anaesthetized dogs (Mukherjee *et al.*, 1979).

Finally, there is the possibility that the relatively high dose of propranolol used in this study may also exert class I anti-arrhythmic activity.

In conclusion, open-chest pentobarbitone-anaesthetized dogs with high sympathetic tone were subjected to a 30 min period of LAD occlusion followed by 15 min of re-perfusion to serve as a model

of acute myocardial ischaemia. Both prazosin and propranolol reduced the incidence of VF in this dog model but not in a similar pig model. The reason for the different efficacy in pigs is not known but may be the result of a different collateral coronary flow function in pigs.

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