*Br. J. Pharmac.* (1978), **64**, 265–272.

# CARDIOVASCULAR EFFECTS OF ACEBUTOLOL FOLLOWING CORONARY ARTERY OCCLUSION AND REPERFUSION IN ANAESTHETIZED DOG

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**1** The effects of 5 mg/kg acebutolol given intravenously were investigated in anaesthetized dogs after (a) ligation of the left anterior descending coronary artery and (b) coronary reperfusion following 60 min of ligation of the left anterior descending coronary artery.

**2** Coronary artery ligation produced, after 4 to 6 h, persistent multiple ventricular ectopic beats and abnormalities of R and T waves and of the S-T segment. Administration of acebutolol, after the development of persistent ventricular arrhythmias, restored normal sinus rhythm within 5 min of injection. Electrocardiographic abnormalities were also reduced.

**3** Coronary artery reperfusion (following 60 min of ligation) resulted in multiple ventricular ectopic beats, ventricular tachycardia and/or ventricular fibrillation. Pretreatment with acebutolol, 15 min before starting reperfusion, markedly reduced the arrhythmias.

**4** Acebutolol did not affect peak inspiratory airway pressure.

**5** Acebutolol produced significant bradycardia and slight, transient, hypotension. It was without effect on left ventricular systolic pressure, left ventricular end-diastolic pressure, cardiac output or pulmonary arterial pressure.

**6** These results suggest beneficial effects of acebutolol in myocardial ischaemia and coronary reperfusion, without any significant risk of cardiodepression or bronchospasm.

## Introduction

The use of $\beta$-adrenoceptor blocking agents in the treatment of acute myocardial infarction has been advocated because these agents decrease myocardial oxygen requirements (Epstein & Braunwald, 1966; Ek & Ablad, 1971) and antagonize a variety of experimentally induced cardiac arrhythmias (Lucchesi, Whitsitt & Stickney, 1967). Several previous studies have demonstrated that propranolol and practolol cause a reduction in the extent of myocardial ischaemic injury and infarct size after experimental coronary artery occlusion in dogs (Maroko, Burnstein, Libby, De Laria, Covell, Ross & Braunwald, 1972a; Libby, Maroko, Covell, Malloch, Ross & Braunwald, 1973; Theroux, Franklin, Ross & Kemper, 1974; Lekven, 1975; Marshall & Parratt, 1976; Shatney, Maccarter & Lillehei, 1976; Reimer, Rasmussen & Jennings, 1976). In patients, propranolol appears to protect the myocardium during anoxic arrest (Reul, Romagnoli, Sandiford, Wukasch, Cooley & Norman, 1974), and if administered in early hours of myocardial infarction, it can significantly reduce the signs of myocardial ischaemic injury (Gold, Leinbach & Maroko, 1976).

Aorto-coronary bypass operations are currently being performed for the treatment of ischaemic heart disease but post-operative arrhythmias are invariably encountered. Although some histological and histochemical studies have demonstrated that experimental coronary artery reperfusion reduces myocardial cell death (Ginks, Sybers, Maroko, Covell, Sobel & Ross, 1972; O'Brien, Carroll, O'Rourke, Rhodes, Gago, Kirch, Morris & Sloan, 1972; Maroko, Libby, Ginks, Bloor, Shell, Sobel & Ross, 1972b), other studies indicate that additional irreversible cardiac damage occurs after re-establishment of coronary blood flow in the ischaemic myocardium (Sommers & Jennings, 1964; Krug, de Rochemont & Korb, 1966; Bresnahan, Roberts, Shell, Ross & Sobel, 1974; Lang, Corday, Gold, Meerbaum, Rubins, Constantini, Hirose, Osher & Rosen, 1974). Recently, it has been shown that reperfusion after 60 to 90 min of coronary occlusion produced further deterioration of cardiac function,

ultrastructure and high energy phosphate stores (Sharma, Varley, Kim, Barwinsky, Cohen & Dhalla, 1975). Though propranolol has not been found to prevent the ventricular fibrillation that often occurs in dogs at the onset of reperfusion (Sommers & Jennings, 1972), this agent reduced the amount of necrosis that develops in the dog heart after 40 min of temporary coronary occlusion (Reimer, Rausmussen & Jennings, 1973). This protective effect of propranolol was related to $\beta$-adrenoceptor blockade (Reimer, Rasmussen & Jennings, 1976).

In spite of their usefulness in the treatment of cardiac arrhythmias and myocardial ischaemia, the clinical application of $\beta$-adrenoceptor blocking agents is limited by their potential to produce cardio-depression (Wolfson, Robbins & Krasnow, 1966). Recently, acebutolol, a cardioselective $\beta$-adrenoceptor blocking agent (Basil, Jordan, Loveless & Maxwell, 1973), has been shown to have minimal cardiodepressant effects in animals (Basil *et al.*, 1973; Dhalla & Lee, 1976) and man (Cuthbert & Owusu-Ankomah, 1971; Coleman & Leary, 1972). Acebutolol has also been reported to antagonize catecholamine-induced arrhythmias in dog, cat and mouse, and ouabain-induced arrhythmias in dog and rabbit (Laddu, 1974; Basil, Jordan, Loveless & Maxwell, 1974). This drug has been found to be useful in the treatment of different types of cardiac arrhythmias in patients (Biron, Proulx, Lapointe, Nadeau & Tremblay, 1975; Ricks, Harrison, Bell & Wenkle, 1976). The present study was undertaken to investigate the protective effects of acebutolol against cardiac arrhythmias induced by coronary ligation and coronary reperfusion in anaesthetized dogs. In addition, some haemodynamic parameters were recorded to assess the effects of this agent on the cardiovascular system during myocardial ischaemia.

## Methods

Twenty healthy mongrel dogs of either sex, weighing between 17 and 24 kg, were used in these experiments. Anaesthesia was induced with sodium pentothal, 25 mg/kg intravenously, and maintained with halothane (0.5%) throughout the duration of each experiment. The animals were intubated and controlled positive pressure respiration was instituted with a Harvard model 613 respirator. A fluotec vaporizer was employed to control the concentration of halothane anaesthesia. Experimental dogs were divided into two groups of 10 dogs each—Group A: permanent coronary occlusion; Group B: temporary coronary occlusion followed by reperfusion.

### *Group A*

Polyethylene catheters were introduced into the abdominal aorta for systemic pressure measurements and into the aortic arch for cardiac output measurements, via the right and left femoral arteries respectively. Left ventricular systolic and end-diastolic pressures were measured with a special Dacron woven cannula introduced into the left ventricle by way of the left carotid artery. A silastic heart catheter was positioned in the right ventricle and a Swan-Ganz heart catheter was placed at the pulmonary artery wedge position; both these catheters were introduced through the left external jugular vein. The silastic catheter was used for injections of cardio-green dye, and the Swan-Ganz catheter for making pulmonary artery wedge pressure measurements. All catheters were filled with a saline-heparin mixture to prevent clotting. Left ventricular, systemic arterial, mean pulmonary arterial and pulmonary wedge pressures were measured by means of P23Bb Statham transducers. Peak inspiratory airway pressure within the trachea was measured by a saline manometer. Standard Lead II of the electrocardiogram was recorded. All recordings were simultaneously transcribed on a Beckman Type R Dynograph recorder. Blood was collected anaerobically and immediately analyzed for $Po_2$, $Pco_2$ and pH with appropriate electrodes (Radiometer type BMX-3 coupled with a digital acid-base analyzer type PHM-72). Cardiac output was determined by the bolus injection of 2.5 mg cardio-green dye (indocynine green) into the right ventricle and sampling arterial blood from the root of the aorta through a Beckman cardio-densitometer with an infusion-withdrawal pump. Cardiac output was calculated by the Stewart-Hamilton method.

Lateral thoracotomy through the fourth intercostal space was employed to expose the heart. The pericardium was incised 1 cm anterior to the phrenic nerve. The left anterior descending artery was dissected for about 1 cm just distal to the origin of the first major perforating septal branch and a silk ligature was placed loosely around the artery. After recording all control measurements, the ligature was tightened to occlude the artery completely and permanently. All parameters were recorded immediately after coronary ligation and every 30 min thereafter. Once the animals developed persistent ventricular ectopic beats (usually 4 to 6 h after coronary ligation) acebutolol was administered intravenously. All observations were made up to 1 h after the administration of acebutolol. In the initial experiments, acebutolol was administered in doses of 1 or 2 mg/kg to 2 dogs each. In the subsequent 6 dogs the drug was given in a dose of 5 mg/kg.

### *Group B*

The left anterior descending artery was visualized and dissected as in Group A dogs. A loop of fine Dacron tape was used to compress the artery against a soft rubber tube so as to cause occlusion without kinking.

The experimental set up and recordings were made as in Group A. After 60 min of myocardial ischaemia, coronary ligature was relieved and reperfusion was allowed. Four dogs were used as control and in 6 dogs acebutolol, 5 mg/kg, was administered intravenously 45 min after coronary ligation and 15 min before the start of reperfusion. All observations were recorded for up to 1 h of coronary reperfusion.

## Results

*Permanent coronary occlusion (Group A)*

Ligation of the left anterior descending coronary artery depressed myocardial function (Table 1) and adversely affected blood gas exchange. There was a significant bradycardia and decreases in left ventricular systolic pressure and cardiac output. The decrease in mean arterial pressure and an increase in left ventricular end-diastolic pressure were not significant. However, there was a slight but significant increase in peak inspiratory airway pressure and a slight decrease in arterial oxygen tension and oxygen saturation (Table 2). In all 10 dogs, coronary artery ligation was followed by occasional ventricular ectopic beats starting at 0.5 to 4 h after myocardial ischaemia. However, persistent multiple ventricular ectopic activity started only 4 to 6 h after ligation. There were electrocardiographic abnormalities such as variable voltage of the R wave, elevated or depressed S-T segment and inverted or biphasic T wave. A typical ECG tracing is shown in Figure 1.

Preliminary experiments in 4 dogs showed that acebutolol, in doses of 1 and 2 mg/kg, was partially effective in reverting the myocardial ischaemia-induced cardiac arrhythmias to normal rhythm, whilst a dose of 5 mg/kg was found to be most effective. In all 6 dogs, injection of 5 mg/kg of acebutolol, 6 to 8 h after coronary artery ligation, reverted the ventricular arrhythmias to normal sinus rhythm within 5 min. Normal rhythm was maintained for at least 1 h (Figure 1). Besides restoration of sinus rhythm, other electrocardiographic abnormalities (those of S-T segment, T wave and R wave) were also reduced. Intravenous administration of acebutolol produced slight but significant hypotension and bradycardia. The effects on other haemodynamic parameters were insignificant. While the hypotensive effect of acebutolol disappeared within a few minutes of drug administration, the negative chronotropic effect continued throughout the 1 h observation period (Table 1). One hour after administration of acebutolol, arterial blood

**Table 1** Haemodynamic effects of acebutolol (5 mg/kg, i.v.) in anaesthetized dogs when administered after coronary artery ligation

| | *Control (pre-ligation)* | *Before drug (post-coronary artery ligation)* | *After drug* |
|---|---|---|---|
| Mean systemic blood pressure | 121 ± 6 | 108 ± 9 | 102 ± 9<br>$P < 0.02$ |
| Heart rate (beats/min) | 132 ± 3 | 105 ± 2<br>$P < 0.005$ | 92 ± 2<br>$P < 0.001$; $P_1 < 0.005$ |
| Left ventricular systolic pressure (mmHg) | 118 ± 6 | 105 ± 8<br>$P < 0.05$ | 101 ± 9<br>$P < 0.05$ |
| Left ventricular end-diastolic pressure (mmHg) | 7.2 ± 1.1 | 11.4 ± 2.8 | 10.7 ± 2.0 |
| Mean pulmonary artery pressure (mmHg) | 16 ± 1 | 14 ± 1 | 13 ± 1 |
| Pulmonary artery wedge pressure (mmHg) | 6.3 ± 0.8 | 7.9 ± 1.4 | 7.8 ± 1.1 |
| Cardiac output (ml/min) | 1795 ± 195 | 1190 ± 115<br>$P < 0.005$ | 1070 ± 82<br>$P < 0.05$ |
| Peak inspiratory airway pressure ($cmH_2O$) | 13.3 ± 0.5 | 15.3 ± 0.4<br>$P < 0.05$ | 15.8 ± 0.6<br>$P < 0.05$ |

Each value is the mean ± s.e. (6 dogs). Acebutolol (5 mg/kg) was given intravenously at 6 to 8 h after coronary artery ligation. Each parameter was recorded before coronary artery ligation (control) and before and 1 h after drug administration. $P$: in relation to control. $P_1$: in relation to 'Before drug'.

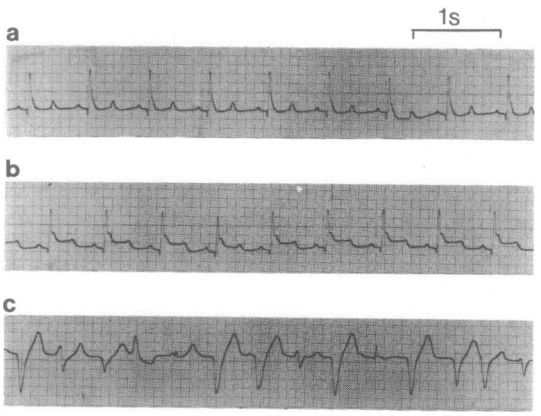


**Figure 1** Effect of acebutolol (5 mg/kg), intravenously on the electrocardiogram (Lead II) of a dog after coronary artery ligation. Similar results were obtained in 6 experiments. (a) Normal sinus rhythm before ligation; (b) ventricular ectopic activity 8 h after coronary occlusion; note also paired sinus beats with variable voltage of R wave, depressed S-T segment and inverted T wave; (c) 1h after acebutolol; note normal sinus rhythm with bradycardia, normal S-T segment and upright T wave.

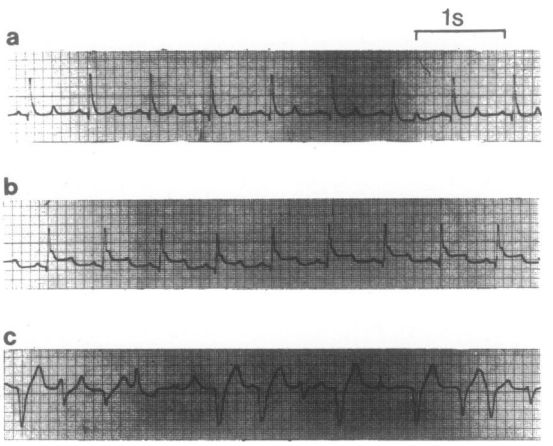


**Figure 2** Electrocardiogram (Lead II) in a control (untreated) dog following coronary artery ligation and reperfusion. The results are typical of all 4 experiments. (a) Normal sinus rhythm before coronary ligation; (b) sinus rhythm with elevated S-T segment 1h after coronary ligation; (c) multiple ventricular ectopic beats 1h after reperfusion.

gases and the hydrogen ion concentration were not significantly different from control values (Table 2).

*Temporary coronary occlusion followed by reperfusion (Group B)*

During the 1 h of coronary occlusion, only 2 out of 10 dogs had occasional ventricular ectopic beats. In 4 control dogs, immediately after the onset of reperfusion, there developed multiple ventricular ectopic beats or bursts of continuous ventricular ectopic activity. One dog later developed ventricular fibrillation. During the 1 h reperfusion observation period, the frequency of ectopic beats was only slightly reduced and arrhythmias persisted in the surviving 3 dogs (Figure 2). In 6 dogs pretreated with acebutolol (5 mg/kg) immediately after starting reperfusion, there were multiple ventricular extra-systoles, but these disappeared within 10 min and normal sinus rhythm was restored. In 2 of the 6 dogs, however, there were occasional ectopic beats. A representative electrocardiogram taken from a dog treated with acebutolol is shown in Figure 3.

**Table 2** Effect of acebutolol (5 mg/kg) on arterial blood gases and pH after coronary artery ligation

| | *Control* | *Before drug (post-coronary artery ligation)* | *After drug* |
|---|---|---|---|
| $Pco_2$ (mmHg) | 40 ± 1 | 39 ± 1 | 39 ± 1 |
| $Po_2$ (mmHg) | 78 ± 2 | 69 ± 6 | 86 ± 7 |
| | | | $P < 0.001$ |
| $O_2$ saturation (%) | 93.5 ± 0.7 | 88.1 ± 2.3 | 95.5 ± 1.1 |
| | | | $P < 0.005$ |
| pH | 7.39 ± 0.01 | 7.38 ± 0.02 | 7.40 ± 0.01 |

Each value is the mean ± s.e. (6 dogs). Acebutolol (5 mg/kg) was given intravenously at 6 to 8 h after coronary artery ligation. Blood samples were taken before coronary artery ligation (control) and before and 1 h after drug administration. *P*: in relation to 'Before drug'.

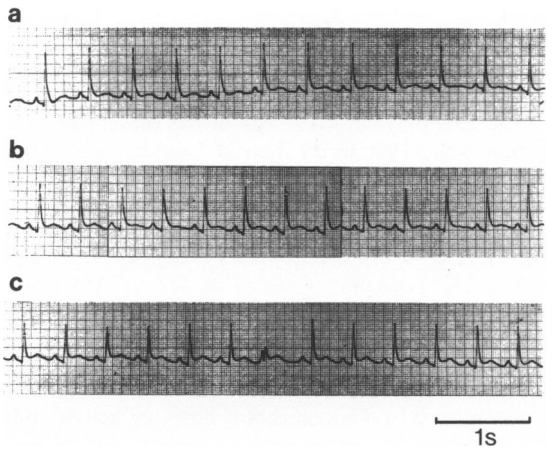


**Figure 3** Effect of acebutolol (5 mg/kg), intravenously, on the electrocardiographic pattern following coronary artery ligation and reperfusion. The results are typical of all 6 experiments. (a) Before coronary artery ligation; (b) 1h after coronary artery ligation and 15 min after administration of acebutolol; (c) almost normal rhythm (one premature ectopic beat) 1h after reperfusion.

## Discussion

In the setting of severe coronary artery disease, the ability of the coronary vascular bed to dilate is limited so that any pharmacological intervention which would decrease myocardial oxygen consumption should prove useful (Braunwald, 1971; Maroko, Kjekshus, Sobel, Watanabe, Covell, Ross & Braunwald, 1971). During recent years, aorto-coronary bypass operations have been performed in patients with acute myocardial infarction based on the expectation of saving jeopardized, but still viable, ischaemic myocardium by correcting the severe imbalance between regional myocardial oxygen demands and supply. However, the early period of reperfusion is often associated with a state of hazardous metabolic, electrophysiological and mechanical cardiac dysfunction (Sharma, Varley, Kim, Barwinsky, Cohen & Dhalla, 1975), which might explain observed failures of surgical revascularization after acute myocardial infarction. Similar cardiac dysfunction is seen following temporary cardiac anoxia and reperfusion in cardio-pulmonary bypass surgery. $\beta$-Adrenoceptor blocking agents are now increasingly used for the treatment of acute myocardial infarction (Snow, 1966; Mueller, Ayres, Religa & Evans, 1974), during post-infarction aorto-coronary bypass surgery and during cardio-pulmonary bypass surgery in order to correct congenital or acquired cardiac defects. The major disadvantages in the use of such drugs is cardiodepression (which may lead to the development of cardiogenic shock, especially in patients with acute myocardial infarction who often have compromised ventricular function; Karliner & Ross, 1971), and lack of cardioselectivity resulting in the possibility of bronchospasm.

Acebutolol, a cardioselective $\beta$-adrenoceptor blocking agent, has been shown to be an effective anti-arrhythmic agent in various species of animals, including man. However, its usefulness against cardiac ischaemia and cardiac arrhythmias induced by coronary reperfusion has not been reported. In the control experiments, occlusion of the anterior descending artery was followed initially by occasional ventricular ectopic beats. However, 4 to 6 h after coronary ligation there were persistent ventricular arrhythmias, indicating that hypoxia alone may not be responsible. If 1 h after coronary occlusion, the ligature was removed and reperfusion initiated, multiple ventricular ectopic activity and later even ventricular fibrillation resulted (confirming the report of Sommers & Jennings, 1972). The possible cause of such cardiac arrhythmias may be the accumulation, and sudden release, of some tissue metabolites in the ischaemic zone.

The present studies show that acebutolol can effectively antagonize cardiac arrhythmias induced by permanent coronary occlusion. Most pronounced was the observation that acebutolol prevented the occurrence of ventricular reperfusion arrhythmias. Besides correcting such dysrhythmias, acebutolol reduced or abolished other electrocardiographic abnormalities, especially that of ST segment. This might indicate that the drug reduces the extent of myocardial necrosis produced by ischaemia and reperfusion. Practolol, a cardio-selective $\beta$-adrenoceptor blocking agent without any membrane stabilizing activity, has been shown to suppress arrhythmias (Dunlop & Shanks, 1968; Jewitt, Mercer & Shillingford, 1969) and reduce abnormalities of ST segment (Libby *et al.*, 1973; Marshall & Parratt, 1976) and cardiac lactate extraction (Marshall & Parratt, 1976) associated with myocardial ischaemia. On the other hand, propranolol, a non-selective $\beta$-adrenoceptor blocker with membrane stabilizing action, does not affect coronary reflow-induced ventricular fibrillation (Sommers & Jennings, 1972; Sharma, Dhalla & Ziegelhoffer, unpublished data), has inconsistent effects on ST segment abnormalities (Maroko *et al.*, 1971; Watanabe, Covell, Maroko, Braunwald & Ross, 1972; Marshall & Parratt, 1976) and does not affect lactate extraction by the ischaemic myocardium (Marshall & Parratt, 1976). It has however been shown to reduce the myocardial necrosis that develops after temporary coronary occlusion (Reimer *et al.*, 1973). Again, a quaternary ammonium compound, UM-424, which is related to

propranolol but is devoid of $\beta$-adrenoceptor blocking activity and has minimum cardiodepressant activity, prevents the development of arrhythmias during both coronary occlusion and reflow phases (Kniffen, Winokur, Counsell & Lucchesi, 1976). Acebutolol, as evidenced from the studies of Basil *et al.* (1973), would be expected to produce marked cardiac $\beta$-adrenoceptor blockade in the dose (5 mg/kg) used in the present study. The absence of any effect of acebutolol on peak inspiratory pressure indicates that there was no bronchospasm, confirming the earlier reports that this agent has no action on $\beta_2$-adrenoceptors (Basil *et al.*, 1973). In view of the beneficial effects of propranolol, practolol and acebutolol in myocardial ischaemia and reperfusion, it can be suggested that the effects of acebutolol are related to its $\beta$-adrenoceptor blocking action and that the membrane stabilizing action of the agent plays only a minor role. The antiarrhythmic action of acebutolol in myocardial ischaemia and reperfusion, and the absence of similar activity when propranolol is administered in comparable doses (Dhalla, Sharma & Ziegelhoffer, unpublished data), suggests that a selective $\beta_1$-adrenoceptor blocking agent is better than a non-selective blocker. In this connection it is relevant to mention that most *in vivo* studies indicate that coronary vascular $\beta$-adrenoceptors are $\beta_2$ (Parratt & Wadsworth, 1970; Mark, Abboud, Schmid, Heistad & Mayer, 1972; Adam & Boyles, 1974; Gross & Feigel, 1975) or at least different from myocardial $\beta_1$-adrenoceptors (Adam, Boyles & Scholfield, 1970; Ross & Jorgensen, 1970). It has been suggested that the administration of propranolol blocks vascular $\beta_2$-adrenoceptors in the ischaemic region and unmasks a vasoconstrictor effect of released noradrenaline on vascular $\alpha$-adrenoceptors present within this region (Parratt, 1967). In fact, Marshall & Parratt (1976) found that propranolol produced further deterioration of the ischaemic region of the myocardium following coronary ligation while the cardioselective agent, practolol, had a beneficial effect.

The haemodynamic records in the present investigations show that, in the dose of 5 mg/kg, acebutolol did not produce any deleterious effect on cardiac function. Thus cardiodepression does not seem to be a major problem with acebutolol. This confirms earlier reports in animals (Basil *et al.*, 1973; Dhalla & Lee, 1976) and man (Cuthbert & Owusu-Ankomah, 1971; Coleman & Leary, 1972). One of the disadvantages of propranolol is cardiodepression; this adverse effect appears to be lacking in acebutolol. Such a basic difference between acebutolol and propranolol is not related to $\beta$-adrenoceptor blocking activity but is related to an action of propranolol on calcium transport and membrane bound enzymes in the heart, systems which are not affected by acebutolol (Dhalla & Lee, 1976; Dhalla, Lee, Anand & Chauhan, 1978). Certainly the present studies indicate that acebutolol, which has been successfully used as an antiarrhythmic agent in man, can antagonize the cardiac arrhythmias induced by coronary ligation as well as reperfusion. Being devoid of a bronchoconstrictor action, and having a minimal cardiodepressant activity, acebutolol deserves further detailed studies in experimental cardiac ischaemia of a permanent or transient nature.

This work was supported by the Manitoba Heart Foundation. P.K.D. was a visiting professor from the Banaras Hindu University, India, and was supported by the Canadian Heart Foundation. We are grateful to Dr Roger Fontaine, Medical Director of the Poulenc Ltd., Montreal, for his interest and generous support during this study. Reprint requests to N.S.D., Dept. of Physiology, University of Manitoba, Winnipeg, Canada R3E 0W3.

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*(Received February 14, 1978.*
*Revised May 4, 1978.)*