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The effects of ablations in the central nervous system on arrhythmias induced by coronary occlusion in the rat

M.J. Curtis, B.A. Macleod & M.J.A. Walker

Department of Pharmacology & Therapeutics, Faculty of Medicine, The University of British Columbia, 2176 Health Sciences Mall, Vancouver, B.C., V6T 1W5, Canada

1 The role of the central nervous system (CNS) in arrhythmogenesis in the 4 h period following occlusion of a coronary artery was investigated in rats by use of CNS ablations and other procedures.

2 Ablations in the CNS included pithing, spinalization and decerebration combined with acute and chronic surgical preparation and noradrenaline/adrenaline infusions.

3 All procedures involving acute surgery reduced the incidence and severity of the arrhythmias induced by occlusion. Such reductions were most marked in the second (0.5–4 h post-occlusion) arrhythmic period.

4 The observed reductions in arrhythmias could not be explained in terms of involvement of the CNS or adrenoceptor activation.

5 When circulating leucocytes, platelets and serum potassium were measured in a group of pithed rats before and after occlusion, reduced levels (20–50%) of both leucocytes and platelets occurred while serum potassium levels rose by 50–100%.

6 Arrhythmias following coronary occlusion may depend in part on factors in the blood such as leucocytes, platelets and serum potassium and these factors may be altered by acute surgery.

Introduction

Arrhythmogenesis following the onset of myocardial ischaemia is believed to result from disordered electrophysiology which in turn depends primarily on ischaemia, and secondarily upon factors that may or may not act independently, namely the activity of the sympathetic system, heart rate and blood pressure (Harris *et al.*, 1951; Gillis, 1971; Myers *et al.*, 1974; Hope *et al.*, 1974; Fowliss *et al.*, 1974).

We routinely produce ischaemia-induced arrhythmias in conscious rats by occlusion of the left anterior descending coronary artery, and have investigated some of the factors mentioned above. Analysis of covariance in over 250 conscious rats showed no correlation between arrhythmias and blood pressure and/or heart rate (Johnston *et al.*, 1983). We have also shown that, in conscious rats, propranolol (acute or chronic treatment), labetalol, or 6-hydroxydopamine (6-OHDA) plus adrenalectomy do not influence arrhythmias produced by coronary occlusion (Botting *et al.*, 1983). However, others, using conscious rats, have found chronic treatment with β-adrenoceptor blockers reduces arrhythmias (Siegmund *et al.*, 1979; Szekeres, 1979).

In acutely prepared anaesthetized rats we found propranolol to have very weak antiarrhythmic activity (Au *et al.*, 1983), although others have demonstrated more powerful antiarrhythmic effects with β-blockers in anaesthetized animals (Campbell & Parratt, 1983). In addition, in anaesthetized rats, β-receptor activation has been found to exacerbate arrhythmias (Marshall *et al.*, 1981). Therefore the arrhythmogenic role of β-adrenoceptor activation remains contentious, although it appears to be more important in anaesthetized than in conscious rats.

In view of the contradictory evidence regarding the importance of the autonomic nervous system in arrhythmogenesis in the rat, we decided to investigate systematically the importance of adrenoceptor activation and the central nervous system, by a series of ablations in the CNS combined, in some cases, with catecholamine infusions.

In rats there are two well defined periods for arrhythmias following coronary occlusion (Johnston *et al.*, 1983). An early phase of arrhythmias begins within the first 5 min, and lasts for a further 5–15 min. A late phase begins approximately 1.5 h after occlusion and lasts for at least 4 h. The arrhythmias in this study have been sub-divided into early (0–30 min

Table 1 Summary of groups studied

Acutely prepared groups	*Code*
Conscious	aC
Anaesthetized	aB
Pithed	aP
Pithed plus catecholamine infusion	aPN
Spinalized	aS
Decerebrated	aD
Chronically prepared groups	
Conscious controls	cC
Conscious plus catecholamine infusion	cCN
Acutely pithed	cP
Others	
Isolated perfused hearts	I

Shown above are the ten groups studied. Details of the surgical preparation required for each group are given in the text.

post-occlusion) and late (30 min–4 h post-occlusion) for clarity. We have no evidence that arrhythmogenesis differs in a major way between the early and late periods, based on the antiarrhythmic actions of drugs in the rat (e.g., Johnston *et al.*, 1983), although we do not rule out this possibility.

Methods

Male Sprague Dawley rats (270–350 g) were used. The technique of coronary occlusion and the methods of measurement of all variables have been described in detail (Johnston *et al.*, 1983).

Ten groups ($n = 9$ per group) were studied. The groups are summarised in Table 1 and are described in detail as follows.

Acutely prepared (a) *rats*

Six groups of rats were surgically prepared and allowed to stabilise before coronary occlusion.

In one group, preparation consisted of inplantation of a floating abdominal aortic blood pressure line, V_3 ECG leads and a coronary occluder, under 1% halothane anaesthesia, as previously described (Johnston *et al.*, 1983). Rats in this group were allowed 1 h to recover from anaesthesia before coronary occlusion, and constituted an *acutely prepared* (a) *conscious* (C) group (i.e., aC).

A second group was prepared under pentobarbitone anaesthesia (60 mg kg^{-1}, i.p.) according to Clarke *et al.* (1980), except that our usual nylon/polyethylene occluder and V_3 ECG leads were used. Coronary occlusion took place after 15 min stabilization. This group constituted the *acutely prepared* (a) *barbiturate anaesthetized* (B) group (aB).

The four other groups were acutely prepared for coronary occlusion, as follows. Anaesthesia was induced with 4% halothane, and, following intubation, was maintained with 1% halothane in 100% O_2. A left carotid blood pressure catheter, right external jugular intravenous catheter, V_3 ECG leads and a loose coronary occluder were all implanted. Following this general preparation, the rats were subdivided and subjected to ablations in the CNS, under positive pressure respiration (stroke volume 10 ml kg^{-1}, 60 cycles min^{-1} using a Palmer pump), which produced P_{O_2} and P_{CO_2} levels within the normal range. The following ablations in the CNS were carried out.

In one group, a steel rod was inserted into the skull through the foramen magnum (level C1), advanced rostrally, and rotated laterally to macerate the brain. This constituted the *acutely prepared spinalized* group (aS). At the time of occlusion, spinal reflexes (such as foot withdrawal to toe pinching) were returning.

In another group, the brain rostral to the midcollicular level was removed using the blunt end (8 mm width) of a spatula, following removal of the overlying skull. The empty skull space was packed with gel foam. This was the *acutely prepared decerebrate* group (aD).

Two groups of rats were pithed via the orbit such that the brain and spinal cord were destroyed. The first of these 2 groups constituted the *acutely prepared, pithed* group (aP). The other group received catecholamine infusions beginning 15 min before occlusion, maintained throughout the experiment, and designed to elevate blood pressure to levels seen in conscious rats (approximately 120/80 mmHg). The infusion contained a noradrenaline/adrenaline mixture (4:1 on a weight basis), and infusion rate varied from 0.2 to 5 μg kg^{-1} min^{-1} noradrenaline. Infusion volume was always below 10 ml kg^{-1} h^{-1}. This group was the *acutely prepared, pithed, noradrenaline/adrenaline treated* group (aPN).

Following pithing, spinalization or decerebration, the halothane/O_2 mixture was replaced with O_2 alone, and the occluder was tightened after 30 min stabilization.

An attempt was made to increase venous return and as a consequence, blood pressure, by vertically mounting all acutely prepared pithed (aP and aPN) and spinalized (aS) rats. In preliminary experiments this manoeuvre resulted in a viable preparation (mean arterial blood pressure at least 60 mmHg) for more than 6 h. In the decerebrate group (aD), blood pressure was high, even when compared with conscious rats, and therefore this group received no postural cardiovascular support. Artificial respiration with

100% O_2 was maintained in all pithed and spinalized rats for the remainder of the experiment. Decerebrate rats (aD) breathed 100% O_2 spontaneously, and did not require artificial respiration. The rectal temperatures of pithed and spinalized rats were regulated by means of a heating lamp connected to a rectal thermocouple.

Chronically prepared (c) *rats*

Three groups of rats were chronically prepared according to our usual technique (Johnston *et al.*, 1983) with V_3 ECG leads, jugular i.v. catheters, abdominal aortic blood pressure catheter and coronary occluders. After 6–8 days, the rats were subjected to coronary occlusion.

Two of the chronically prepared groups received no ablations in the CNS. One of these constituted a group of *chronically prepared* (c) *conscious* (C) control rats (i.e., cC). The other group received an infusion of noradrenaline and adrenaline (in the same manner as the aPN group, starting 15 min before occlusion). This infusion was designed to elevate blood pressure to levels seen in the aD (decerebrate) group. This group constituted the *chronically prepared, conscious, noradrenaline/adrenaline treated* group (cCN).

The third group of chronically prepared rats was pithed 30 min before occlusion. This group constituted the *chronically prepared* acutely *pithed* group (cP). Following pithing, this group of rats received the same cardiovascular and respiratory support as the aP group.

Isolated hearts (I)

Hearts were removed from rats following cervical dislocation and exsanguination. During perfusion by the Langendorff method at 37°C with a Krebs-Henseleit solution (K^+ concentration 5.3 mEq) the left anterior descending coronary artery was occluded in a manner similar to that described by Woodward (1981). The high K^+ concentration was used to prevent pre-occlusion arrhythmias.

Measured variables

In all animals, blood pressure, heart rate, ECG and arrhythmias were continuously recorded for 30 min before occlusion of the left anterior descending coronary artery and for 4 h after occlusion. Occluded zone estimates (Johnston *et al.*, 1983) were made for all animals either immediately after death, at 4 h post-occlusion in anaesthetized and CNS ablated rats, or 24 h post-occlusion in surviving conscious rats.

Blood pressure and ECG were recorded with a Grass polygraph. A delayed loop ECG monitor (Honeywell, Model PM-2A) was used to help in arrhythmia analysis. As in our usual method, manual tapping of the chest wall was undertaken in an attempt to revert episodes of ventricular tachycardia (VT) and fibrillation (VF) lasting longer than 10 s. Deaths were classified as being arrhythmic or non-arrhythmic. In animals with intact nervous systems, non-arrhythmic death was considered to have occurred when mean blood pressure fell below 30 mmHg for 5 min. Arrhythmic deaths were those in which an irreversible severe arrhythmia occurred. When a severe arrhythmia reverted to sinus rhythm, but blood pressure subsequently remained below the levels stipulated above, a non-arrhythmic death was recorded. Characteristically, the latter occurred only in pithed animals.

Arrhythmia scores were determined as previously described (Johnston *et al.*, 1983). The arrhythmia score was as follows: 0 = no more than 49 premature ventricular contractions (PVC); 1 = 50–499 PVC; 2 = no more than 1 episode of spontaneously reverting VT or VF; 3 = more than 1 episode of VT and/or VF, irrespective of whether spontaneously or non-spontaneously reverting, lasting no more than 59 s total duration; 4 = VT and/or VF lasting 60–119 s total duration; 5 = VT and/or VF lasting for longer than 119 s total duration; 6 = death caused by VT or VF unresponsive to manual defibrillation, before 4 h post-occlusion; 7 = death caused by VT or VF before 15 min post-occlusion; 8 = death caused by VT or VF before 4 min post-occlusion; 9 = death caused by VT or VF before 1 min post-occlusion. The arrhythmia score for the 30 min to 4 h period was identical with the 0–30 min score with the exception that the scores 7; 8 and 9 were not used, since they refer to arrhythmia-induced death during the 0–15 min period following occlusion.

Leucocytes, platelet and serum potassium levels in aP rats

In a separate group of aP rats, blood samples were taken before pithing, 30 min after pithing, 1 min before occlusion, 30 min and 4 h after occlusion. Erythrocyte, differential white blood cell and platelet counts were made by conventional techniques. Samples of serum were used to determine potassium concentrations with a Kodak Ektachem 400 Analyzer.

Statistical analysis was by the procedures previously described (Johnston *et al.*, 1983). Gaussian distributed variables are expressed as mean ± s.e.mean. For the sake of simplicity, each group was compared with conscious chronically prepared controls (cC) in the results section, although full range test data are available on request. In view of the complex nature of the preparations it was not possible to perform blind experiments although a random design was used.

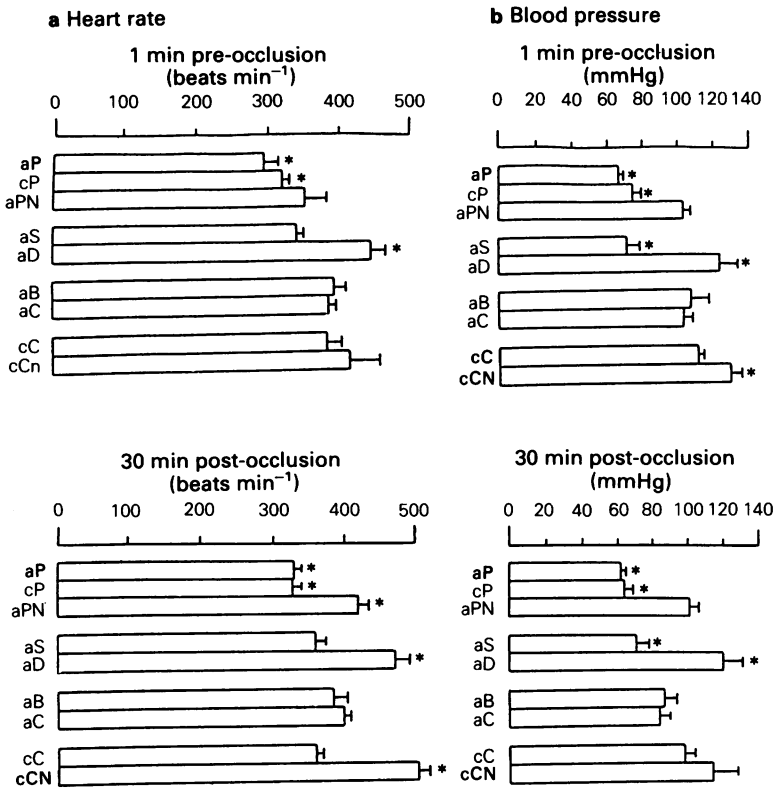

Figure 1 Heart rates (a) and blood pressure (b) before (− 1 min) and after (30 min) coronary occlusion. Each value is $\bar{x}$ of 5–9 animals with s.e.mean shown by horizontal lines. Groups are indicated by the code: a for acutely prepared, c for chronically prepared, P for pithed, S for spinalized, D for decerebrate, B for pentobarbitone-anaesthetized, C for conscious and N for noradrenaline/adrenaline infusion (see Methods).
*$P < 0.05$ versus chronically prepared conscious rats (cC).

Results

Effects of occlusion on blood pressure, heart rate and occluded zone

The effects of occlusion on heart rate and blood pressure are summarized in Figures 1a and b respectively. As might be expected, heart rate and blood pressure were generally lowest in pithed and spinalized animals. When rats were pithed seven days after chronic surgical implantation of occluder and cannulae (cP), higher blood pressures and heart rates were seen compared with acutely prepared pithed rats (aP). The highest pressures and heart rates were seen in the decerebrate (aD) and conscious catecholamine-infused (cCN) groups. In the aPN pithed group, catecholamine infusion restored blood pressure and heart rate to control (cC) levels. In isolated hearts (I), ventricular systolic pressure was 130 ± 8 mmHg at a diastolic pressure of 10–15 mmHg (not shown).

Occlusion only produced definite falls in blood pressure in rats without surgical CNS ablations (aB, aC, cC, cCN) (Figure 1). The effect of occlusion on heart rate (Figure 1a) was generally slight in all groups. Heart rate in isolated hearts (not shown) was 168 ± 14 beats min^{-1} before occlusion and 160 ± 13 beats-min^{-1} 30 min after occlusion. Corresponding developed ventricular pressures were 96 ± 7 and 57 ± 6 mmHg.

Occluded zone size (not shown) ranged from 33 ± 3 (% ventricular weight) in aS rats to 45 ± 2 in cP rats. Differences in mean occluded zone size between groups were not statistically significant (except for the aS group) by analysis of variance and did not account for variations in blood pressure, heart rate or arrhythmias.

Arrhythmias

There were considerable differences between the

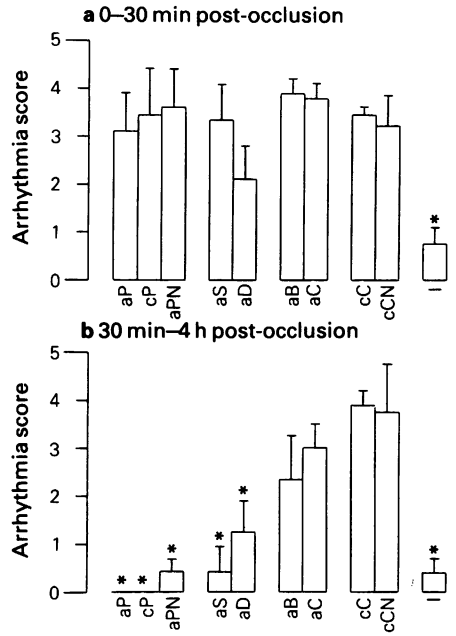

Figure 2 Arrhythmia scores in the 0–30 min (a) and 0.5–4 h (b) post-occlusion periods. Each value is $\bar{x}$ ($n = 9$) with s.e.mean shown by vertical lines. Groups and statistical significance are as indicated in Figure 1.

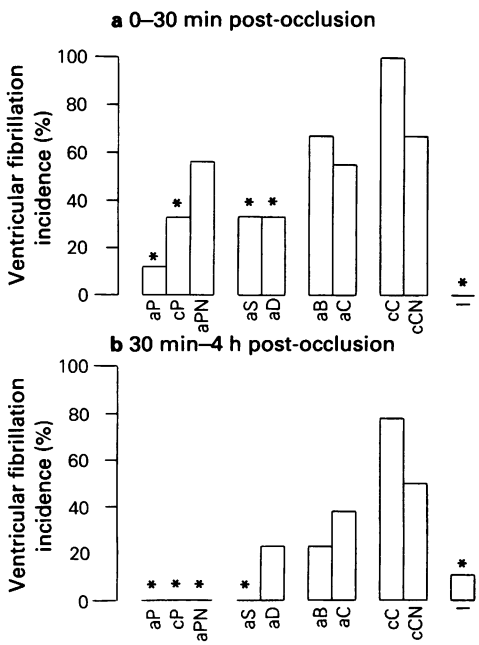

Figure 3 Incidence of ventricular fibrillation, as the percentage of animals in the group having one or more episodes of the arrhythmia, in the 0–30 min (a) and 0.5–4 h (b) post-occlusion periods. Groups and statistical significance are as indicated in Figure 1.

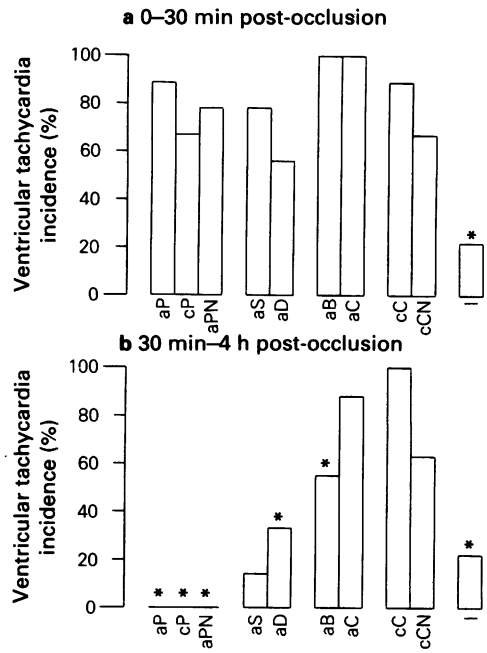

Figure 4 Incidence of ventricular tachycardia, as the percentage of animals in the group having one or more episodes of the arrhythmia, in the 0–30 min (a) and 0.5–4 h (b) post-occlusion periods. Groups and statistical significance are as indicated in Figure 1.

groups with regard to arrhythmias, which are summarized (Figure 2) as mean arrhythmia scores for the early (0–30 min) and late (0.5–4 h) periods. The most notable findings were in the 0.5–4 h post-occlusion period. A dramatic fall in arrhythmia score was seen in all acutely prepared animals, in isolated hearts, and also in chronically prepared, but acutely pithed, rats. In most pithed and spinalized rats not even a single PVC was seen in the late (0.5–4 h) period. Only one isolated heart had VF (at 3.75 h post-occlusion).

VF in the 0.5–4 h period was absent in all pithed rats including those receiving catecholamine infusions (Figure 3b). It was also absent or of low incidence in the aS, aD, aB, and aC groups. VF incidence during the early period (Figure 3a) was qualitatively similar to that seen during the late period, although the differences between the groups were less pronounced.

Changes in the incidences of VT (Figure 4) resembled the changes seen in the incidences of VF. The most marked changes were seen in the late period during which the incidence was low or abolished in all acutely prepared rats and all pithed groups. As with late period VF, late period VT was absent in all pithed rats (aP, cP and aPN).

Log_{10} PVC in the early period (Figure 5) was similar in all groups. Values were highest in the two acutely

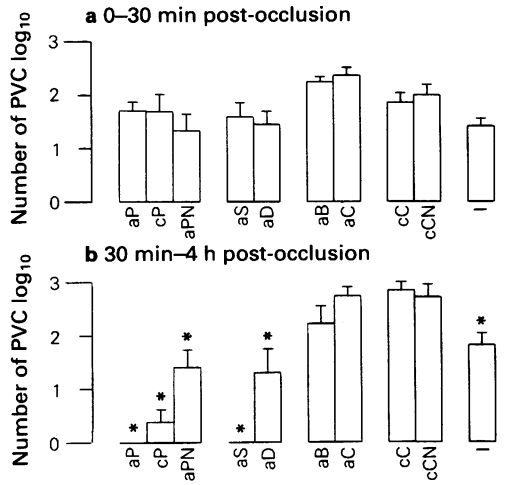

Figure 5 The $\log_{10}$ number of premature ventricular contractions (PVC) in the 0–30 min (a) and 0.5–4h (b) periods. Each value is $\bar{x}$ for $n = 9$, vertical lines show s.e.mean. Groups and statistical significance are as indicated in Figure 1.

prepared non-ablated groups (aB and aC). In the late period (0.5–4 h), $\log_{10}$ PVC was reduced by all types of surgical ablation in the CNS. PVC were in fact absent in the aP and aS groups. PVC were also slightly lower in the aB group versus conscious controls (cC).

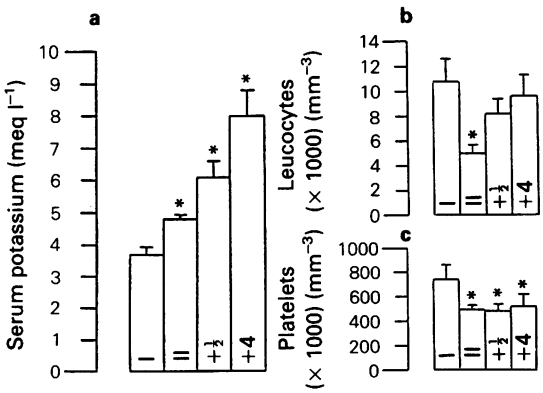

Figure 6 Changes in serum potassium, platelets and leucocytes in pithed rats before and after coronary occlusion. The levels of K^+ (a), platelets (b) and leucocytes (c) are shown immediately following preparative surgery (I), after pithing and 1 min before occlusion (II), 30 min after occlusion (+ ½) and 4 h after occlusion (+ 4). Each value is $\bar{x}$ for $n = 8$, vertical lines show s.e.mean.
*$P < 0.05$ from post surgery (I) values.

ECG changes

Coronary artery occlusion produced characteristic changes in the ECG. These changes included an increase in the size of the R-wave and 'S-T' segment elevation (dSTR). The only statistically significant ECG difference was a delay in the development of maximum 'S-T' segment elevation in the aP and cP groups, versus all other groups (not shown). No other obvious trends were apparent.

Platelets, white blood cells and serum potassium

These variables were measured in an ancillary group of acutely prepared pithed rats only. The most striking finding was an elevation in serum K^+ following pithing (Figure 6a). At the same time periods the white blood cell and platelet counts fell. The white cell count returned toward the pre-pithing value by 4 h after occlusion. Arrhythmias in this ancillary group (not shown) were almost identical to those seen in the original aP group.

Discussion

In this study, acute ablations in the CNS greatly reduced arrhythmias following coronary occlusion in rats, almost abolishing the late arrhythmias (those occurring between 30 min and 4 h after occlusion). However, we were unable to find a simple relationship between the functional status of the CNS and arrhythmia incidence. When CNS integrity, and/or peripheral adrenoceptor activity, was systematically altered in a graded manner the arrhythmias induced by occlusion were not similarly graded. According to blood pressure and heart rate data, sympathetic activity was relatively normal in the aS group, above normal in the aD group, and absent in aP and cP rats while arrhythmias were reduced in all four groups. An infusion of noradrenaline and adrenaline sufficient to restore blood pressure and heart rate to normal in a pithed group (aPN) did not restore arrhythmias. Likewise catecholamine infusions in normal conscious chronically prepared rats (cCN) did not increase arrhythmias. When the CNS was obtunded by pentobarbitone anaesthesia (aB) there was no reduction in the arrhythmias compared with conscious animals (aC).

In contrast to the lack of correlation between CNS ablations, adrenoceptor activation and arrhythmias there appeared to be an inverse relationship between the extent of acute surgery and the arrhythmias produced by occlusion. We have previously demonstrated this relationship with similar groups (Walker *et al.*, 1984) in which almost identical results were obtained.

If such a correlation exists, what might be the mechanism? Possibly acute surgical preparation and CNS destruction releases an anti-arrhythmic substance into the circulation, or removes an arrhythmogenic substance from the circulation. In this regard, pithing depleted circulating platelets and leucocytes (Figure 6). The fall in platelets following pithing has also been observed by others (J.H. Botting, personal communication). There have been many reports suggesting that interference with the properties of platelets and white blood cells, by use of drugs or antisera, may reduce both ischaemia-induced myocardial tissue damage and also arrhythmias (Jolly & Lucchesi, 1983; Lucchesi, *et al.*, 1983; Romson *et al.*, 1983; Cahn & Borzeix, 1983; Fagbemi, 1984; Fiedler, 1983; Mullane *et al.*, 1984; Coker & Parratt, 1984a,b; Flynn *et al.*, 1984; J.H. Botting, personal communication). Therefore, leucocytes, and/or platelets, may play an important role in governing arrhythmias and other responses of the myocardium to ischaemia.

If platelets, and/or leucocytes, trapped within, or migrating to, the ischaemic zone are partly responsible for ischaemic arrhythmogenesis, particularly in the late period, then it is possible that acute surgery produces tissue damage which acts as a trap for leucocytes, and/or platelets, thereby reducing their availability for participating in ischaemia-induced arrhythmogenesis. Adjuvant arthritis, which may cause similar trapping, has been shown to reduce arrhythmias in conscious rats (Koltai *et al.*, 1982).

Elevations in serum K^+ are known to occur following acute surgery, and were observed in this study following pithing (Figure 6a). Serum K^+ elevation may contribute to the results of this study. Elevation of serum K^+ is associated with a fall in the incidence of ventricular fibrillation in patients with acute myocardial infarction (Nordrehaug & von der Lippe, 1983; Solomon, 1984). In isolated perfused hearts, elevation of the K^+ concentration of perfusate drastically reduces arrhythmias induced by coronary occlusion (Harris, 1966; Daugherty & Woodward, 1981; Daugherty *et al.*, 1982). In our isolated heart group a low incidence of arrhythmias was seen. This was not unexpected since the hearts were exposed to 5.3 mM K^+ in the perfusing solution. Finally, in this regard, preliminary results of experiments in which KCl infusion and other treatments were used to alter serum K^+ produced changes in VF incidence. The group incidence of VF was 100%, 77%, 44% and 11% in groups of rats whose serum K^+ were in the ranges 3.0–3.9, 4.0–4.9, 5.0–5.9 and $>5.9\,mM\,l^{-1}$ respectively.

Regardless of the mechanisms by which acute surgery lowers the incidence and type of arrhythmias following coronary occlusion the results of this study may have implications regarding the suitability of models of myocardial ischaemia involving acutely prepared animals. Even acutely prepared conscious (aC) or pentobarbitone-anaesthetized (aB) rats had fewer episodes of ventricular fibrillation and tachycardia than conscious chronically prepared (cC) animals in this study. Moreover, it is also possible that some antiarrhythmic drugs such as β blockers (see Introduction) produce different effects in acutely prepared versus chronically prepared animals. In this regard, it is known that catecholamines reduce serum K^+ (Brown *et al.*, 1983). Therefore, β-adrenoceptor blockers may reduce arrhythmias in acutely prepared rats by simply exacerbating the effect of acute surgery in raising serum K^+.

In conclusion, acute surgery appears to reduce arrhythmias (particularly those occurring between 30 min and 4 h) after coronary occlusion in a manner graded with the degree of surgery, and this effect is independent of, and little affected by, the extent of adrenoceptor activation. In contrast, the functional status of the central nervous system does not appear to influence ischaemia-induced arrhythmias in the rat.

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