An investigation into the characteristics of reperfusion-induced arrhythmias in the anaesthetized rat and their susceptibility to antiarrhythmic agents

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1   Reperfusion-induced arrhythmias were elicited in the pentobarbitone-anaesthetized rat by occlusion of the left main coronary artery and subsequent release.

2   These arrhythmias were rapid in onset, occurring within 20 s after release of the ligature, and were of short duration (1–2 min). Their severity was dependent upon the duration of the preceding occlusion. A 5 or 15 min occlusion period produced the most severe arrhythmias on release, the incidence of ventricular fibrillation being 56 and 50% respectively.

3   Evidence that reperfusion had occurred was provided by fluorescein dye distribution and intramyocardial temperature studies.

4   The severity of reperfusion arrhythmias and mortality was unaffected by bilateral vagotomy, β-adrenoceptor blockade by atenolol (2 mg kg^{-1} i.v.) or a combination of the two.

5   The incidence of reperfusion-induced ventricular fibrillation was significantly reduced by Org 6001 (which blocks the fast inward sodium current), melperone (which acutely prolongs the cardiac action potential duration) and bepridil (which blocks both fast and slow inward currents). It was unaffected by nitroglycerine and the calcium antagonists verapamil, prenylamine and nifedipine.

6   We have shown that reperfusion-induced cardiac arrhythmias can be consistently elicited in the anaesthetized rat and that they are particularly susceptible to drugs that can block the fast inward sodium current.

Introduction

It has been known for some time that in experimental animals restoration of blood flow to the myocardium, after a brief period of ischaemia, is associated with the occurrence of severe ventricular arrhythmias (Sewell *et al.*, 1955). More recently, it has been suggested that such reperfusion-induced arrhythmias may be of clinical importance since it has been shown that sudden cardiac death, due to ventricular fibrillation, is not always accompanied by a permanent obstruction of a coronary artery (Schaffer & Cobb, 1975). In man, release of coronary artery spasm or platelet disaggregation causing restoration of blood flow to a previously ischaemic region of the myocardium could be the underlying cause of ventricular fibrillation and sudden cardiac death.

Experimentally such arrhythmias have been studied either in large animals *in vivo* (Corbalan *et al.*, 1976; Penkoske *et al.*, 1978) or *in vitro* using Langendorff-perfused rat hearts (Lubbe *et al.*,

1978). The aim of this study was to develop a model for the production of reperfusion-induced arrhythmias in the rat *in vivo* which could be used to assess the effectiveness of a variety of drugs in protecting against this type of arrhythmia. A preliminary account of these results has been presented to the British Pharmacological Society (Kane *et al.*, 1983).

Methods

Male Sprague-Dawley rats (220 g–350 g) were anaesthetized with sodium pentobarbitone, 60 mg kg^{-1} administered intraperitoneally. The femoral vein was cannulated to allow drug and dye administration, and the trachea for artificial respiration. Systemic blood pressure was monitored from the carotid artery by means of a Statham P23 1D transducer. A standard lead 1 ECG was recorded,

together with systemic blood pressure, on a Mingograf 82 ink jet recorder (Elema-Schönander, Stockholm).

The chest was opened using a left thoracotomy, followed by sectioning of ribs 4 and 5, approximately 2 mm to the left of the sternum. Positive pressure artificial respiration was started immediately with room air, using a volume of $1.5 \, ml \, 100 \, g^{-1}$ and a rate of $54 \, strokes \, min^{-1}$ to maintain normal PCO_2, PO_2 and pH parameters. After incising the pericardium the heart was eased out of the chest, using gentle pressure on the rib cage. A 6/0 braided silk suture attached to a 10 mm micropoint reverse cutting needle (mersilk W8 12, Ethicon) was placed under the left main coronary artery, as described by Selye *et al.* (1960). The heart was replaced in the chest and the animal left to recover for 15 min. Any animal in which this procedure produced arrhythmias or a sustained fall in blood pressure to less than 70 mmHg was discarded.

A small plastic button was threaded through the ligature and placed in contact with the heart. The artery could then be occluded by applying tension to the ligature and reperfusion achieved by releasing the tension. The coronary artery was occluded for periods of up to 30 min before release in order to assess the effect of duration of occlusion on the severity of reperfusion arrhythmias. In a few animals only, release of the ligature had to be delayed for up to a maximum of 30 s to ensure that the animal was in sinus rhythm at the time of reperfusion. In the first series of experiments electrocardiographic recordings were continued for a period of 30 min after starting reperfusion. However, since no further arrhythmias occurred between 10 and 30 min, the observation period was reduced to 10 min post-reperfusion in all subsequent experiments.

Two studies were undertaken to determine whether reperfusion was in fact occurring. In the first of these $0.1 \, ml \, 100 \, g^{-1}$ (body wt.) of a 10% w/v solution of fluorescein (Aldrich Chemical Co.) was administered intravenously, immediately after release of the ligature. The heart was rapidly removed from the chest and placed in ice cold KCl solution (10% w/v) for 1 min to stop it beating. A gross examination of the heart was made under u.v. light to determine whether areas of non-perfused myocardium were present. These appeared dark blue under u.v. light whereas perfused areas were stained green. The hearts were then photographed under u.v. light to give a permanent record. As a comparison this procedure was also carried out in hearts with a permanent ligation, after 5 min of ischaemia.

For the second study thermocouples were used to detect temperature changes in the myocardium ($n = 8$) during occlusion and reperfusion. A copper-constantan thermocouple (SWg 40) was inserted into the myocardium of the left ventricle below the site of occlusion, at the same time as insertion of the ligature. A reference thermocouple was present in the rectum. Fifteen minutes later the artery was occluded for 5 or 10 min, followed by reperfusion. Changes in myocardial temperature were monitored using a Kipp and Zonen recorder.

In order to determine whether autonomic neural influences on the heart were important in the genesis
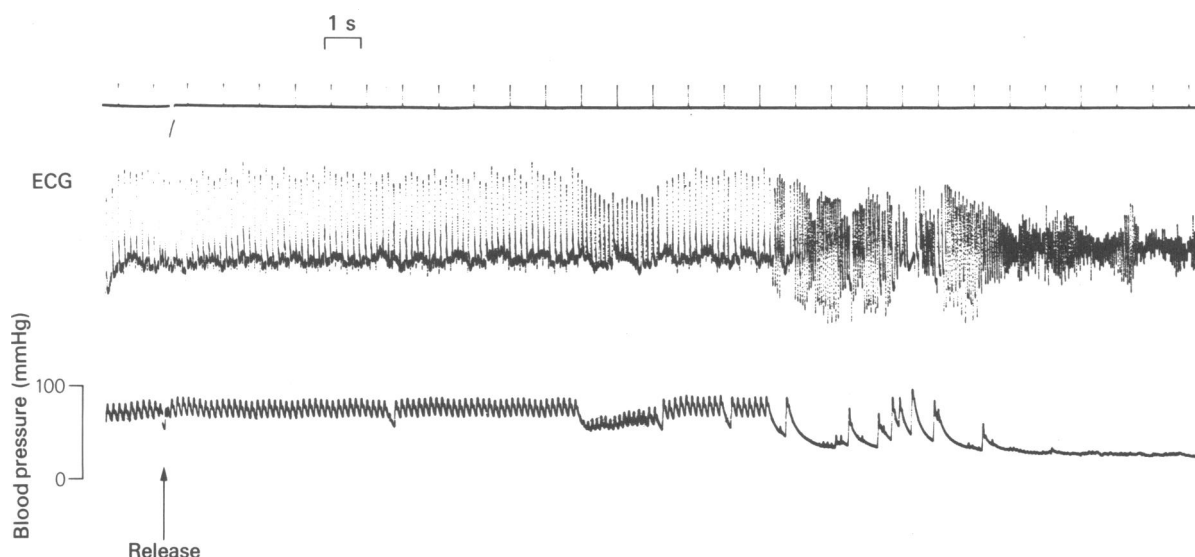
Figure 1   Characteristic electrocardiogram and arterial blood pressure trace of an anaesthetized rat subjected to coronary artery occlusion for 5 min followed by reperfusion.

of these arrhythmias the effects of following experimental procedures were investigated: bilateral vagotomy 10 min pre-occlusion, β_1-adrenoceptor blockade achieved by administration of atenolol (ICI), 2 mg kg^{-1} i.v. 10 min pre-occlusion, and a combination of vagotomy and β_1-blockade. This dose of atenolol caused a 25 fold shift to the right of the isoprenaline chronotropic dose-response curve.

The drugs and doses used in this study were as follows: Org 6001 (Organon International) 2 and 10 mg kg^{-1}; melperone (A.B. Ferrosan) 2 and 10 mg kg^{-1}; nitroglycerine (Arnar-Stone Laboratories Inc.) 15 μg kg^{-1} min^{-1}; bepridil (Organon International) 2 and 5 mg kg^{-1}; verapamil (Knoll, A-G) 0.01 and 0.05 mg kg^{-1}; prenylamine (Hoechst AG) 1 mg kg^{-1} and nifedipine (Bayer) 1, 10 and 25 μg kg^{-1}. All of the drugs were administered intravenously 10 min before occlusion and the ligature released after a 5 min occlusion period. Nitroglycerine was given as an infusion throughout the experiment and the other drugs as bolus injections. The solvent for nitroglycerine contained lactose, monobasic potassium phosphate, 10% w/v alcohol and water for injection; the solvent alone was infused in those animals which served as controls for the nitroglycerine-treated group. Nifedipine was dissolved in ethanol to a concentration of 1 mg ml^{-1} and further dilutions made with saline. The drug and solutions were protected from light at all times. It was weighed out under sodium light, the container, syringes, needles and 3 way taps were covered in aluminium foil and the venous cannula coated with black paint. All other drugs were dissolved in saline. Drug-treated groups were compared with a similar number of control experiments performed over the same time period.

Statistical analysis

Statistical analysis of differences in the incidence of arrhythmias and in the mortality was carried out using a Chi squared test. For changes in haemodynamic parameters a paired Student's t test was used.

Results

Characteristics of the arrhythmias induced by reperfusion and the relationship between the duration of occlusion and their severity

The arrhythmias that occur upon occlusion of the coronary artery start within 2–4 min and last for about 20 min. Following different periods of occlusion, 5, 15 or 30 min, reperfusion elicits arrhythmias within 8–26 s which continue for only 1–2 min. Ventricular tachycardia (VT) is usually observed and is often followed by ventricular fibrillation (VF), which is not always terminal in the rat since spontaneous reversion to sinus rhythm can occur. Figure 1 shows a typical trace upon release of the ligature after a 5 min occlusion period. Evidence that these arrhythmias are not merely a continuation of those initiated by occlusion is shown in Table 1. It compares the severity of the arrhythmias which occur during the first minute of reperfusion after either a 5 or 15 min occlusion period with those that occur during the corresponding time periods but with the occlusion still present. The arrhythmias that occur during reperfusion are clearly more serious than those that occur, over the same period, during ischaemia alone.

In this model the severity of the reperfusion-induced arrhythmias is related to the duration of the preceding occlusion (Table 2). The most severe arrhythmias occur after an occlusion period of 5 or 15 min when 56 and 50% of the animals developed VF respectively. If the duration of occlusion is shortened to 2 min or extended to 20 min the number of arrhythmias is markedly reduced and no VF occurred. During occlusion the most severe arrhythmias are observed between 5 and 20 min post-ligation.

Table 1 The severity of ventricular arrhythmias that occur during the first minute of reperfusion following either a 5 or 15 min coronary artery occlusion: compared with those arrhythmias that occur during the corresponding time periods (i.e. between 5th and 6th min and between the 15th and 16th min) but with the occlusion still present

Time		n	Mean number of VEBs (over 1 min)	%VT	%VF	Duration of VT
5–6 min	occlusion	27	70±24	44	7	3.9±1.5
5–6 min	reperfusion	16	359±39**	100**	56**	11.8±4.0
15–16 min	occlusion	17	18±8.5	18	6	2.8±2
15–16 min	reperfusion	10	156±34**	70**	50**	12.2±4

The table shows the mean number of ventricular ectopic beats (VEBs), the incidence and duration of ventricular tachycardia (VT) and the incidence of ventricular fibrillation (VF) over the 1 min period
** $P < 0.01$

Table 2 The effect of the duration of coronary artery occlusion on the severity of ventricular arrhythmias which occur during occlusion and when the myocardium is reperfused

Duration of occlusion (min)	n	Arrhythmias during occlusion:					Arrhythmias on reperfusion				
		Total VEBs	VEBs min^{-1}	%VT	%VF	% Mortality	Total VEBs	VEBs min^{-1}	%VT	%VF	% Mortality
2	6	0	0	0	0	0	2.4±1.0	—	0	0	0
5	16	159±9	32	56	0	0	591±140	529	100	56	44
15	13	991±213	66	90	54	23	302±120	149	70	50	8
20	9	1543±678	77	79	44	22	87±40	42	14	0	0
30	10	1483±429	49	100	30	20	72±20	70	37.5	0	0

Given are the total number of ventricular ectopic beats (VEBs), which occurred over the occlusion and reperfusion periods, the number of VEBs per min, the percentage incidence of ventricular tachycardia (VT), of ventricular fibrillation (VF) and the mortality.

Evidence for the occurrence of reperfusion following release of the occlusion

Examination of the photographs obtained of hearts excised from rats administered fluorescein dye shows that when the occlusion is maintained, most of the left ventricle appears dark blue, indicating that it is not perfused. However, the left ventricles of all hearts, in which the ligature was released after ischaemic periods of 5 ($n=6$), 15 ($n=6$) or 30 min ($n=5$) are for the most part stained green showing that reperfusion of the majority of the myocardium has indeed occurred. With the longer periods of occlusion, in particular, small blue areas in the left ventricle are apparent, suggesting either that reperfusion is incomplete or that in some areas it occurs more slowly. Figure 2 illustrates the temperature changes recorded from the ischaemic area during a 5 min occlusion period and subsequent reperfusion. On occlusion, myocardial temperature falls and is maintained at that level throughout the occlusion period. Release of the ligature results in a rapid rise in temperature to pre-occlusion values within 30 s. A similar pattern of temperature changes is also seen during and following a 10 min occlusion period.

Effect of bilateral vagotomy, β_1-adrenoceptor blockade or a combination of the two on the severity of reperfusion arrhythmias

Release of the occlusion leads to VT in all of the control rats and 50% of them fibrillated (Table 3). Sectioning of the vagi or administration of an effective β-blocking dose of atenolol did not affect the incidence of VT or VF. A combination of bilateral vagotomy plus atenolol results in a slightly lower incidence of VF, but this change is not statistically significant. Prior to occlusion, heart rate is significantly increased by vagotomy (381±20 vs 419±15 beats min^{-1}) and reduced by atenolol pretreatment (421±27 vs 351±18 beats min^{-1}). No change in heart rate occurs following the combination of β-adrenoceptor blockade and bilateral vagotomy. Prior to occlusion, arterial blood pressure in the three treated groups is not markedly different from that of control animals, i.e. 81±4 mmHg.

Coronary artery occlusion itself results in a statistically significant fall in arterial blood pressure in all 4 groups (approximately 25% at 1 min post occlusion) but does not alter heart rate. By 5 min post occlusion, blood pressure has almost returned to pre-occlusion levels except in those animals receiving atenolol. By 10 min post-reperfusion, blood pressure has reached pre-occlusion values in all of the groups.
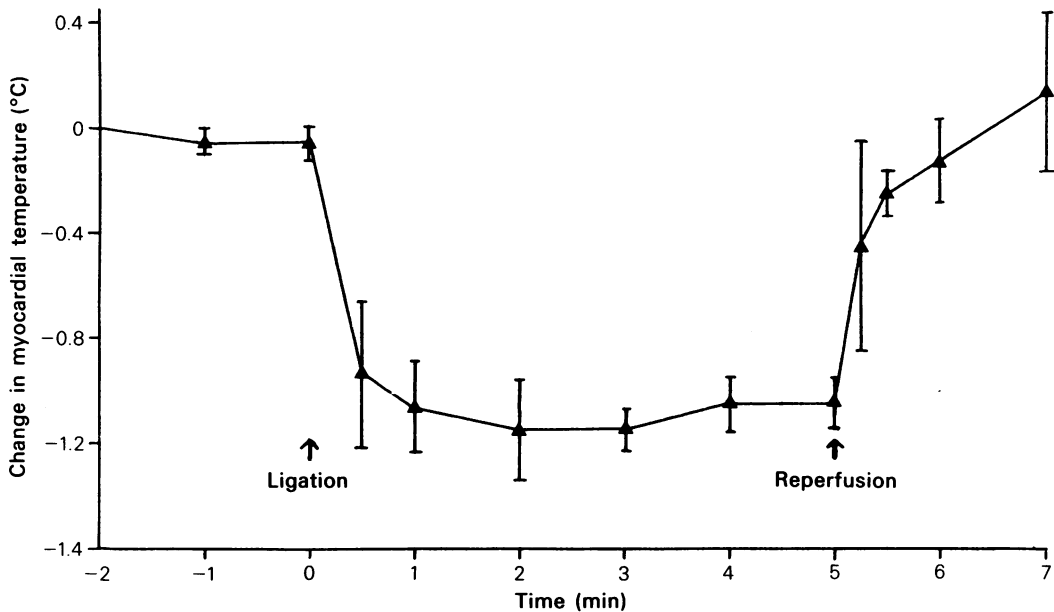
Figure 2   Intramyocardial temperature changes recorded in the ischaemic area following coronary artery occlusion for 5 min and subsequent reperfusion ($n = 8$)

Effect of antiarrhythmic agents on reperfusion-induced arrhythmias

The effect of Org 6001, melperone and nitroglycerine on the incidence of VT, VF and mortality following reperfusion is shown in Table 4. Org 6001 causes a dose-dependent reduction in the incidence of VT and VF. Mortality too is reduced by the drug, although this just failed to reach statistical significance at the higher dose ($P = 0.055$). Ventricular fibrillation and mortality are also significantly reduced by melperone. The exceptionally high mortality and incidence of ventricular fibrillation in this control group compared to those observed in the other studies is probably a consequence of the more marked haemodynamic effects of coronary artery occlusion in this particular group of rats. (e.g. mean arterial blood pressure fell from 88 ± 8 to 53 ± 3 mmHg at 1 min post ligation). Nitroglycerine,

on the other hand, has no antiarrhythmic effect in this model, at the concentration studied, i.e. $15 \, \mu g \, kg^{-1}$. In animals administered the solvent alone, the severity of the arrhythmias is less than in saline controls. Table 5 summarises the effects of the calcium channel blockers, bepridil, verapamil, prenylamine and nifedipine on the incidence of these arrhythmias and mortality. Bepridil was the only drug to be effective against reperfusion-induced arrhythmias. The incidence of VT is significantly reduced by both doses of the drug and VF by the higher dose only.

Haemodynamic effects of the antiarrhythmic drugs

Both Org 6001 and melperone reduced heart rate in these experiments. It fell from 398 ± 21 to 346 ± 17 beats min^{-1} following the administration of Org 6001, $10 \, mg \, kg^{-1}$. A similar reduction is observed with the lower dose of melperone whilst the

Table 3   The incidence of ventricular tachycardia (VT), ventricular fibrillation (VF) and mortality on reperfusion after 5 min occlusion in control rats and those receiving atenolol 2 mg kg^{-1}, bilateral vagotomy or a combination of the two

Treatment	n	% incidence VT	% incidence VF	% mortality
Saline	18	100	50	22
Bilateral vagotomy	9	100	56	44
Atenolol (2 mg kg^{-1})	9	100	67	22
Vagotomy + atenolol	8	100	37.5	25

Table 4   The incidence of ventricular tachycardia (VT), ventricular fibrillation (VF) and mortality on reperfusion in control and drug-treated rats

Treatment	n	% incidence VT	% incidence VF	% mortality
Saline control	8	100	63	38
Org 6001 (2 mg kg^{-1})	9	89	22	11
Org 6001 (10 mg kg^{-1})	8	37.5**	12.5*	0
Saline control	8	100	100	87.5
Melperone (2 mg kg^{-1})	8	87.5	37.5**	37.5**
Melperone (10 mg kg^{-1})	8	87.5	37.5**	12.5**
Solvent (control)	8	87.5	37.5	25
Nitroglycerine 15 μg kg^{-1} min^{-1}	8	87.5	25	25

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

higher dose causes a more marked fall from 429 ± 18 to 284 ± 22 beats min^{-1}. These changes are all statistically significant ($P < 0.01$). Arterial blood pressure is not significantly reduced by Org 6001 whereas with the higher dose of melperone it falls from 95 ± 7 to 56 ± 11 mmHg ($P < 0.05$). Similarly, nitroglycerine causes a sustained fall in blood pressure from 84 ± 11 to 63 ± 1 mmHg ($P < 0.01$) before occlusion, as does its solvent, 94 ± 7 to 81 ± 2 mmHg. Nitroglycerine administration does not alter heart rate.

The calcium antagonists, with the exception of bepridil, cause no changes in heart rate. Bepridil, 5 mg kg^{-1}, reduces heart rate from 384 ± 20 to 340 ± 12 beats min^{-1}. A maintained fall in arterial blood pressure is observed only after the administration of 25 μg kg^{-1} of nifedipine (82 ± 4 vs 72 ± 3 mmHg at 10 min post-injection). The other calcium antagonists did tend to cause a fall in blood pressure on injection but these changes are transient. On occlusion, the changes observed in blood pressure in these drug-treated animals are similar to those recorded in the control group.

Discussion

This study demonstrates that reperfusion-induced cardiac arrhythmias can be reliably and consistently produced in the anaesthetized rat. One of the most distinctive features of these arrhythmias in this model is their rapid onset and short duration when compared with those that occur when the occlusion is present. A similar profile of reperfusion-induced arrhythmias has previously been described in larger animals (Axelrod *et al.*, 1975; Penkoske *et al.*, 1978). Another similarity observed between this and the larger animal models is the pattern and severity of the arrhythmias. Following reperfusion, ventricular tachycardia occurred within 30 s and rapidly degenerated into fibrillation in many instances. In contrast, arrhythmias which occur during occlusion generally begin with isolated ectopic beats which may or may not lead to fibrillation.

The severity of these arrhythmias was dependent upon the duration of the occlusion, as has been noted both in the dog *in vivo* (Balke *et al.*, 1981) and in the

Table 5   The effect of calcium antagonists on the severity of reperfusion-induced arrhythmias and mortality

Treatment	n	% incidence VT	% incidence VF	% mortality
Saline	17	94	71	29
Bepridil 2 mg kg^{-1}	10	40**	20	0
Bepridil 5 mg kg^{-1}	10	50**	10*	10
Verapamil 0.01 mg kg^{-1}	8	100	50	37.5
Verapamil 0.05 mg kg^{-1}	8	100	75	50
Distilled water	8	100	50	0
Prenylamine 1 mg kg^{-1}	9	100	44	33
Solvent control	16	87.5	56	25
Nifedipine 0.001 mg kg^{-1}	7	71	43	14
Nifedipine 0.01 mg kg^{-1}	7	71	29	29
Nifedipine 0.25 mg kg^{-1}	8	100	50	25

* $P < 0.05$ ** $P < 0.01$.
Abbreviations as for Table 4.

rat *in vitro* (Crome *et al.*, 1983). Release of the occlusion after a 5 or 15 min ischaemic period led to the most severe arrhythmias with 56 and 50% of the animals fibrillating respectively. Following longer periods of occlusion e.g. 30 min, no fibrillation was observed upon reperfusion. We think that this reduced severity of the arrhythmias following longer periods of ischaemia is not due to failure to re-establish blood flow to the myocardium since the studies carried out with fluorescein dye indicate that most of the left ventricle is perfused irrespective of the duration of the occlusion. However since these studies were carried out in a limited number of animals, we cannot state categorically that rapid reperfusion occurred on release in every instance. Supportive evidence that blood flow was being re-established on reperfusion was provided by the measurement of temperature of the ischaemic myocardium. Whilst occlusion was accompanied by a rapid fall in temperature, reperfusion led to a sharp rise, indicating a return of blood flow and increase in metabolic activity. The rat does differ from other species, in this respect, in that e.g. in the dog, arrhythmias can be elicited following occlusion periods of up to 60 min. It may be that due to the much faster heart rate of the rat, cells in the ischaemic area die faster and hence the tissue is electrically inexcitable by 20–30 min post-ligation. Indeed by this time, even if the occlusion is still present, the early arrhythmias have virtually ceased (Clark *et al.*, 1980). The 5 rather than 15 min occlusion period before release of the ligature was selected for further experiments thus avoiding the exclusion of animals from the reperfusion study which died during the occlusion phase.

We have also shown in this study that such reperfusion-induced arrhythmias in the rat are unaffected by bilateral vagotomy, β_1-adrenoceptor blockade with atenolol or a combination of the two. It would seem unlikely, therefore, that the autonomic nervous system plays a major role in the genesis of these arrhythmias. This is in contrast to occlusion-induced arrhythmias in both the cat and the rat, the severity of which has been shown to be reduced by removal of both parasympathetic and sympathetic nervous influences (Gillis, 1971; Harris *et al.*, 1982).

Comparable studies relating to the effects of vagotomy either alone or in combination with β-blockade specifically on the severity of reperfusion-induced arrhythmias do not appear to have been done in other species. However, it has been shown that β-adrenoceptor blocking agents *per se* do not appear to protect against this type of arrhythmia (Sheridan *et al.*, 1980; Williams *et al.*, 1982). Furthermore, propranolol was ineffective in preventing the change in ventricular fibrillation threshold observed following reperfusion (Corbalan *et al.*, 1976) supporting our observation that β-blockade is not protective against this type of arrhythmia.

The drugs which we found to be effective antiarrhythmics in this model were Org 6001, melperone and bepridil. As in the rat *in vivo* both Org 6001 and bepridil have been shown to prevent reperfusion-induced fibrillation in the perfused isolated heart of the rat (Winslow *et al.*, 1980; Marshall *et al.* 1982). This antiarrhythmic action of Org 6001 is likely to be related to its ability to reduce the fast inward sodium current in cardiac tissue, a Class I effect according to the Vaughan Williams classification (Salako *et al.*, 1976). Other Class I antiarrhythmic drugs such as lignocaine, quinidine and procainamide have also been shown to reduce the severity of reperfusion induced arrhythmias in the rat (Lubbe *et al.*, 1978; Bergey *et al.*, 1982) although in the dog conflicting results concerning their effectiveness have been obtained (Naito *et al.*, 1981; Bergey *et al.*, 1982).

Melperone and bepridil also share this property of reducing the fast inward sodium current in cardiac tissue (Kane & Winslow, 1980; Millar & Vaughan Williams, 1983) but they have other effects which might underly their antiarrhythmic actions. For instance, melperone is an α-adrenoceptor blocking agent (Peterson, 1981) and it prolongs the duration of the cardiac action potential (Arlock, 1978). Both of these actions may contribute to the marked protection against reperfusion-induced arrhythmias since drugs with similar properties such as prazosin (Sheridan *et al.*, 1980) and amiodarone (Lubbe *et al.*, 1979) have also been reported to be effective. Bepridil is also a calcium channel blocker (Vogel *et al.*, 1979) but the fact that the other calcium antagonists studied were ineffective in this model suggests that in the case of bepridil, its effects on the fast sodium channel may be of more importance. It should also be noted, that in doses which were antiarrhythmic in this study, Org 6001, melperone and bepridil all significantly reduced heart rate. A reduction in heart rate, *per se*, however, cannot be the basis of their antiarrhythmic action since atenolol also had a marked negative chronotropic effect but was not antiarrhythmic. This does not of course exclude the possibility that these drugs may be acting by suppression of abnormal automaticity in the myocardium.

Nitroglycerine was found to be ineffective against these reperfusion-induced arrhythmias. This is in contrast to the results obtained by Stockman *et al.* (1979) who reported a reduction in the incidence of reperfusion fibrillation in the dog particularly when nitroglycerine was administered with phenylephrine. It may be that in our experiments any possible antiarrhythmic effect of the drug was masked either by the unusually low incidence of fibrillation in the solvent control group or by the rather marked fall in arterial blood pressure observed, which presumably in the experiments of Stockman *et al.*, (1979) was coun-

teracted by the simultaneous administration of phenylephrine.

The other calcium antagonists studied, verapamil, nifedipine and prenylamine were also not antiarrhythmic in this model. In the case of both nifedipine and verapamil some dog studies have shown protection (Brooks et al., 1980; Coker & Parratt, 1983) whilst others have not (Ribeiro et al., 1980; Naito et al., 1981). In the isolated working heart of the rat, prenylamine but not nifedipine reduced the severity of reperfusion arrhythmias (Manning et al., 1983) and prenylamine has also been shown to protect against the fall in ventricular fibrillation threshold observed upon reperfusion in the dog (Schoeneberger et al., 1979). These conflicting results may be due to differences in species, in doses used, or it may be that the size of the ischaemic area is crucial to the beneficial effect of this type of drug. For instance, in the in vitro studies with prenylamine, a concentration high enough to exhibit Class I antiarrhythmic activity was used but we have observed that in the rat in vivo, such concentrations cannot be studied due to their marked vasodepressor actions. At the concentrations used in the present study, all of these calcium antagonists (i.e. verapamil, nifedipine and prenylamine) reduce the severity of the early arrhythmias that occur when the occlusion is present (Fagbemi & Parratt, 1981; Fagbemi et al., 1983). This suggests that these reperfusion-induced arrhythmias show a different sensitivity to drugs with calcium channel blocking activity than those which occur upon occlusion, but are similarly influenced by drugs that possess Class I antiarrhythmic activity (Kane et al., 1980).

In summary, therefore, we have described a model which consistently elicits a high incidence of reperfusion-induced arrhythmias in the anaesthetized rat. These arrhythmias, in contrast to those that occur when the occlusion is present, do not appear to be influenced by alterations in autonomic nervous activity or by administration of calcium channel blocking drugs. However, drugs that block the fast inward sodium channel are effective, particularly in reducing the incidence of reperfusion-induced ventricular fibrillation.

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