

# Effects of prostaglandin E<sub>2</sub>, propranolol and nitroglycerine with halothane, pethidine or pentobarbitone anaesthesia on arrhythmias and other responses to ligation of a coronary artery in rats

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- 1 The effects of various cardiovascular drugs (prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), propranolol and nitroglycerine) and anaesthetic regimens (halothane, pethidine and pentobarbitone), upon the outcome of coronary artery ligation in acutely prepared rats were determined.
- 2 Effects upon arrhythmias, blood pressure, heart rate, mortality, ECG and the size of the occluded zone were determined for each drug in the presence of each anaesthetic.
- 3 PGE<sub>2</sub> and nitroglycerine had no statistically significant effects on the outcome of ligation whatever the anaesthetic. Propranolol had limited antiarrhythmic actions.
- 4 The anaesthetic used had major effects upon the outcome of ligation, regardless of the cardiovascular drugs administered.
- 5 Pentobarbitone anaesthesia resulted in the highest mortality, and most arrhythmias.
- 6 Pethidine-N<sub>2</sub>O anaesthesia was associated with fewer arrhythmias.
- 7 Halothane-N<sub>2</sub>O anaesthesia markedly decreased the incidence and severity of arrhythmias, independent of the cardiovascular drug.
- 8 It was concluded that the anaesthetic used can have a major influence on ligation-induced arrhythmias in acutely prepared anaesthetized rats.

## Introduction

The rat is increasingly used for studying the effects of antiarrhythmic, and other drugs, on arrhythmias and other responses to ligation of a coronary artery. Au, Collins, Harvie & Walker (1979a), Clark, Foreman, Kane, McDonald & Parratt (1980) and Marshall, Muir & Winslow (1981) have all described methods for producing coronary ligation in open-chest anaesthetized rats. Lepran, Koltai & Szekeres (1980), Kane, Lepran, McDonald, Parratt & Szekeres (1980) and Johnston, MacLeod & Walker (1981) have also described chronic preparations for ligation studies in conscious rats so avoiding complications of recent surgery and anaesthesia.

To determine what effect an anaesthetic has on the outcome of ligation in acutely prepared anaesthetized rats, we investigated three different types of anaesthetics in animals treated with three drugs which may have beneficial actions in myocardial ischaemia. The anaesthetics given were halothane-

nitrous oxide in oxygen, pethidine (i.v.)-nitrous oxide in oxygen and the standard laboratory anaesthetic, pentobarbitone. Drugs tested included propranolol, which has been shown, but not in conscious rats (Botting, Johnston, MacLeod & Walker, 1983), to have beneficial antiarrhythmic and other actions following coronary ligation (see Parratt, Campbell & Fagbemi, 1981); nitroglycerine which may have beneficial actions (Epstein, Kent, Goldstein, Borer & Redwood, 1975; Opie, 1980) and PGE<sub>2</sub>. We have shown infusions of PGE<sub>2</sub>, begun before ligation, reduced arrhythmias produced by ligation in anaesthetized rats (Au *et al.*, 1979a). In this study, we determined whether an infusion of PGE<sub>2</sub>, started immediately after ligation, had the same effect as that previously shown for infusions started pre-ligation. Drugs and anaesthetics were given according to a randomized block design such that each drug and vehicle control, was examined in

the presence of each anaesthetic. This procedure resulted in an array of 12 drug-anaesthetic groups (4 drug treatments, including saline control, times 3 anaesthetics). In order to reveal anaesthetic effects, independent of drug treatment, and drug effects, independent of anaesthetic regimen, we accumulated data for each anaesthetic regimen ( $n = 24$ ) and for each drug treatment ( $n = 18$ ). This method of analysis allowed drug effects, anaesthetic effects and drug-anaesthetic effects to be analysed separately. An initial communication of parts of this work has been given (Au, Collins, MacLeod & Walker, 1979b).

## Methods

### Anaesthetics

Anaesthesia was produced in one of three ways: pentobarbitone ( $50 \text{ mg kg}^{-1}$ ) i.p.; halothane (0.5–1.0%)-nitrous oxide (30%) in oxygen; or pethidine ( $1 \text{ mg kg}^{-1}$  i.v.) with nitrous oxide (30%) in oxygen. A constant level of surgical anaesthesia was maintained by intravenous injections of pentobarbitone or pethidine, or by altering the inspired halothane concentration to abolish reflex responses to a standardized squeeze of a hind foot. Rats receiving halothane- $\text{N}_2\text{O}$  or pethidine- $\text{N}_2\text{O}$  anaesthesia, were induced with  $10 \text{ mg kg}^{-1}$  thiopentone (i.v.). All rats were ventilated at  $1 \text{ ml kg}^{-1}$  at a rate of 60 per min through an endotracheal tube (Jelco 14 G. i.v. catheter). Blood gases ( $\text{O}_2$  and  $\text{CO}_2$ ) and blood pH were maintained at normal levels.

### Drug treatments

Drugs were administered for 3 h after ligation, beginning 2 min post-ligation, according to the following schedules:  $\text{PGE}_2$  was infused at  $1 \mu\text{g kg}^{-1} \text{ min}^{-1}$  after a  $1 \mu\text{g kg}^{-1}$  bolus. Nitroglycerine was given at  $5 \mu\text{g kg}^{-1}$  followed by a  $20 \mu\text{g kg}^{-1} \text{ min}^{-1}$  infusion. Propranolol was given at  $0.2 \text{ mg kg}^{-1}$  followed by a  $1.0 \mu\text{g kg}^{-1} \text{ min}^{-1}$  infusion. In trial experiments, this propranolol schedule produced a maintained 10–20 dose ratio shift of isoprenaline dose-response (tachycardia or blood pressure fall) curves. All drug solutions were kept at  $0^\circ\text{C}$  in 0.9% saline containing 3% ethanol and  $40 \text{ mg ml}^{-1}$  lactose. They were matched in appropriate dilutions and given at a maximum infusion volume of  $1 \text{ ml kg}^{-1} \text{ h}^{-1}$ . The experimenter was unaware of the drug given.

### Surgical preparation

Two groups of male Wistar rats, weighing 300–400 g, were used for left anterior descending (LAD) coronary artery ligation according to our

variation (Au *et al.*, 1979a) of the technique of Selye, Bajusz, Grasso & Mendell (1960). Under clean conditions a lateral chest wall incision was used to expose the heart and a loose ligature was placed through the tissue surrounding the LAD artery using a 6.3 mm curved needle and 4–0 silk. Blood pressure was recorded from a ventral tail artery through a 22 G. cannula (Jelco i.v. catheter). The pulse pressure by this technique varied from 10 to 55 mmHg. Injections, or infusions, were via a 23 gauge needle in a lateral tail vein.

### Ligation

Ligation was performed after 30 min stabilization. If ventricular tachycardia or fibrillation occurred, and the animal did not spontaneously defibrillate within 10 s, reversion was attempted with sharp chest taps. Defibrillation, spontaneous or induced (1–3 taps), occurred in 95% of cases. If mean blood pressure fell below 30 mmHg for 5 min, or more, the rat was killed. After ligation, the chest incision was closed and 3 h later the pneumothorax was reduced, sutures made permanent, and cannulae sealed. Wounds were infiltrated with bupivacaine (0.5%) and anaesthesia discontinued. Twenty four hours later, after a second blood pressure recording, the animal was killed, and its heart removed. The heart was perfused (Langendorff Technique) with Krebs solution at  $30^\circ\text{C}$  and 100 mmHg pressure before dye perfusion to reveal unperfused pale tissue (*occluded zone*) which was weighed and recorded as percentage of total ventricular weight. This estimation was performed blind.

### Arrhythmias

Arrhythmias were detected from ECG and blood pressure records. The incidence of premature ventricular contractions (PVC), ventricular tachycardia, ventricular flutter and ventricular fibrillation were recorded. The latter were often difficult to differentiate from each other and so were grouped as one event (VT-VF). The incidence, number and duration of episodes of VT-VF were recorded together with ease of reversion by precordial taps (number of taps noted).

### Arrhythmia scoring

PVC incidence was scored as  $\log_{10}$  total PVC in the 3 h post-ligation period.  $\log_{10}$  PVC data are normally (Gaussian) distributed and thus permit the use of parametric statistics.

A previously described (Au *et al.*, 1979a), arrhythmia scoring system was also used. It is similar to, but not identical to the one we used in conscious rats (Johnston *et al.*, 1981). Both were designed to permit

**Table 1** Mortality 3 h after coronary artery ligation

<i>(a) Drug-anaesthetic groups</i>	<i>Saline</i>	<i>PGE<sub>2</sub></i>	<i>Propranolol</i>	<i>Nitroprusside</i>
Pentobarbitone	1/6	1/6	1/6	0/6
Halothane-N <sub>2</sub> O	0/6	1/6	0/6	2/6
Pethidine-N <sub>2</sub> O	1/6	1/6	2/6	1/6
<i>(b) Drug groups</i>	<i>Arrhythmic</i>	<i>Non-Arrhythmic</i>		<i>Total</i>
Saline	2/18	0/18		2/18
PGE <sub>2</sub>	2/18	1/18		3/18
Propranolol	3/18	0/18		3/18
Nitroprusside	1/18	2/18		3/18
<i>(c) Anaesthetic groups</i>				
Pentobarbitone	3/24	0/24		3/24
Halothane-N <sub>2</sub> O	0/24	3/24		3/24
Pethidine-N <sub>2</sub> O	5/24	0/24		5/24

Details of drug treatments and anaesthetic regimens are given in Methods. In (a) mortality by 3 h post-ligation is considered for each of the 12 drug-anaesthetic groups. Mortality data are also accumulated for each drug group, regardless of anaesthetic used, (b), ( $n = 18$ ) and for anaesthetic groups regardless of drug treatment (c), ( $n = 24$ ), in an attempt to reveal drug or anaesthetic effects. No statistical differences were observed.

the use of parametric statistical tests. They assign integer values to the severity of arrhythmias as determined by the type of arrhythmia, its incidence and duration.

ECGs were analysed for Q-waves, changes in RS-waves (as a measure of QRS complex size) and in T-waves as an index of ischaemia-induced 'S-T' segment changes. The recorded ECG, heart rate and blood pressure were sampled, for analysis, at  $-10$ ,  $-1$ ,  $2$ ,  $5$ ,  $10$ , and  $30$  min as well as  $1$ ,  $3$  and  $24$  h. Zero represents the time of ligation. The number of rats dead by the end of the 3 h treatment period was recorded.

#### *Experimental design and statistical analysis*

The statistical null hypothesis test was; anaesthetic or drug treatments do not influence responses to ligation in the rat. In the 12 groups, each of six rats, drug administration was blind and random. Choice of anaesthetic was random, but administration could not be blind.

Statistical evaluation was by analysis of variance using computer packages (GENLIN (Greig & Bjerring, 1978) and ANOVAR (Greig & Osterlin, 1977)). Statistical significance is shown by \* for  $P < 0.05$  for difference from appropriate means by Duncan's multiple range test. Means are given either for individual (drug-anaesthetic) groups ( $n = 6$ ), for accumulated drug ( $n = 18$ ) or accumulated anaesthetic ( $n = 24$ ) groups.

## **Results**

All anaesthetics produced a satisfactory anaesthesia as judged by equal obtundation of responses to stimuli. There was no evidence of adverse interactions between drugs and anaesthetics.

The typical response to ligation of the coronary artery consisted of a fall in blood pressure, change in ECG and the development of arrhythmias. ECG changes were a rapid rise in RS-wave size (QRS complex) followed by 'S-T' segment changes. The RS-wave increase began within  $1-2$  s of ligation and was maximal within 60 s. 'S-T' segment changes began more slowly (2 min) and were maximal within 1 h. Q-waves occasionally appeared 1 to 3 h after ligation.

A typical arrhythmic response consisted of occasional PVC on ligation, sinus rhythm for 4–5 min, followed by the reappearance of PVC. By 10 min after ligation, bouts of ventricular tachycardia, flutter and/or fibrillation occurred. Arrhythmias usually occurred within 30 min of ligation, although some later episodes were seen.

Mortalities with treatments are shown in Table 1. The 3 h mortality was approximately the same for all drug and anaesthetic groups. However, while most mortality was due to irreversible VT-VF, halothane-treated rats died of non-arrhythmic cardiac output failure. None of the treatments altered occluded zone size to a statistically significant degree and there was no obvious correlation between occluded zone size

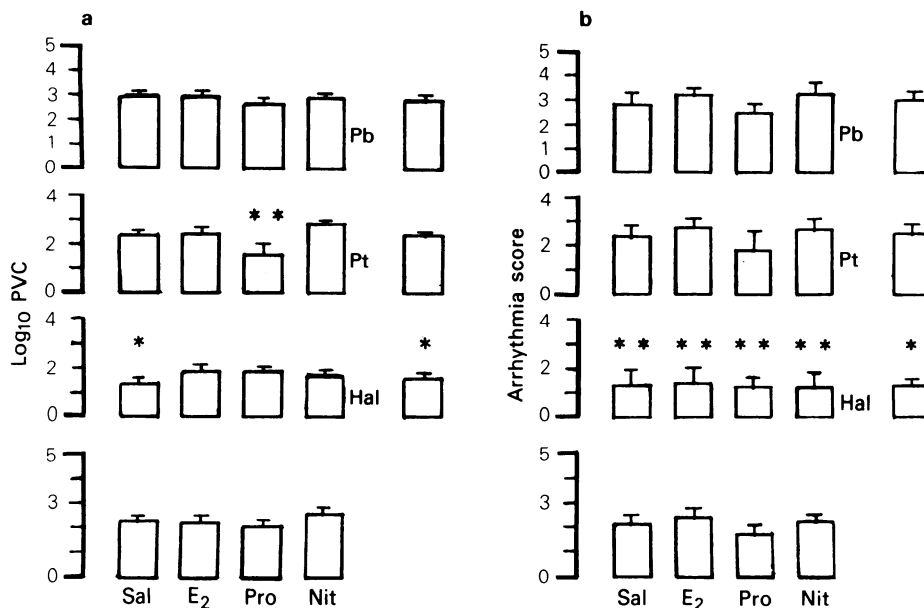
(between 28% and 35% of the total weight of the ventricles) and mortality.

Antiarrhythmic effects of the treatments (drugs or anaesthetics) are summarized in Figures 1 and 2 as  $\log_{10}$  PVC and arrhythmia score (Figure 1), and as the incidence and duration of VT-VF (Figure 2). The arrhythmia score (Figure 1b) incorporates both PVC and VT-VF and summarizes arrhythmia history.

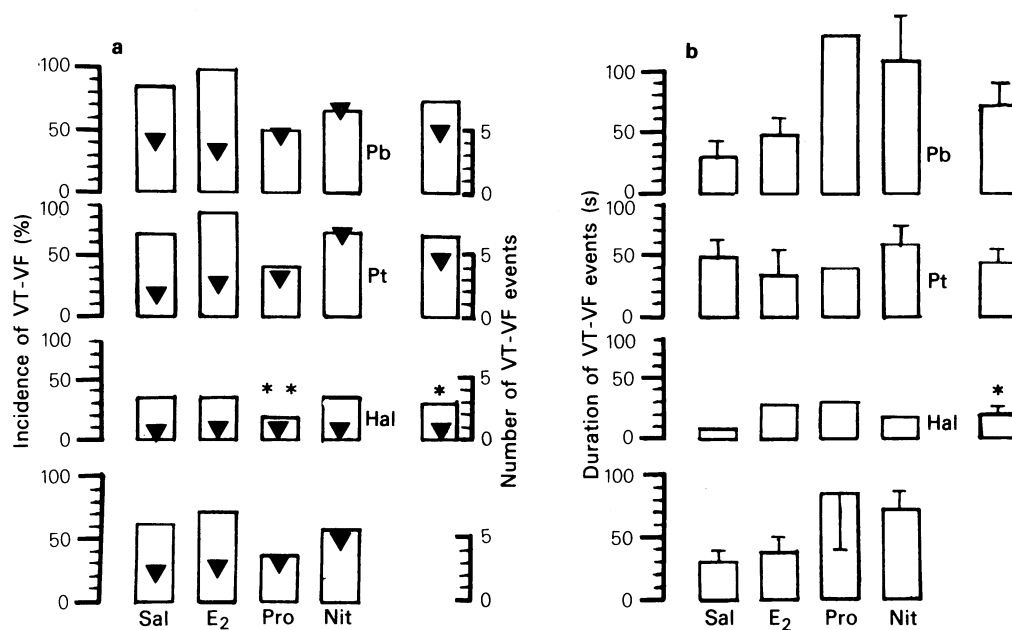
Figures 1 and 2 show that the major antiarrhythmic effect was due to halothane anaesthesia and not to drug treatments. In the presence of halothane, the  $\log_{10}$  PVC values (Figure 1a) were lower for all drug treatments, although only statistically so for the control group. When the accumulated anaesthetic groups were examined, halothane statistically significantly reduced PVC. The pethidine group had fewer PVC than the pentobarbitone group. In accumulated drug groups statistically significant reductions were not seen, although values were least for propranolol-treated rats.

Arrhythmia score (Figure 1b) is a better indicator of antiarrhythmic effects. Again, the most powerful influence was that due to halothane. With halothane, all treatments including saline, statistically significantly reduced arrhythmia score when compared with high values (pentobarbitone groups). Accumulated halothane values were statistically less than those for either pethidine or pentobarbitone. Mean values ( $\pm$  s.e.mean) were  $1.2 \pm 0.3$ ,  $2.5 \pm 0.3$  and  $3.0 \pm 0.4$ , respectively. Thus arrhythmias with halothane were decreased 40% when compared with pethidine and 80% when compared with pentobarbitone. In accumulated drug groups, propranolol produced the lowest scores.

VT-VF occurrence is analysed in Figure 2. Halothane statistically reduced the incidence of one or more episodes of VT-VF (Figure 2a). The propranolol-halothane group had a statistically significant lower incidence compared with the propranolol-pentobarbitone group. This antiar-



**Figure 1** Arrhythmias as  $\log_{10}$ PVC (a) and arrhythmia score (b) by 3 h postligation in the various drug-anaesthetic groups. A total of 12 groups (control vehicle, PGE<sub>2</sub>, propranolol and nitroglycerine, with one of three anaesthetics, pentobarbitone, pethidine-N<sub>2</sub>O, and halothane-N<sub>2</sub>O) were examined. Values are given for each individual drug-anaesthetic group and accumulated drug (bottom row) and anaesthetic groups (last column). In (a) the mean  $\pm$  s.e.mean number of PVC (as  $\log_{10}$ ) is shown, while (b) shows the mean arrhythmia score ( $\pm$  s.e.mean). Sal indicates vehicle control, E<sub>2</sub> is PGE<sub>2</sub> infused for 3 h as  $1.0 \mu\text{g kg}^{-1} \text{min}^{-1}$  beginning 2 min post-ligation, Pro is propranolol  $0.2 \text{ mg kg}^{-1}$  bolus plus  $1.0 \mu\text{g kg}^{-1} \text{min}^{-1}$  and Nit is nitroglycerine  $5 \mu\text{g kg}^{-1}$  bolus plus  $20 \mu\text{g kg}^{-1} \text{min}^{-1}$ . For the anaesthetics, Pb is pentobarbitone  $50 \text{ mg kg}^{-1}$  i.p., Pt is pethidine ( $1 \text{ mg kg}^{-1}$  plus N<sub>2</sub>O) anaesthesia, while Hal is halothane (0.5–1.0%) plus N<sub>2</sub>O anaesthesia. For each drug-anaesthetic group  $n = 6$ , for each accumulated anaesthetic group  $n = 24$ , and for each accumulated drug group  $n = 18$ . S.e.mean values are not given when  $n < 5$ . \*Indicates a mean different from other means in group at  $P < 0.05$ . \*\*Indicates that the mean was statistically significantly different from highest values in comparison group. Analyses were made for the 12 drug-anaesthetic groups, for the 3 accumulated anaesthetic groups and for the 4 accumulated drug groups.



**Figure 2** Arrhythmias as the group incidence, number and duration of VT-VF events by 3 h post-ligation. Details of treatments and groups are as in the previous figure. In (a) the column height indicates the group incidence of VT-VF while the symbol ▼ indicates the average number of such events (scale is on right hand side). (b) shows the mean duration ( $\pm$ s.e.mean) of VT-VF events where zero values are ignored. Significance values, drugs and anaesthetics are as in the previous figure (Figure 1).

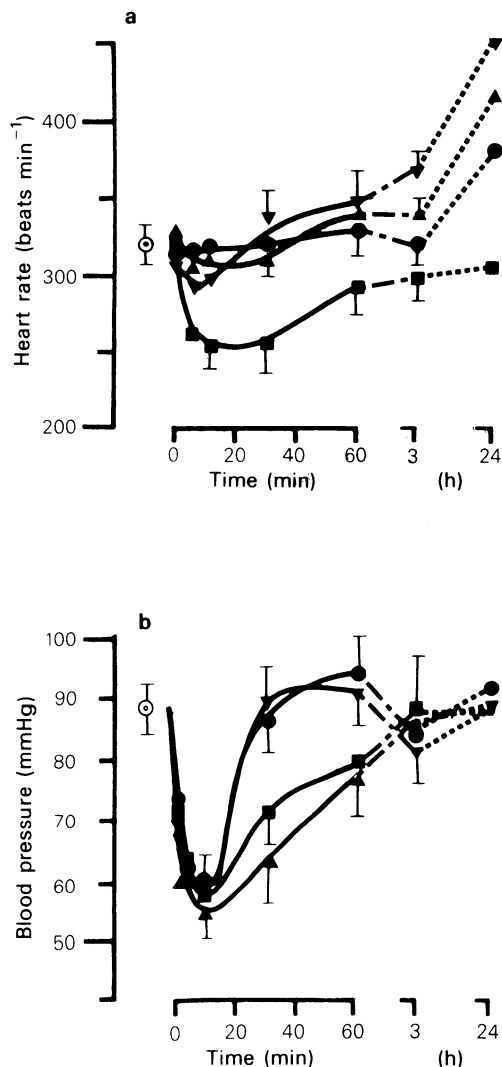
rhythmic effect of halothane was best seen in the accumulated anaesthetic groups where, in addition to reducing the incidence of VT-VF, it also appeared to reduce the number of episodes of VT-VF in those animals having VT-VF.

Finally (Figure 2b), halothane statistically reduced the duration of VT-VF events. However, the non-normally distributed nature of duration, and the small *n* values, prevented statistical significance being reached amongst the drug-anaesthetic groups.

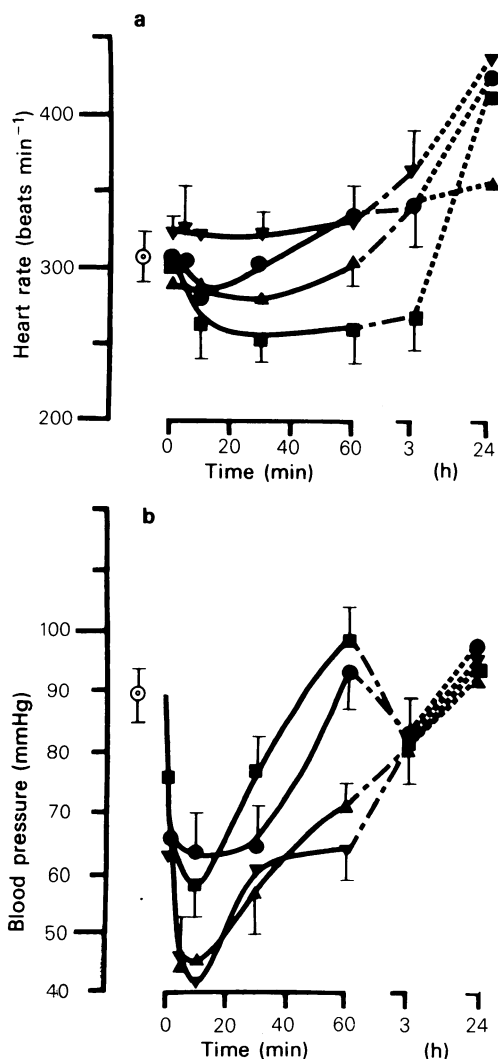
In the ECG, an analysis of RS-wave changes, T-wave changes, and Q-wave appearance in drug-anaesthetic groups showed no major effects of drug and/or anaesthetic treatments. RS-wave and T-wave changes were not significantly different for any of the various groupings. T-wave values (expressed as mean  $\pm$  s.e.mean) varied from  $90 \pm 58 \mu\text{V}$  for halothane to  $120 \pm 90 \mu\text{V}$  for pentobarbitone. RS-wave heights were similar. Thirty min after ligation, 30–40% of animals showed Q-waves and 24 h later 50–80% of each group showed Q-waves. Time to Q-wave appearance indicated that they tended to appear earlier with pentobarbitone, although neither the time nor the highest incidence of Q-waves (in the pentobarbitone group) was statistically significant.

Figures 3, 4 and 5 summarize heart rate and mean blood pressure responses. Heart rates varied with anaesthetic and drug treatment; propranolol lowered heart rates to 250 beats  $\text{min}^{-1}$  by 10–30 min post-ligation. Anaesthesia and surgery also lowered heart rates (particularly with pentobarbitone) and ligation caused an additional fall. Heart rates with nitroglycerine and PGE<sub>2</sub> were not different from controls.

Anaesthetics had marked effects on blood pressure; pressures with halothane (Figure 3b) and pentobarbitone (Figure 4b) were lower than with pethidine (Figure 5b) by 20 mmHg. Ligation produced dramatic falls in mean blood pressure and the fall was greatest with pentobarbitone (Figure 4b) and least with halothane (Figure 3b). By 3 h post-ligation, blood pressures had returned to pre-ligation values, with the rate of return most rapid with halothane. By 3 h post-ligation, all drug-treated groups had lower blood pressures than saline controls. The lowest blood pressures were encountered with nitroglycerine and PGE<sub>2</sub> infusions in the presence of pentobarbitone anaesthesia (Figure 4b). Twenty-four hours after ligation, blood pressures were similar for all groups.



**Figure 3** The effect of drugs in the presence of halothane-N<sub>2</sub>O anaesthesia on heart rate and blood pressure. In (a) each point represents the average heart rate for the different drug groups anaesthetized with halothane. The time axis indicates post-ligation time zero being the time of ligation of the left anterior descending coronary artery. In (b) each point represents the mean of mean blood pressures for the groups. Standard errors are indicated by bars; they are omitted when *n* was small or values overlapped. Each point is the mean of 4-6 determinations, except for the 3 and 24 h values where the number of surviving animals was smaller. In (a) and (b) (▲) = PGE<sub>2</sub>; (▼) = nitroglycerine; (■) = propranolol, and (●) = vehicle control. For exact details of treatments, see Methods. The symbol (○) indicates the mean for overall anaesthetic group at 10 min before ligation.



**Figure 4** The effect of drugs in the presence of pentobarbitone anaesthesia on heart rate and blood pressure at different post-ligation times. Details are as in Figure 3 except that the anaesthetic was pentobarbitone: (a) shows heart rate and (b) shows blood pressure with (▲) = PGE<sub>2</sub>; (▼) = nitroglycerine; (■) = propranolol, and (●) = vehicle control.

## Discussion

This study demonstrates that choice of anaesthetic is a major determinant of outcome after coronary artery ligation in acutely prepared rats. Most studies of drug effects on arrhythmias induced by ligation have used acutely-prepared pentobarbitone-anaesthetized animals, such as rats and dogs, al-

though the influence of this anaesthetic regimen had not been rigorously assessed (Fozzard, 1975).

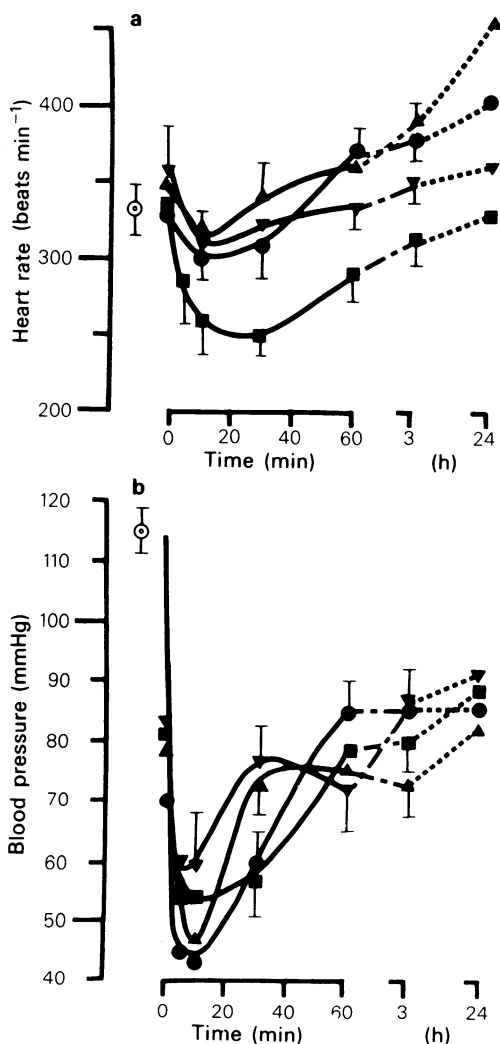
The importance of anaesthetic regimen in this study was particularly marked for halothane. It gave such a low incidence of arrhythmias that it may be difficult to detect other antiarrhythmic actions in its presence. Pentobarbitone, however, gave a great increase in arrhythmia incidence; presumably, this increased incidence is one reason for the wide use of pentobarbitone. However, pentobarbitone, while permitting many arrhythmias, may also hide weak antiarrhythmic effects. Propranolol had antiarrhythmic effects and these were best seen when the anaesthetic was pethidine- $N_2O$ .

The antiarrhythmic effect of halothane may be, at first sight, difficult to understand, in view of its ability to potentiate the arrhythmogenic actions of catecholamines (Zink, Sasyniuk & Dresel, 1975). However, the arrhythmogenic action of ischaemia is probably different, in both magnitude and aetiology, from catecholamine arrhythmogenesis. Halothane, when compared with conscious controls, was antiarrhythmic in chronically prepared rats subjected to ligation (MacLeod, Augereau & Walker, 1983). This action was seen at sub-anaesthetic concentrations and has also been seen with anaesthetic concentrations of chloroform and enflurane, but not with other halogenated hydrocarbons (Jang, MacLeod & Walker, 1983). Similar results have been described in dogs (Fukuyama, Marmor & Roberts, 1981; Kroll & Knight, 1982).

A decreased severity of arrhythmias with halothane may be due to direct myocardial effects, changes in haemodynamics, or to electrophysiological actions. Changes in occluded zone correlate with arrhythmia incidence, (Austin, Wenger, Harrell, Luzzi & Strauss, 1982), but, as halothane did not change the size of the zone in our study this was not the mechanism of antiarrhythmic action. Halothane has marked actions upon myocardial action potentials which may be antiarrhythmic (Lynch, Vogel & Sperelakis, 1981).

The relative lack of effect of the drugs tested in this study, compared with halothane, was most noticeable. In rats, prostaglandin infusions begun pre-ligation, have antiarrhythmic actions against ligation-induced arrhythmias (Au *et al.*, 1979a; Martinez & Crampton, 1981). The lack of effect with a  $PGE_2$  infusion begun post-ligation indicates that pre-ligation infusion somehow reduces the subsequent arrhythmogenic actions of ischaemia.

Propranolol, at a dose producing a moderate  $\beta$ -blockade, had a real but limited antiarrhythmic action. This is in contradiction to a study in conscious rats where propranolol (acute and chronic treatment) had no antiarrhythmic action; sympathectomy and labetalol made arrhythmias worse (Botting *et al.*,



**Figure 5** The effect of drugs in the presence of pethidine- $N_2O$  anaesthesia on heart rate and blood pressure at different post-ligation times. Details are as in Figure 3 except that the anaesthetic was pethidine- $N_2O$ : ( $\nabla$ ) =  $PGE_2$ ; ( $\Delta$ ) = nitroglycerine; ( $\blacksquare$ ) = propranolol, and ( $\bullet$ ) = vehicle control.

1983). Parratt *et al.*, (1981) and Parratt (1980) have carefully discussed the action of  $\beta$ -blockers in ischaemia and infarction. Propranolol was variously antiarrhythmic (see their Table 4) in different studies in dogs but not in rats. However, other  $\beta$ -blockers, such as oxprenolol and pindolol were antiarrhythmic (Campbell & Parratt, 1981). Propranolol probably has weak but real antiarrhythmic actions at  $\beta$ -blocking doses (as opposed to local anaesthetic

doses) which requires testing of large numbers of animals to reveal.

Nitroglycerine decreases myocardial damage under some circumstances (Epstein *et al.*, 1975; Chiariello, Gold, Leinbach, Davis & Maroko, 1976). In our study the effect of the anaesthetic may well have overwhelmed the beneficial effects of this drug (and perhaps the other drugs). Changes in blood pressure with ligation varied with the anaesthetic used. Blood pressure changes may have altered the conditions of the myocardium sufficiently that nitroglycerine was not beneficial under our experimental conditions.

Our experiments have shown that anaesthetic regimen influences the outcome of coronary ligation experiments and interactions between anaesthetic and drug may mask or distort drug effects. Studies of the effects of drug treatments upon the outcome of coronary ligation should be repeated, where possible, in conscious chronically-prepared animals.

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