HALOTHANE AND THE RESPONSES OF THE HEART TO AUTONOMIC NERVE STIMULATION

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SUMMARY

The effect of halothane on the responses to stimulation of the efferent autonomic nerves to the heart was determined in dogs lightly anaesthetized with chloralose. In the absence of nerve stimulation halothane (inspired concentration 0.8%) led to significant falls in heart rate and blood pressure and in the maximum rate of change of left ventricular pressure measured at a constant paced heart rate. The slowing of the heart produced by vagal stimulation was not altered by halothane. The increases in heart rate produced by stimulating the right and left ansae subclaviae were not affected by halothane. Using LV dP/dt max at a constant heart rate as an index of the inotropic state of the heart, halothane shifted to the right the response curve resulting from stimulation of the left ansa; this shift could be accounted for by a fall in blood pressure produced by halothane. It was concluded that halothane in this concentration did not produce changes in the cardiovascular system by altering the responsiveness of the heart to the acetylcholine and noradrenaline released at the local nerve endings.

In common with all general anaesthetic drugs, halothane produces direct effects on the heart and blood vessels. The direct effect on the heart produces some depression of cardiac function (e.g. Burn et al., 1957). But the properties of the cardiovascular system can be modified greatly by alterations in the activity of the efferent autonomic nerves. It is known that halothane has some ganglion-blocking properties (Biscoe and Millar, 1966; Price and Price, 1967) and there is some evidence that it reduces the responses of the peripheral blood vessels to noradrenaline (Black and McArdle, 1962). The experiments reported here were designed to determine whether halothane had an additional effect in altering the responses of the heart to stimulation of the efferent postganglionic sympathetic nerves and parasympathetic nerves. The results show that whilst halothane had a significant direct effect on the heart in anaesthetized dogs, the responses to stimulation of the autonomic nerves were not altered.

METHODS

Nine dogs weighing between 10 and 25 kg were studied. Responses were measured in an initial and final control period when the animals were anaesthetized with chloralose and an intervening period when halothane was given. Anaesthesia was induced with thiopentone 25 mg/kg i.v. and maintained in a light plane with chloralose (initial dose 50 mg/kg followed by approximately 10 mg/kg every 30 min). No chloralose was given when halothane was administered. Each animal was ventilated via a tracheostomy with a mixture of 40% oxygen and 60% nitrogen using an anaesthetic machine incorporating a Starling Ideal pump (Ledsome, Linden and Norman, 1967). When the chest was opened a resistance to expiration was created by placing the outlet of the pump under 2–3 cm of water. The ventilation was adjusted to maintain an arterial carbon dioxide tension of approximately 40 mm Hg.

A scheme of the preparation is shown in figure 1. The chest was opened by dividing the sternum. The stellate ganglia were identified and the limbs of the ansae subclaviae crushed at their origins from the ganglia. The vagus nerves were divided in the neck. Light shielded bipolar silver electrodes were placed around the distal cut end of the right vagus nerve and around the limbs of the ansae distal to the sites of crushing. Supramaximal square wave stimuli of 2 msec duration for these electrodes were generated by Palmer stimulators (model 8038) isolated from earth by Devices isolation units (model 2533).

The pericardium was opened and sutured to the sternal edges. Two small silver electrodes were
FIG. 1. Scheme of experimental preparation.

Experimental preparation.

R. Stellate ganglion

Vagus nerve

Stimulating electrodes

L. Stellate ganglion

stimulating electrodes

Ventricular pressure

Left ventricular pressure

Femoral artery blood pressure

Heart rate

E.C.G.

B.P.

sutured to the tip of the right atrial appendage and used for pacing the heart at a constant rate. A short stainless steel cannula (1.5 mm bore) was placed in the left ventricle through the apical dimple. A second similar cannula was placed in the right femoral artery. The ventricular and femoral arterial pressures were measured by attaching to the cannulae Statham P23Gb strain gauges. The outputs of the gauges were amplified and recorded on an ultraviolet light recorder (SE Laboratories carrier amplifiers and recorder). The manometers were calibrated in a stepwise manner using a mercury manometer and zero pressure was recorded postmortem as the pressure at the cannula tip with the tip in air free of blood and tissue. The frequency response of the whole system was flat (±5%) to better than 80 Hz as determined by the method of Ardill, Fentem and Welland (1967). The rate of change of the left ventricular pressure pulse (LV dP/dt) was measured by differentiating the signal from the carrier amplifier using an operational amplifier (Tektronix model 3A8) and a simple capacitor-resistance network. The system was calibrated using a sine wave generator by the method of Neal, Halpern and Reeves (1960) and showed a linear gain in amplitude with increasing frequency and a 90° phase shift from 1.5 to 100 Hz. The resulting wave form was recorded, as was an electrocardiogram, using the ultraviolet light recorder. Heart rate was counted over 20-sec periods from the e.c.g. or the blood pressure record.

Arterial blood samples taken from the left femoral artery were analysed for pH, and carbon dioxide and oxygen tensions using an EIL blood-gas analyser (model 48C). The accuracies for these measurements (95% tolerance limits) were: pH ± 0.01 units, carbon dioxide tension ± 2.5% of the predicted value, and oxygen tension ± 2 mm Hg. Any non-respiratory acidemia was corrected by infusing a 4.2% solution of sodium bicarbonate. The animal temperature was maintained between 35 and 39°C by adjusting heating lamps beneath the animal table. Dextran (Dextran 150 in 5% dextrose; Fisons Pharmaceuticals) was infused in a volume of up to 150 ml during the preparation of each animal to replace blood lost. Additional volumes of up to 100 ml were infused when halothane was administered.

Following the determining of the cardiac responses during the initial control period, halothane was
administered in an inspired concentration of 0.8% by drawing the inspired gases through a Fluotec Mk II vaporizer. The vaporizer was calibrated for this delivery system using a calibrated Hook & Tucker halothane meter. On stopping halothane administration the animals made some spontaneous movements after some 10-15 min, at which stage the chloralose administration was restarted.

The determination of the responses to stimulation of the nerves took at least an hour in each period. The responses were determined when halothane was given beginning 10-15 min after starting the administration.

Mean values and standard deviations were calculated using conventional formulae. Regression analyses were performed using the methods described by Armitage (1971). These calculations were performed using programmes written for a Wang 500 programmable calculator.

RESULTS

Acid-base state.

The pH of the arterial blood samples varied from 7.24 to 7.40 with a mean value of 7.32 (SD 0.06). The carbon dioxide tension varied from 33 to 55 mm Hg with a mean value of 41 mm Hg (SD 8 mm Hg). The average arterial oxygen tension was 154 mm Hg (SD 61 mm Hg) and the range 80-235 mm Hg.

Effect of halothane on the heart.

When halothane was given, within some 5 minutes, the heart rate, the blood pressure and the maximum rate of increase in the left ventricular pressure (LV dp/dt max) fell. In some animals the fall in blood pressure was so large as to cause concern as to the viability of the preparation. An infusion of dextran was used to restore an adequate pressure. On stopping the halothane the heart rate, the blood pressure and LV dp/dt max rose. The results obtained in the three stages—before, during and after halothane were given beginning 10-15 min after starting the administration.

The responses to stimulation of the right vagus nerve.

Stimulation of the distal cut end of the right vagus nerve with pulses of supramaximal intensity (10-20V) produced an immediate slowing of the heart. If the stimulation rate was high enough (approximately 20 Hz) the heart would stop for a varying length of time before the ventricles would resume a slow, often irregular, beat. The responses to vagal stimulation were determined in the following way. An initial record was obtained and the heart rate measured. The vagus nerve was stimulated successively at 1, 2, 5 and 10 Hz and the heart rate measured over 20-sec periods at each rate. The responses were measured in five dogs, usually once before, during and after halothane was given. The results are summarized in table II with the results obtained in the two control periods grouped together.

Table I. Effect of halothane on the cardiovascular state.

<table>
<thead>
<tr>
<th>Period</th>
<th>Initial</th>
<th>Halothane</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>148 ±23</td>
<td>136 ±23</td>
<td>145 ±25</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>144 ±26</td>
<td>111 ±21</td>
<td>135 ±22</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>100 ±22</td>
<td>72 ±17</td>
<td>91 ±19</td>
</tr>
</tbody>
</table>

Values are means ±1 SD.

Table II. Effect of halothane on the response to right vagus nerve stimulation.

<table>
<thead>
<tr>
<th>Vagus nerve stimulation rate (Hz)</th>
<th>Control (9 observations)</th>
<th>Halothane (5 observations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>147±25</td>
<td>151±29</td>
</tr>
<tr>
<td>1</td>
<td>128±23</td>
<td>136±33</td>
</tr>
<tr>
<td>2</td>
<td>118±27</td>
<td>127±32</td>
</tr>
<tr>
<td>5</td>
<td>89±30</td>
<td>103±36</td>
</tr>
<tr>
<td>10</td>
<td>53±31</td>
<td>71±50</td>
</tr>
</tbody>
</table>

Values are means ±1 SD. Results obtained in 5 dogs.

Figure 2 shows the mean values obtained together with the regression lines calculated for the heart rates as a function of the logarithm of the stimulation rate. The equations are:

Control periods

Heart rate=135.7–73.6 log stimulation rate (9 stimulation sequences, r=−0.72; P<0.001)
RESPONSES OF THE HEART TO AUTONOMIC NERVE STIMULATION

Halothane period
Heart rate = 141.6 - 64.2 log stimulation rate
(5 stimulation sequences, \( r = -0.58; P < 0.01 \))

These equations do not include the heart rates measured when the nerve was not stimulated. Although the response to vagal stimulation is diminished when halothane was given this was not statistically significant. The slopes of the lines do not differ \( (t=0.41; 0.7 > P > 0.6) \) neither do the positions of the lines \( (t=1.40; 0.2 > P > 0.1) \). Thus halothane in an inspired concentration of 0.8% did not modify the chronotropic response to vagal stimulation.

![R. Vagus Stimulation Rate Hz](image)

Fig. 2. Average responses to stimulation of the right vagus nerve. Circles: responses in control stages. Squares: responses in halothane stage. Open symbols: results in absence of stimulation. Closed symbols: results during stimulation. Results obtained in seven dogs.

Chronotropic responses to stimulation of the ansae subclaviae.

Stimulation of either ansa subclavia produced an increase in heart rate provided the stimulation rate was high enough. The increases became apparent within some 2-4 sec and reached a stable value after some 20 sec. At any stimulation rate the heart rate was greater when the right ansa was stimulated. The response to stimulation of each ansa was determined as follows. An initial record was obtained and the rate measured. The ansa was stimulated supramaximally (10-30V pulses) successively at 1, 2, 5 and 15 Hz. Records were taken beginning 30 sec after stimulation. After stimulation at 15 Hz some 3-5 min were needed for the effects of stimulation to subside. Two sets of responses to stimulation of each ansa were obtained in each control period and when halothane was given.

The results for the nine dogs are summarized in tables III and IV with the results obtained in the two control periods grouped together. The mean values are shown in figures 3 and 4 together with the regression lines calculated for the heart rate as a function of the logarithm of the stimulation frequency. The equations for stimulation of the right ansa are:

**Control periods**
Heart rate = 193 + 60.8 log stimulation rate (36 stimulation sequences, \( r = +0.73; P < 0.001 \))

**Halothane period**
Heart rate = 179 + 72.4 log stimulation rate (18 stimulation sequences, \( r = +0.80; P < 0.001 \))

The response curve has a greater slope when halothane was given but this is not statistically significant \( (t=1.41; 0.2 > P > 0.1) \). The curve is displaced to the right of that found in the control periods and this...
displacement is significant \((t=1.981; P<0.05)\). The equations for stimulation of the left ansa are:

Control periods

Heart rate = 153 + 45.1 log stimulation rate (36 stimulation sequences, \(r=+0.66; P<0.001\))

Halothane period

Heart rate = 140 + 51.8 log stimulation rate (18 stimulation sequences, \(r=+0.73; P<0.001\))

Inspection of figure 4 shows again that halothane led to a shift of the response curve to the right and a greater slope. Statistically the difference in the slopes of the two lines is not significant \((t=0.92; 0.4>P>0.3)\) but the shift in position is \((t=2.91; P<0.005)\).

The shift of the responses to stimulation of both ansae may be associated with the lower heart rates seen with halothane in the unstimulated stages (table I). The increases in the slope values are not significant and do not lead to a faster heart rate when halothane was given at the highest stimulation rate. Incidentally in these preparations even maximal stimulation of the ansae (15 Hz) did not lead to any arrhythmias when halothane was given.

**Inotropic response to stimulation of the left ansa subclavia.**

Assessment of the inotropic responses to sympathetic nerve stimulation is often made difficult by the concomitant increase in heart rate produced by the stimulation. This can be overcome by pacing the heart at a rate greater than that produced by the sympathetic stimulation. The assessment is easier to make when the left ansa is stimulated, for its stimulation produces smaller heart rate changes. The index of the inotropic response used was the maximum rate of increase in the left ventricular pressure.

The responses were determined in seven of the dogs in the following way. Initially the heart rate was increased by pacing (2 msec pulses, 1–2 V) to a level just below that at which pulsus alternans appeared. Control records were taken. The left ansa was stimulated successively at 1, 2, 5 and 10 Hz and records taken beginning 30 sec after the start of stimulation. Figure 5 shows parts of the records of one such stimulation sequence. The highest stimulation rate used (10 Hz) usually did not lead to a further gain in heart rate over the paced rate; if it did the increase was never more than 20 beats/min. The responses were determined once in each control period and once when halothane was given. In each animal the paced heart rate was the same in each period. Table V summarizes the results for both LV \(dP/dt\) max and for the mean arterial blood pressure. Mean pressure was calculated as the diastolic pressure plus one-third of the pulse pressure.

The average results and the corresponding regression lines are shown in figure 6. Halothane appears to lead to a shift of the inotropic response curve to the right. The equations are:

Control periods (14 stimulation sequences)

- LV \(dP/dt\) max = 2410 + 2868 log stimulation rate (mm Hg/sec) \((r=+0.80; P<0.001)\)
- Mean BP = 131 + 19 log stimulation rate (mm Hg) \((r=+0.35; P<0.01)\)

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**TABLE V. Effect of halothane on the response to stimulation of the left ansa at constant heart rate.**

<table>
<thead>
<tr>
<th>Left ansa stimulation rate (Hz)</th>
<th>LV dP/dt max (mm Hg/sec)</th>
<th>Mean blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Halothane</td>
</tr>
<tr>
<td>0</td>
<td>1936±531</td>
<td>1100±535</td>
</tr>
<tr>
<td>1</td>
<td>2536±577</td>
<td>1614±445</td>
</tr>
<tr>
<td>2</td>
<td>3100±625</td>
<td>2257±1261</td>
</tr>
<tr>
<td>5</td>
<td>4393±926</td>
<td>3514±1261</td>
</tr>
<tr>
<td>10</td>
<td>5271±1054</td>
<td>4157±1333</td>
</tr>
</tbody>
</table>

Values are means ±1 SD. Results in 7 dogs, with 14 observations in the control periods and 7 in the halothane period.

Halothane period (7 stimulation sequences)

LV dP/dt max = 1570 + 2630 log stimulation rate (mm Hg/sec) ($r = +0.73; P<0.001$)

Mean BP = 96 + 33 log stimulation rate (mm Hg) ($r = 0.54; P<0.01$)

Statistically the slope values for the equations for LV dP/dt max are not significantly different ($t=0.45; 0.7>P>0.6$) but the shift to the right is ($t=4.78; P<0.001$). Similarly the slopes of the lines for the mean blood pressure changes are not significantly different ($t=0.97; 0.4>P>0.3$) but the position of the lines do differ ($t=5.34; P<0.001$).

One factor determining LV dP/dt max is the mean aortic blood pressure (Furnival, Linden and Snow, 1970). This was not controlled in the preparations.
FIG. 6. Inotropic responses to stimulation of the left ansa subclavia with the heart rate held constant. Above: the maximum rate of rise of left ventricular pressure (LV dP/dt max). Below: the mean arterial blood pressure. Symbols as in fig. 2. Results obtained in seven dogs.

FIG. 7. Responses to stimulation of the ansa subclavia at constant heart rate and comparable mean blood pressure. Square symbols: results obtained during halothane. Triangles: results obtained in the final control stage after bleeding. Results obtained in three dogs.

described here and it is probable that much of the shift of the LV dP/dt response curve was due to the fall in blood pressure produced by the halothane. To examine this, in three experiments, after obtaining responses in the final control period the animals were bled to lower the blood pressure to the same level as that found when halothane was given. The responses to stimulation of the left ansa with the heart rate held constant were then redetermined and compared with the responses seen in these three animals when halothane was given. Table VI summarizes these results and the mean values and the corresponding regression lines are shown in figure 7. The equations are:

Control periods—bled (3 stimulation sequences)

LV dP/dt max = 2104 + 3025 log stimulation rate (mm Hg/sec) (r = +0.96; P < 0.001)
Mean BP = 113 + 24 log stimulation rate (mm Hg) (r = +0.47; P > 0.1)

Halothane periods (6 stimulation sequences)

LV dP/dt max = 1813 + 2924 log stimulation rate (mm Hg/sec) (r = +0.81; P < 0.001)
Mean BP = 110 + 31 log stimulation rate (mm Hg) (r = 0.68; P < 0.05)

The equations for both the LV dP/dt max and the mean blood pressure in the two periods differ statistically neither in slope nor position. (LV dP/dt max: slope comparison t = 0.15; P > 0.8; position comparison t = 1.33; P > 0.1: mean BP: slope comparison t = 0.50; P > 0.6; position comparison t = 0.05; P > 0.95).

Thus the inotropic response of the heart to stimulation of the left ansa subclavia was not significantly altered by halothane.

DISCUSSION

The results presented here show that whilst halothane has a marked effect on the heart the responses to stimulation of the vagus nerve and the efferent
TABLE VI. Effect of halothane on the response to stimulation of the left ansa at constant heart rate and comparable blood pressure.

<table>
<thead>
<tr>
<th>Left ansa stimulation rate (Hz)</th>
<th>LV dP/dt max (mm Hg/sec)</th>
<th>Mean blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Halothane</td>
<td>Bled</td>
</tr>
<tr>
<td>0</td>
<td>1133 ± 234</td>
<td>1433 ± 666</td>
</tr>
<tr>
<td>1</td>
<td>1833 ± 207</td>
<td>2167 ± 404</td>
</tr>
<tr>
<td>2</td>
<td>2617 ± 504</td>
<td>2933 ± 116</td>
</tr>
<tr>
<td>5</td>
<td>3967 ± 1122</td>
<td>4200 ± 265</td>
</tr>
<tr>
<td>10</td>
<td>4683 ± 1277</td>
<td>5167 ± 651</td>
</tr>
</tbody>
</table>

Values are means ± 1 SD. Results obtained in 3 dogs, with 6 observations in the halothane period and 3 in the bled control period (see text).

In order to examine the effect of halothane it was necessary to use a basal anaesthetic. Ideally no such anaesthetic should be used. In one dog in which a decerebration was performed the responses to stimulation of the nerves were similar to those reported here. Decerebration of the dog involved a considerable addition to the trauma involved in the preparation and its advantages were not thought sufficient. Chloralose was used as the basal anaesthetic; a prolonged period of light anaesthesia can be easily maintained with it (Ledsome, Linden and Norman, 1971). Skovsted, Price and Price (1970) found halothane and chloralose to interact in cats so that, after chloralose, halothane led to a marked reduction in pre-ganglionic sympathetic activity, whilst after nitrous oxide the reduction was smaller. They did not find a similar interaction in dogs and it appears acceptable to use chloralose as a basal anaesthetic in this type of preparation.

The responses to stimulation of the nerves are presented as the absolute values of heart rate and LV dP/dt max obtained. To allow a statistical comparison of the results, regression equations were calculated using the results and the logarithms of the stimulation rates. It is not intended that these should be regarded as dose-response curves; they were calculated as reasonably straight lines emerged and the statistical techniques for the comparison of these lines are readily available (Armitage, 1971).

In this near normal state to avoid the known effects of an acidosis in potentiating vagal responses and attenuating sympathetic responses (Campbell, 1955; Linden and Norman, 1969).

sympathetic nerves do not change. The results were obtained in dogs in which the vagi were divided and the ansae subclaviae crushed. These manoeuvres divide the efferent autonomic pathways to the heart (Mizeres, 1958), allowing the responses to stimulation of the distal ends of the nerve to be examined without secondary reflex changes supervening. The acid-base state of the animals was maintained in a
at the start of each individual stimulation sequence. When halothane was given, stimulation of the left ansa led to a greater percentage increase than that seen in the control periods. This is significant statistically ($t=2.52; P<0.02$). Does this mean that halothane is sensitizing the heart to sympathetic stimulation? Panel B shows the results expressed as the absolute increases in LV $dP/dt$ max brought about by stimulation. The regression lines coincide (statistically they differ neither in slope ($t=0.37$) nor position ($t=0.37; P>0.5$ in both cases). An interpretation could be that halothane had no effect. Panel C shows the results as presented in figure 6. The slopes of the lines do not differ but the positions do. With, in addition, the control values without stimulation being shown it is apparent that halothane produces an effect in the absence of stimulation and that the heart responds to stimulation of the ansa when halothane is given. All the information obtained is presented.

The inspired halothane concentration used was low (0.8%) and of the order that at equilibrium would just abolish the response to pain in dogs (Eger et al, 1965). But the preparation used was sensitive to any higher concentration. In some initial experiments higher concentrations killed the dogs and this concentration often produced marked hypotension. The situation appears similar to that seen with acidaemia in dogs where a greater degree of acidaemia can be tolerated if the sympathetic nervous system is intact (Clowes, Hopkins and Simeone, 1955). Presumably the sympathetic pathways to the heart must be intact if dogs are to survive either an acidaemia or deep halothane anaesthesia.

The fall in heart rate produced by vagal stimulation was not changed by halothane. Higher halothane concentrations than that used here can affect other cholinergic transmission sites. The neuromuscular junction may show a diminished transmission especially if another drug such as tubocurarine is used to enhance the effect (Gissen, Karis and Nastuk, 1966; Katz and Katz, 1968). Cholinergic transmission through the stellate ganglion is only depressed by halothane in the concentration used here when drugs are used which block either the muscarinic or nicotinic receptors in the ganglion cells (Alper, Fleisch and Flacke, 1969). The cardiac receptors appear not to be affected.

The increases in heart rate seen when the ansa subclaviae were stimulated were not affected by halothane although the response curves show some shift to the right. This shift is associated with a fall in the control heart rate when halothane was given. Perhaps halothane slows the spontaneous rate of depolarization of the pacemaker fibres which, however, retain their sensitivity to catecholamines. Prys-Roberts and his colleagues (1970) reported similar results to those presented here with stimulation of the right ansa. Price and his colleagues (1968) claimed that both halothane and cyclopropane potentiated the chronotropic response to stimulation of the left ansa. However, they used only one stimulation rate (between 5 and 8 Hz) and the results are not presented in sufficient detail to check their conclusions. Alper, Fleisch and Flacke (1969) found halothane to have no effect on heart rate increase produced by stimulation of stellate ganglion cells by close intra-arterial injections of acetylcholine. Presumably both the ganglion cells and the cardiac receptors retain their normal sensitivity when exposed to halothane.

Thus chronotropic responses do not change when halothane is given. The assessment of inotropic responses is much more difficult. What was wanted for these experiments was an index which would show reasonable changes when the sympathetic nerves were stimulated. Rushmer (1962) pointed out that whilst sympathetic nerve stimulation produces changes in absolute quantities such as blood pressure, ventricular end-diastolic pressure and atrial pressure, the effects on rates of changes of pressure, flow and work are much more dramatic. One such rate—the maximum rate of change of left ventricular pressure—has become a popular index, as it is relatively easy to make an accurate measurement. Furnival, Linden and Snow (1970) showed it to be an index of the inotropic state of the heart if it was measured at a constant heart rate and at a constant mean aortic blood pressure. In the experiments described here LV $dP/dt$ max was measured with the heart rate maintained constant. Blood pressure was not controlled. Halothane produced a fall in blood pressure and shifted the response curve to the right. But when the mean aortic blood pressure was reduced in the final control period to the same level as that seen in the halothane period (table VI, fig. 7) the lines coincided. It seems, therefore, that halothane in this concentration is not altering the inotropic responses to sympathetic nerve stimulation. Prys-Roberts and his colleagues (1970) used a 'different index of inotropism—LV $dP/dt$ max divided by the intraventricular pressure at the time of LV $dP/dt$ max. Using this index they found halothane to produce a slight diminution of the inotropic effects.

Halothane does depress the peripheral circulatory
responses to catecholamines (Akester and Brody, 1967; Black and McArdle, 1962; Price and Price, 1962). The reduction in the blood pressure change produced by noradrenaline with halothane anaesthesia reported by Price and his colleagues (1959) may well be accounted for by the changed peripheral response rather than a cardiac effect.

The results presented here suggest that the profound circulatory changes produced by halothane are not due to an altered responsiveness of the cardiac nerve receptors and they further imply that any un-toward depression could be countered by activation of the postganglionic sympathetic nerves to the heart. Any ganglionic block produced by halothane is not complete (Biscoe and Millar, 1966). Price and associates (1970) found that in man halothane produced an initial fall in cardiac output but over the subsequent hours the output returned towards normal values. This subsequent increase was not seen in subjects given a β-receptor blocking drug. They could not account for the increase in output by the development of an acidemia or by an increase in the oxygen consumption and were left speculating whether halothane activated the β-receptors directly or indirectly by an increased sympathetic activity. The results presented here suggest that an increase in sympathetic activity would have an effect and need not be large to produce the changes they found. Stimulation at 1 Hz of either ansa always produced marked effects.

ACKNOWLEDGEMENTS

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HALOTHANE ET REPONSES CARDIAQUES A UNE STIMULATION DU SYSTEME NERVEUX AUTONOME

SOMMAIRE
Les effets de l'halothane sur les réponses du coeur à une stimulation des fibres nerveuses éfferentes appartenant au système nerveux autonome, ont été étudiés chez des chiens légalement anesthésiés au chloralose. En l'absence d'une stimulation nerveuse, l'halothane (inhalé à la concentration de 0,8%) a entraîné des chutes significatives de la fréquence cardiaque et de la pression sanguine, ainsi que du taux maximum de variation de la pression ventriculaire gauche, mesurée pour une fréquence cardiaque constante et normale. Le ralentissement cardiaque engendré par une stimulation du vague n'a pas été modifié par l'halothane.

Les augmentations de la fréquence cardiaque provoquées par la stimulation des anses de Vieussens droite et gauche n'ont pas été affectées par l'halothane. En se servant de LV dP/dt max à une fréquence cardiaque constante, en tant qu'indicateur de l'inotropie cardiaque, l'halothane a entraîné un déplacement vers la droite de la courbe de réponse consécutive à une stimulation de l'anse de Vieussens gauche; ce décalage a pu être attribué à une chute de la pression sanguine engendrée par l'halothane. On en a conclu que l'halothane administré à cette concentration n'avait pas déterminé de modifications au niveau du système cardio-vasculaire en altérant la réponse cardiaque à l'acétylcholine et à la noradrénaline libérées au niveau des terminaisons nerveuses "in situ".

HALOTHANE UND DIE REAKTIONEN DES HERZENS AUF DIE REIZE DES AUTONOMEN NERVENSYSTEMS

ZUSAMMENFASSUNG

EL HALOTHANE Y LAS RESPUESTAS DEL CORAZON A LA ESTIMULACION NERVIOSA

RESUMEN
En perros ligeramente anestesiados con cloralosa se determinó el efecto del halothane sobre las respuestas del corazón a la estimulación del nervio eferente autónomo. En ausencia de estimulación del nervio, el halothane (concentración inspiratoria de 0,8%) produce una caída significativa de la frecuencia cardíaca, de la presión arterial y del valor máximo de cambio de presión del ventrículo izquierdo, medida como una constante del valor de la ación cardíaca. El enlentecimiento del corazón producido por la estimulación vagal no era alterado por el halothane. El aumento de la frecuencia cardíaca, producido por estimulación de las ramas subclavias derecha e izquierda, no era afectado por el halothane. Utilizando LV dP/dt máx. como una constante de la función cardíaca, como índice del estado inotrópico del corazón, el halothane desvió hacia la derecha la curva de respuesta, resultante de la estimulación de la rama izquierda; este cambio podría ser explicado por una caída de la tensión arterial producida por el halothane. Se concluyó, que el halothane, en esta concentración, no producía cambios en el sistema cardiovascular, alterando la disposición de respuesta del corazón respecto a la acetilcolina y noradrenalina liberadas en la terminación nerviosa local.