Br. J. Pharmac. (1978), **62**, 67–73

THE CARDIOVASCULAR EFFECTS OF CYCLOPROPANE IN THE INTACT, DECEREBRATE AND PITHED RABBIT PREPARATIONS

R.L. HUGHES & J.E. MACKENZIE

University Department of Anaesthesia, Royal Infirmary, Glasgow G4 OSF

1 The anaesthetic cyclopropane was given to intact, decerebrate and pithed unanaesthetized rabbit preparations to determine the relative importance *in vivo* of its central and peripheral cardiovascular effects.

2 Cyclopropane elevated both the heart rate and the mean arterial pressure in the intact rabbit.

3 In the decerebrate rabbit, cyclopropane elevated the heart rate and efferent cervical preganglionic nerve activity and diminished the magnitude of these components of the aortic baroreceptor reflex, the mean arterial pressure being unaffected.

4 Apart from slight myocardial depression, cyclopropane was largely without effect in the pithed rabbit.

5 It is concluded that cyclopropane produces its cardiovascular effects by supra-collicular activation eliciting an elevation of mean arterial pressure, a central sub-collicular activation producing an increase in heart rate, and that *in vivo* the peripheral effects of cyclopropane are of minimal importance in comparison to these central effects.

Introduction

Although it is well established that the inhalation anaesthetic, cyclopropane, produces a pressor effect in man (Eger, Smith, Cullen, Cullen & Gregory, 1971), it is not clear by which mechanism or mechanisms this is achieved. It has been shown in the dog cross-perfusion preparation that cyclopropane in the circulation of the head produces a pressor effect, but in the circulation of the body produces a depressor response (Price, Cook, Deutsch, Linde, Mishalove & Morse, 1963). Subsequently, it was demonstrated that cyclopropane increases efferent sympathetic discharge in the rabbit and the cat (Biscoe & Millar, 1966; Price, Warden, Cooperman & Millar, 1969). It has also been shown that cyclopropane produces stimulation of hypothalamic units in the cat (Millar & Silver, 1971).

Whilst this may seem strong evidence for the pressor effect of cyclopropane being centrally mediated, other investigations have shown that cyclopropane can produce vasoconstriction independently of the central nervous system, e.g. on the rat aorta *in vitro* (Price & Price, 1962). An action at vascular smooth muscle is not necessarily in conflict with the proposal that cyclopropane has centrally mediated pressor effects; however, it is not known to what degree each of the effects of peripheral vasoconstriction and central sympathetic excitation influence the general haemodynamics to produce the pressor effects seen. In order to clarify the situation three cardiovascular models have been used. These show the effects of cyclopropane on the whole rabbit ('intact'), a rabbit without a hypothalamus but with the vasomotor centres of the medulla oblongata (decerebrate rabbit), and thirdly a rabbit model without any central control (pithed rabbit). These preparations were selected so that no 'background' or 'basal' anaesthesia was required, thus excluding a limitation of most previous studies.

Methods

The experiments were carried out on male New Zealand white rabbits (weights 2.8–3.5 kg).

Intact

The rabbit was placed in a standard restraining box, the left ear shaved and a No. 20 Medicut cannula introduced into the central ear artery. Once in place, the cannula was connected to a manometer line and thence to a Bell & Howell pressure transducer, and the pressure changes recorded on an MX19 Devices 8-channel recorder. Heart rate was obtained from the

pressure channel by means of a Devices instantaneous rate-meter.

A close-fitting mask was then positioned over the rabbit's mouth and nose. The rabbit was left for 15–30 min before control measurements were made. Cyclopropane was then given until the heart rate and blood pressure stabilized at the new levels. Cyclopropane 0, 12.5, 25 and 50% was administered with 25% O_2, the remainder being N_2. Although in the following preparations cyclopropane was given in O_2 alone, it has been shown that various combinations of O_2 and N_2 do not alter the observed parameters, providing at least 20% O_2 is given (MacKenzie, unpublished observations). Furthermore, the same effects were seen in intact rabbits with cyclopropane in O_2. Increasing concentrations of cyclopropane induced anaesthesia without an obvious 'excitement' phase (i.e. classical stage 2 effects).

Decerebrate

The decerebrate group was initially anaesthetized with 3% halothane in 100% O_2. The experimental protocol was essentially that described by McGrath, MacKenzie & Millar (1975). The rabbits were tracheotomized and cannulae were inserted into the left femoral artery and vein. A hole was made in the parietal bone with a trephine (13 mm); the hole was then enlarged with bone nibblers and a mid-collicular decerebration was performed by suction. Halothane administration was stopped and the rabbits mechanically ventilated with 100% O_2 (Harvard Instruments ventilator Model 613) so that the end-tidal CO_2 was maintained at 4% (measured with an LB2 Beckman analyser). Gallamine 1 mg/kg was given as necessary.

Both aortic depressor nerves were divided. The desheathed central end of the left aortic depressor nerve was placed over a pair of silver wire electrodes for stimulation (0.1 ms pulse width, 50 Hz for 20 s at supramaximal voltage (≃ 5V)), with a Devices gated pulse generator and isolated stimulator.

Nerve activity was recorded from multifibre strands of the central end of the divided left preganglionic cervical sympathetic nerve with bipolar platinum electrodes. The amplified signal (Tektronix 122) was then passed via a dual beam oscilloscope (Tektronix D12) to a pulse height selector and thence to a Panax rate-meter. The mean integrated sympathetic discharge rate was displayed on a Devices MX19 recorder. Blood pressure and heart rate were recorded as in intact rabbits. The decerebrate series were exposed to 7.5, 15 and 30% of cyclopropane.

Pithed

The pithed group was also anaesthetized with 3% halothane in 100% O_2, tracheotomized and intubated.

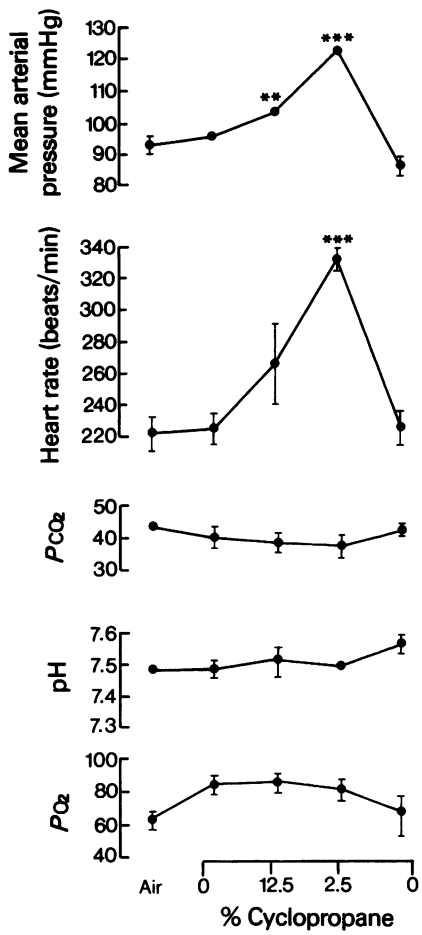

Figure 1 The effects of cyclopropane (25% O_2 with balance N_2) on the heart rate, mean arterial pressure, P_{CO_2}, pH and P_{O_2} in the intact rabbit. Note the increase in heart rate and mean arterial pressure without alteration of P_{CO_2} or pH. Each point represents the mean of six observations. Bars indicate s.e. mean. (** denotes $P < 0.01$; *** denotes $P < 0.001$).

Anaesthesia was then maintained with 1% halothane in O_2. The left carotid artery was cannulated with a concentric double cannula which had each lumen connected to a Bell & Howell pressure transducer. The inner cannula was introduced until its tip lay in the left ventricle, demonstrated by the characteristic pulse wave, and the outer cannula was left with its tip in the carotid artery approximately 10 mm from the aorta. A thermistor tipped probe was introduced into the right carotid artery until its tip lay in midstream in the aorta. A cannula was introduced into the right external jugular vein for administration

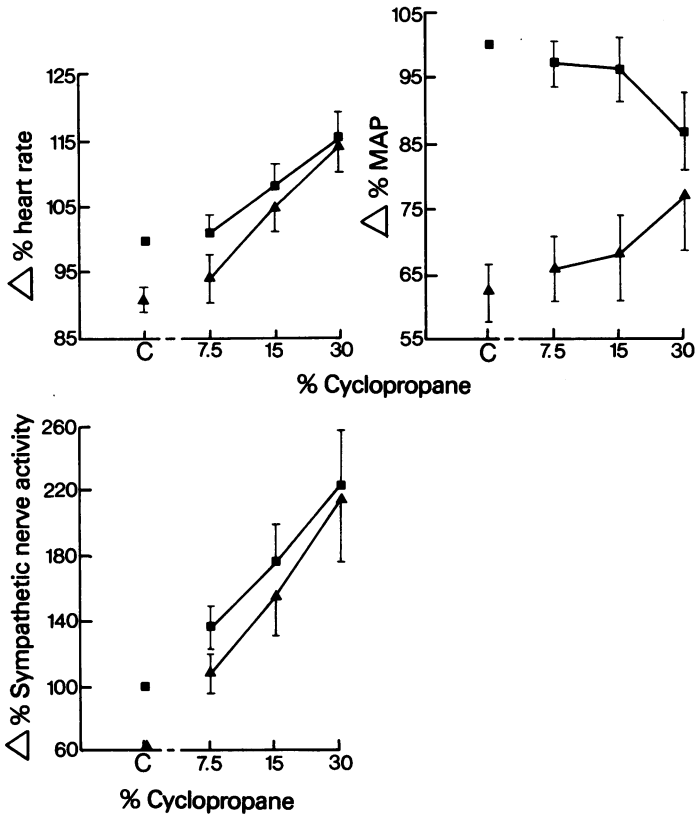

Figure 2 The effects of cyclopropane (approximately 30 min after exposure to each concentration) in the decerebrate rabbit baroreceptor reflex. Upper curve on each graph (■) represents the values of heart rate, mean arterial pressure (MAP) and cervical preganglionic sympathetic nerve activity, whilst the lower curve (▲) represents the lowest value produced by depressor nerve stimulation. For each parameter the resting and reflex values are expressed as a percentage of the pre-cyclopropane controls ($n = 6$). In each graph the reflex before cyclopropane is indicated at C. Mean control values were: mean arterial pressure 106 ± 11 mmHg, heart rate 278 ± 19 beats/min, and sympathetic nerve activity 61 ± 10 impulses/second. Bars indicate s.e. mean.

of drugs and of cold saline (0.9% w/v NaCl solution) for measurement of cardiac output by the thermal dilution method (Fegler, 1954).

The rabbit was decerebrated as before, given gallamine, mechanically ventilated, and subsequently fully pithed via the enlarged trephine hole. The pithing rod consisted of a stainless steel rod (2 mm diameter), covered with a teflon sheath (o.d. 3.6 mm) except for 12 mm at its tip. An indifferent electrode of silver wire was placed subcutaneously dorsal and parallel to the cervical vertebrae. The rod was withdrawn to the level of T8 where stimulation produced no change in heart rate but produced a rise in arterial pressure due solely to the direct vasopressor effect of the stimulated sympathetic nerves (McGrath & MacKenzie, 1977).

Cyclopropane (7.5, 15 and 30% in O_2) was given in two situations: (a) during a 5 min cycle of electrical stimulation (1 ms at supramaximal voltage (≃ 90V) at 10 Hz for 20 s), (b) during a 12 min cycle of noradrenaline additions (0.3 μg/kg). (Note that the minimum anaesthetic concentration in rabbit is ≃ 15%; MacKenzie, 1977).

In each run the cyclopropane was given for approximately 30 min (attaining >95% of equilibrium; Eger, 1974) before readings were taken. From the mean arterial pressure (MAP), heart rate (HR) and cardiac output (CO), the peripheral resistance PR (= MAP/CO) and stroke volume SV (= CO/HR) were calculated. In addition to the left ventricular systolic and end diastolic blood pressure, the intraventricular cannula was used to provide a measurement of left ventricular dP/dt (from which left ventricular dP/dt *max* was obtained by feeding an output from

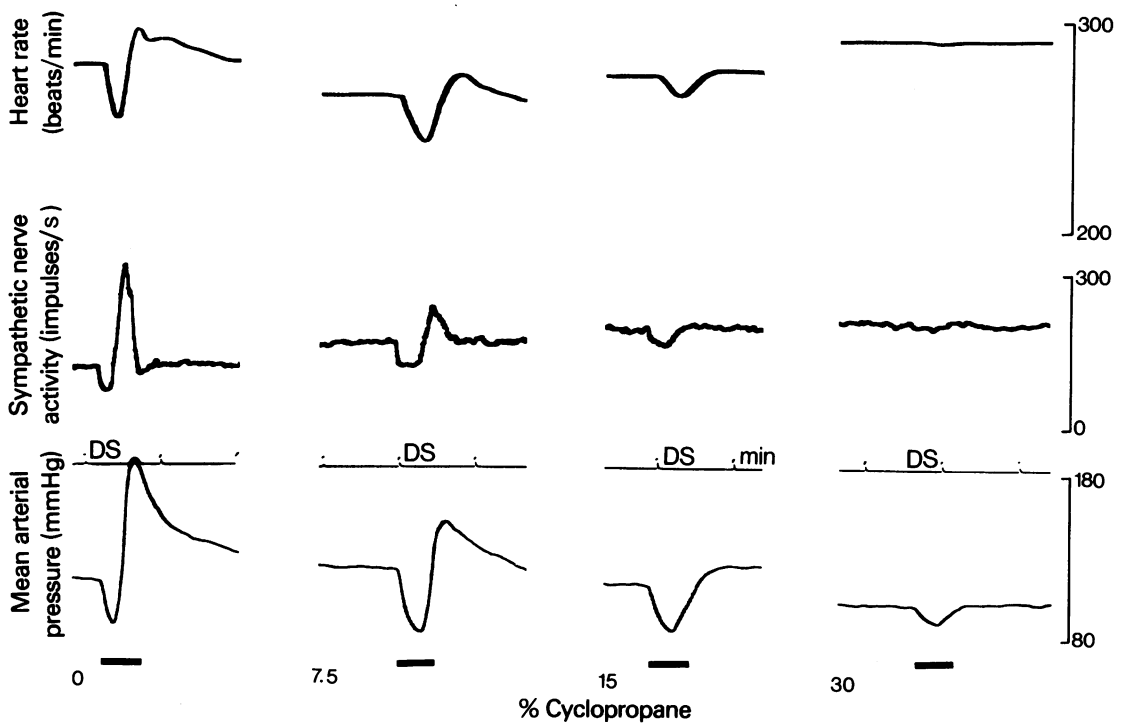

Figure 3 The effects of 30 min exposure to 7.5, 15 and 30% cyclopropane in O_2 on the baroreceptor reflex of the decerebrate rabbit. DS denotes depressor nerve stimulation. Note the increase in background sympathetic nerve activity and heart rate and the reduced magnitude of the baroreceptor reflex.

the pressure amplifier into a Devices differentiator unit.

In all experiments arterial blood samples were taken at the end of each run for analysis of P_{O_2}, P_{CO_2} and pH (IL Model 213); base excess was calculated and corrected for with the appropriate amount of sodium bicarbonate.

Rectal temperature was maintained at 38°C ± 0.5C with a homoeothermic blanket (C. F. Palmer).

Variables were recorded on a Devices MX19 8-channel recorder and cardiac output curves were recorded on a Servoscribe Pen recorder.

Drugs used were: halothane (ICI), cyclopropane (BOC), gallamine triethiodide (May & Baker) and (−)-noradrenaline.

The data were analysed for significance by means of Student's t test. The term significance means a probability of < 0.05.

Results

Intact

Cyclopropane (12.5 and 25%; $n = 6$) produced a marked increase in heart rate and mean arterial pressure without alteration of pH, P_{CO_2} or P_{O_2} (Figure 1). On reverting to the control conditions the mean arterial pressure fell to beneath the control level. When a higher concentration of cyclopropane was used (50%), a greater elevation of mean arterial pressure and heart rate was obtained but this was associated with respiratory difficulties and associated elevations of P_{CO_2}.

Decerebrate

As these data were more variable they are presented (with the exception of Figure 3) in terms of the control values (= 100%). Whilst the mean arterial pressure was not significantly altered by cyclopropane in the concentrations used, both the heart rate and the sympathetic nerve activity were increased ($n = 6$; Figures 2 and 3) by all doses (significantly by 15 and 30% cyclopropane).

Although the magnitude of the mean arterial pressure component of the baroreceptor reflex was unaltered by 7.5 and 15% cyclopropane, it was reduced by 30% of the anaesthetic.

The magnitude of the heart rate and sympathetic nerve activity components of the baroreceptor reflex

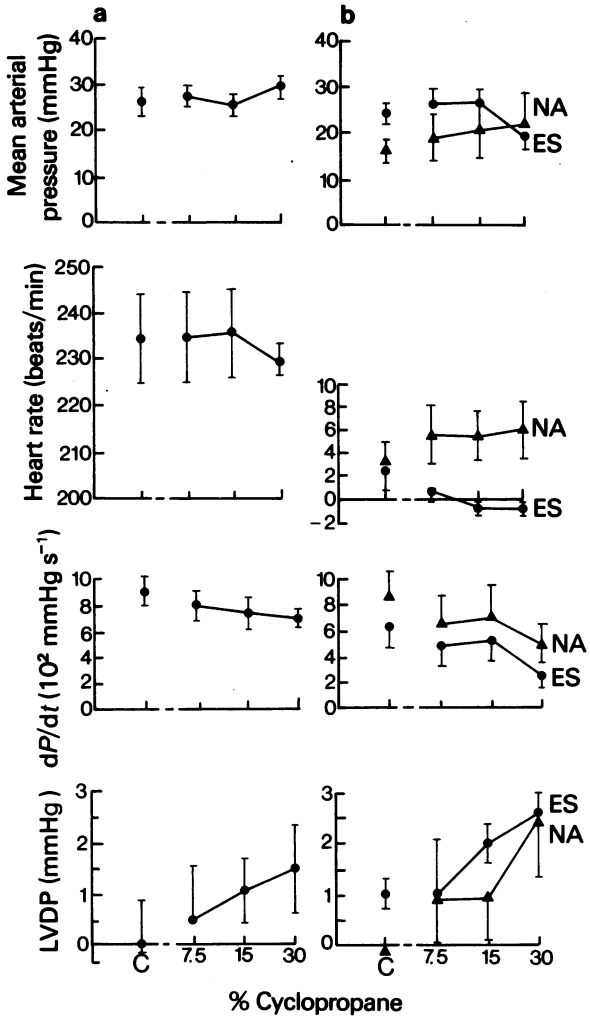

Figure 4 The effects of cyclopropane on the mean arterial pressure, heart rate, left ventricular d*P*/d*t max* and left ventricular end diastolic pressure (LVDP) of the pithed rabbit in comparison with the control situation C (a) on the background activity and (b) on the effects produced by electrical stimulation (ES; T8; 10 Hz, 20 s supramaximal voltage) and noradrenaline (NA; 0.3 μg/kg) ($n = 6$). Measurements made approximately 30 min after exposure to each concentration of cyclopropane. Bars indicate s.e. mean.

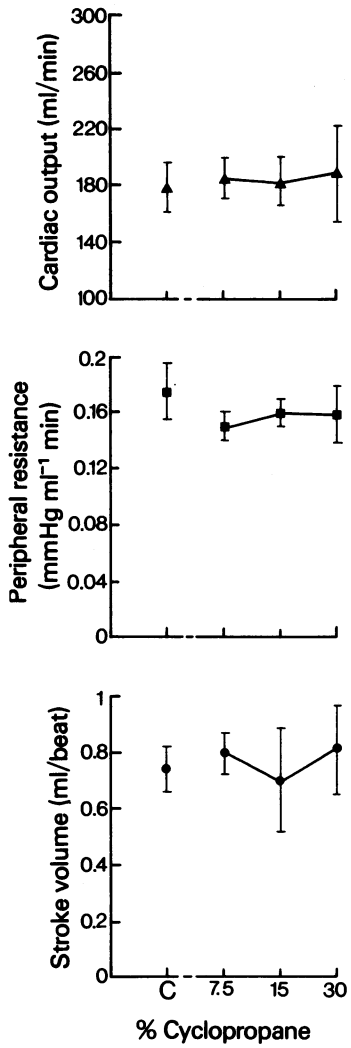

Figure 5 The effects of cyclopropane on the cardiac output, peripheral resistance and stroke volume of the pithed rabbit in comparison to the control responses C at approximately 30 min after exposure to each concentration of cyclopropane. ($n = 6$). Bars indicate s.e. mean.

were progressively reduced by increasing cyclopropane concentrations (Figures 2 and 3).

Pithed

The pithed rabbits ($n = 6$) were little affected by cyclopropane. Although there was a progressive reduction in left ventricular d*P*/d*t* and left ventricular end diastolic pressure (LVDP), these were not statistically significant effects (Figure 4a). The mean arterial pressure, heart rate, cardiac output, peripheral resistance and stroke volume were unaltered by cyclopropane up to 30% ($n = 6$; Figures 4a and 5).

Cyclopropane produced minimal progressive depressant effects on the responses of left ventricular d*P*/d*t* and left ventricular end diastolic pressure to electrical stimulation and noradrenaline (Figure 4b)

and again cardiac output, peripheral resistance, stroke volume, mean arterial pressure and heart rate were largely unaffected by cyclopropane. There was a small (not statistically significant) increase in heart rate and depression of left ventricular dP/dt with the highest concentration used (30%).

Discussion

Cyclopropane increased both the heart rate and the mean arterial pressure in the intact rabbit, the heart rate alone in the decerebrate rabbit and neither the heart rate nor the mean arterial pressure in the pithed rabbit.

From these results one may deduce that the anaesthetic, cyclopropane, produces its cardiovascular effects by supracollicular activation (possibly at the hypothalamus; Millar & Silver, 1971) eliciting an elevation of mean arterial pressure, and a central subcollicular activation producing an elevation of heart rate.

Studies on animals with an intact central nervous system invariably show a pressor response to cyclopropane (Millar & Biscoe, 1965; Price *et al.*, 1969). As decerebration eliminated the pressor effect but not the elevation of heart rate, the increases in sympathetic nerve activity in these earlier studies may have been disproportionately related to the observed elevations of mean arterial blood pressure and in fact may be primarily associated with changes in heart rate.

The elevations of heart rate also reported by Millar & Biscoe (1965) and Robins & Baxter (1940) in the rabbit and dog respectively are unlikely to be due to a direct action of cyclopropane as several workers have shown *in vitro* that cyclopropane is without effect on the heart rate (Acierna & Palma, 1951; Price & Helrich, 1955; Levy, Ichiyanaga & Frederickson, 1963).

The observed increases in sympathetic nerve activity confirm previous studies on the rabbit (Millar & Biscoe, 1965; Biscoe & Millar, 1966) and the cat (Price *et al.*, 1969).

Whilst this effect could have resulted from peripheral efferent nerve densensitization, it has been shown by Millar & Biscoe (1965) that in the de-afferented preparation, cyclopropane still elicits an increase in sympathetic nerve activity, thus supporting the contention that the effect is of a central origin.

The close association between the increase in heart rate and sympathetic nerve activity, and their similarly reduced magnitude of baroreceptor reflex (in the absence of any significant changes in mean arterial pressure), indicates that the increase in heart rate results from the enhanced efferent sympathetic activity.

The decrease in the heart rate and sympathetic nerve activity components of the baroreceptor reflex after cyclopropane confirmed in unanaesthetized rabbits the findings of Biscoe & Millar (1966) in nembutal-anaesthetized rabbits.

The small reductions of left ventricular dP/dt *max* and increase in left ventricular end diastolic pressure in the pithed rabbit indicate a weak cardiodepressant effect of cyclopropane; it may be that this effect is masked in the intact animal by the enhanced sympathetic drive.

The slight (not significant) decreases in heart rate and mean arterial pressure responses to electrical stimulation but not exogenous noradrenaline provide some evidence for a diminished neuronal transmission at ganglia (Normann & Löfström, 1955) or the nerve ending (Roizen, Thoa, Moss & Kopin, 1976). Similarly, the enhanced response of the heart rate to noradrenaline could be taken as confirmation of the *in vitro* studies (Price & Price, 1962); however, in general the neuronal and peripheral vascular effects of cyclopropane were negligible *in vivo* in comparison to the marked increases in mean arterial pressure and heart rate seen in the intact animal. This is especially so when one considers the extreme sensitivity of pithed animals to vasopressor agents.

It is concluded that in the rabbit without background anaesthesia the central effects of cyclopropane in increasing mean arterial pressure (at a supra-collicular level) and heart rate (at a sub-collicular level) considerably overshadow its peripheral effects.

Technical assistance was provided by Mr R. Jowett and Mr F. Toal. This work was supported by a grant from the Medical Research Council.

References

ACIERNA, L.J. & Di PALMA, J.R. (1951). Effects of ether, cyclopropane and chloroform on the isolated auricles of the cat. *Anesthesiology*, **12**, 567–573.

BISCOE, T.J. & MILLAR, R.A. (1966). The effects of cyclopropane, halothane and ether on central baroreceptor pathways. *J. Physiol. Lond.*, **184**, 535–559.

EGER, E.I. II. (1974). *Anesthetic Uptake and Action*. p. 91. Baltimore: Williams and Wilkins.

EGER, E.I. II, SMITH, N.T., CULLEN, D.J., CULLEN, B.F. & GREGORY, G.A. (1971). A comparison of the cardiovascular effects of halothane, fluoroxene, ether and cyclopropane in man. A resumé. *Anesthesiology*, **34**, 25–41.

FEGLER, G. (1954). Measurement of cardiac output in anaesthetised animals by a thermo-dilution method. *Q. J. exp. Physiol.*, **39**, 153–164.

LEVY J.V., ICHIYANAGA, K. & FREDERICKSON, E.L.

(1963). Effect of cyclopropane anesthesia on myocardial contraction and membrane potentials. *Anesthesiology*, **24,** 185–193.

MACKENZIE, J.E. (1977). Determination of MAC for halothane, cyclopropane and ether in the rabbit. *Br. J. Anaesth.*, **49,** 319–322.

MCGRATH, J.C. & MACKENZIE, J.E. (1977). The effects of intravenous anaesthetics on peripheral sympathetic responses in the pithed rabbit. *Br. J. Pharmac*, **61,** 199–212.

MCGRATH, J.C., MACKENZIE, J.E. & MILLAR, R.A. (1975). Effects of ketamine on central sympathetic discharge and the baroreceptor reflex during mechanical ventilation. *Br. J. Anaesth.*, **47,** 1141–1147.

MILLAR, R.A. & BISCOE, T.J. (1965). Preganglionic sympathetic activity and anaesthetics. *Br. J. Anaesth.*, **37,** 804–832.

MILLAR, R.A. & SILVER, I.A. (1971). Excitation of certain posterolateral hypothalamic units by cyclopropane and ether. *Br. J. Pharmac.*, **42,** 315–327.

NORMANN, N. & LÖFSTRÖM, B. (1955). Interaction of d-tubocurarine, ether and cyclopropane and thiopental on ganglionic transmission. *J. Pharmac. exp. Ther.*, **114,** 231–239.

PRICE, H.L., COOK, W.A., DEUTSCH, S., LINDE, H.W., MISHALOVE, R.D. & MORSE, H.T. (1963). Hemodynamic and central nervous actions of cyclopropane in the dog. *Anesthesiology*, **24,** 1–10.

PRICE, H.L. & HELRICH, M. (1955). The effect of cyclopropane, diethyl ether, nitrous oxide, thiopental and hydrogen ion concentration on the myocardial function of the dog heart-lung preparation. *J. Pharmac. exp. Ther.*, **115,** 206–216.

PRICE, H.L., WARDEN, J.C., COOPERMAN, L.H. & MILLAR, R.A. (1969). Central sympathetic excitation caused by cyclopropane. *Anesthesiology*, **30,** 426–438.

PRICE, M.L. & PRICE, H.L. (1962). Effects of general anaesthetics on contractile responses of rabbit aortic strips. *Anesthesiology*, **23,** 16–20.

ROBINS, B.H. & BAXTER, J.H. (1940). Studies of cyclopropane: The effects of premedication with morphine or amytal upon the heart rate rhythm and blood pressure in dogs under cyclopropane anaesthesia. *J. Pharmac. exp. Ther.*, **68,** 85–95.

ROIZEN, M.F., THOA, N.B., MOSS, J. & KOPIN, I.J. (1976). Inhibition by cyclopropane of release of norepinephrine but not dopamine-β-hydroxylase from the guinea-pig vas deferens. *Anesthesiology*, **44,** 54–56.

(Received April 5, 1977.
Revised June 13, 1977.)