THE EFFECT OF INHALATIONAL ANAESTHETICS ON HYPOXIC PULMONARY VASOCONSTRICTION AND PULMONARY VASCULAR RESISTANCE IN THE PERFUSED LUNGS OF THE DOG AND CAT


SUMMARY

Alveolar hypoxia produced an increase in pulmonary vascular resistance in isolated cat and dog lungs or lobes perfused at constant flow. This response was abolished for varying periods of time by the administration of high concentrations of inhalational anaesthetic agents. In these preparations 5 per cent halothane caused pulmonary vasodilatation whereas 15 per cent ether, 1.5 per cent trichloroethylene and 79 per cent nitrous oxide caused vasoconstriction. Two per cent methoxyflurane did not cause a significant change in pulmonary vascular resistance. It is postulated that the abolition of the pulmonary vasoconstrictor response to hypoxia may increase the proportion of blood flowing through shunts or areas of lung with a low ventilation/perfusion ratio and so may contribute to a decrease in arterial oxygen tension during anaesthesia. The pulmonary vasodilatation or vasoconstriction produced by inhalational agents may augment this effect.

There have been many reports of an increase in the alveolar-to-arterial oxygen tension difference (A-a \( P_{\text{O}_2} \)) after the induction of general anaesthesia in man (Campbell, Nunn and Peckett, 1958; Marshall, 1966; Marshall and Grange, 1966; Prys-Roberts, Kelman and Greenbaum, 1967; Marshall et al., 1969; Bergman, 1970; Foëx, Meloche and Prys-Roberts, 1971).

Whilst an increase in A-a \( P_{\text{O}_2} \) difference may indicate an increase in ventilation/perfusion inequality or right-to-left shunt, it may also arise as a result of a change in the oxyhaemoglobin dissociation curve, anaemia or a fall in cardiac output. It now seems unlikely that anaesthetics affect the dissociation curve (Weiskopf, Nishimura and Severinghaus, 1971; Millar, Beard and Hulands, 1971) and the fall in cardiac output after induction of anaesthesia does not appear to be sufficient to account for the increase in A-a \( P_{\text{O}_2} \) difference (Panday and Nunn, 1968). It therefore seems likely that the change in A-a \( P_{\text{O}_2} \) difference is caused by an increase in ventilation/perfusion inequality or to an increase in intrapulmonary shunt.

Bergman (1967) measured the A-a \( P_{\text{O}_2} \) difference in anaesthetized patients breathing 25 to 30 per cent and 100 per cent oxygen and found that the calculated venous admixture was similar with both gas mixtures. He therefore concluded that most of the increase in A-a \( P_{\text{O}_2} \) difference was attributable to shunt. However, Bergman did not sample mixed venous blood and it was only in the studies of Marshall and associates (1969) and Price and associates (1969) that an increase in right-to-left shunt was specifically demonstrated. Foëx, Meloche and Prys-Roberts (1971) found no increase in shunt immediately after induction in a group of hypertensive patients but an increase was demonstrated in the later stages of anaesthesia and in the postoperative period. Further evidence implicating shunts in the causation of the increase in A-a \( P_{\text{O}_2} \) difference was provided by Hulands and associates (1970) and Rehder and associates (1971). Both groups found little evidence of a marked increase in ventilation/perfusion inequality during anaesthesia and concluded that most of the increase in A-a \( P_{\text{O}_2} \) difference must be caused by shunt.

The mechanism of the shunt is not yet clear but it is postulated that it may be due to an increase in terminal airway closure associated with a fall in functional residual capacity, progressive atelectasis, an increase in the proportion of blood flowing through existing intrapulmonary shunts, or the opening of new shunt pathways.

It is known that the distribution of pulmonary blood flow is governed mainly by the relation between alveolar, pulmonary arterial and pulmonary venous pressures (West, 1970). However, there is now evidence that alveolar gas concentrations may play an important role in the matching of perfusion to ventilation at alveolar level, a fall in alveolar \( Po_2 \) or rise in alveolar \( Pco_2 \) causing pulmonary vasoconstriction and so diverting blood away from underventilated or non-ventilated alveoli (Barer, 1966; Barer et al., 1969; Barer, Howard and Shaw, 1970). This mechanism is present in both innervated and denervated lungs perfused at constant flow and is highly active in the cat (Hebb and Daly, 1966). However, it is also present in the isolated perfused lungs of the dog, rat and calf (Duke, 1957; Hauge, 1968; Silove, Inoue and Grover, 1968). Indirect evidence for the existence of such a mechanism in man has been provided by experiments in which it has been shown that blood is diverted away from a lung which is ventilated with a hypoxic gas mixture (Blakemore, Carlens and Björkman, 1955; Himmelstein et al., 1958; Defares et al., 1960). Generalised alveolar hypoxia has also been shown to divert blood from the lower to the upper zones thus making distribution more uniform (Fowler and Read, 1963; Dugard and Naimark, 1967).

The purpose of this homeostatic mechanism is presumably to minimise the effects of maldistribution of ventilation: it may therefore be of great importance in patients with obstructive airways disease (Lee and Read, 1967). If it were to be obtunded, an increase in venous admixture might be expected to occur. The hypothesis proposed by the present authors is that the pulmonary vasoconstrictor response to alveolar hypoxia might be abolished by anaesthetic agents, thereby permitting more blood to flow through hypoxic areas of lung and increasing the venous admixture due to ventilation/perfusion inequality and right-to-left shunt. It is also possible that anaesthetic agents might act directly or indirectly on the pulmonary vasculature in such a way that more blood is diverted through poorly ventilated areas of lung. Such an effect would be produced by vasodilatation in hypoventilated areas of lung or vasoconstriction in normal or hyperventilated areas.

These hypotheses have been examined in three types of animal preparation:

1. Closed-chest dogs rendered unconscious by decerebration or by chloralose.
2. Open-chest dogs maintained on right and left heart bypass (to eliminate the effects of changes of cardiac output on the innervated pulmonary circulation).
3. Isolated perfused lungs of the dog and cat (to eliminate effects mediated via the autonomic system as well as effects caused by changes in cardiac output).

With this protocol it was hoped that it would be possible to isolate the direct effects of the anaesthetic agent on the pulmonary vasculature from those mediated by the autonomic system and then to observe how these might be modified by circulatory changes in the intact animal.

The present paper describes right and left heart bypass and isolated lung perfusion experiments which were designed to answer two questions. Firstly, do anaesthetic agents abolish the normal pulmonary vasoconstrictor response to alveolar hypoxia; and secondly, do they act directly or indirectly on the pulmonary vasculature causing pulmonary vasoconstriction or dilatation?

**METHODS**

The various preparations used are summarized in table I.

**Right and left heart bypass preparations.**

Greyhound dogs (20–30 kg) were anaesthetized with nitrous oxide-oxygen-halothane, intubated and ventilated with air and 0.5–1.0 per cent halothane by a Cape ventilator. The respiratory frequency was 20 b.p.m. and the tidal volume was adjusted to maintain the end-tidal \( CO_2 \) concentration between 4 and 5 per cent. A normal acid-base status was maintained by the addition of 4.2 per cent sodium bicarbonate when required. A pressure-operated collect valve (Sykes, 1969) was interposed between the ventilator patient connection port and the endotracheal tube to separate expired gas from the gas compressed within the ventilator tubing, and a gravity-operated valve was connected to the expiratory port of the collect valve so that an end-expiratory pressure of 5–10 cm \( H_2O \) could be applied to the lungs when the chest was open. Expired gas passed through a mixing unit (Sykes, 1968) and the expired volume was measured with a calibrated dry gas meter.
Table 1. Summary of Preparations Used.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Species</th>
<th>Successful Perfusions</th>
<th>Anaesthesia</th>
<th>+ hypoxic response</th>
<th>Perfusate</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. and L. heart bypass (fig. 1)</td>
<td>Dog</td>
<td>21/24</td>
<td>N₂O, halothane</td>
<td>2</td>
<td>homologous venous blood</td>
<td>PAP, LAP, FAP, AP, flow, gas exchange</td>
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<td>Isolated lung (fig. 2)</td>
<td>Dog</td>
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<td>N₂O halothane</td>
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<td>autologous venous blood</td>
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<td>4</td>
<td>I.V. chloralose</td>
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<td>I-P. pentobarbitone</td>
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<td></td>
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<tr>
<td>Left lower lobe (fig. 3)</td>
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<td>8</td>
<td>I-V, pentobarbitone</td>
<td>4</td>
<td>autologous venous blood</td>
<td>PAP, LAP, AP, flow</td>
</tr>
<tr>
<td>- Cat</td>
<td></td>
<td>2</td>
<td>I-P. pentobarbitone</td>
<td>2</td>
<td>autologous venous blood and dextran</td>
<td>PAP, LAP, AP, flow</td>
</tr>
<tr>
<td>Isolated lung (fig. 4)</td>
<td>Cat</td>
<td>22/24</td>
<td>I-P. pentobarbitone</td>
<td>22</td>
<td>autologous arterialised blood + dextran</td>
<td>PAP, LAP, AP, flow</td>
</tr>
</tbody>
</table>

PAP = pulmonary artery pressure
LAP = left atrial pressure
FAP = femoral artery pressure
AP = airway pressure

The hypoxic response was considered positive (+) when the pulmonary artery pressure rose by more than 2 mm Hg during the inhalation of 3–5% oxygen in nitrogen for 3–5 min.

When the pulmonary and femoral arteries had been cannulated, the halothane was turned off and anaesthesia maintained with intravenous injections of chloralose, the initial dose being 50–80 mg/kg body weight and subsequent increments 0.5 g. Oxygen was added to the inspired gas during thoracotomy but at all other times the animal inspired air either alone or with the inhalational anaesthetic agent under test.

The perfusion circuit is shown in figure 1. The tubes were made of silicone rubber, the connections of nylon and the reservoirs of glass or Perspex. The circuit was scrupulously cleaned before use* and primed with heparinised blood from a donor animal which had also been anaesthetized with chloralose. The roller pumps were shown to be occlusive against a hydrostatic pressure of at least 100 mm Hg before each perfusion and blood flow was checked at intervals by diverting the left atrial drainage into a graduated flask and noting the time required to accumulate 500 ml. All perfusions were conducted at 37°C and at a flow rate of approximately 100 ml/min/kg body weight. This resulted in mean pulmonary arterial pressures between 15 and 30 mm Hg and mean femoral artery pressures between 50 and 120 mm Hg. Mean left atrial pressures were kept between 5 and 10 mm Hg by adjustment of the height of the reservoir.

After the perfusion had been commenced the acid-base status was corrected by the addition of sodium bicarbonate. The hypoxic pressor response was then tested by administering 3–5% O₂ in N₂ for 3–5 minutes. Control readings were taken after a further 30 minutes ventilation on air and the anaesthetic agent was then given for the next 30 minutes. After a second set of measurements had been obtained, the animal was once again ventilated with air and a second set of control readings was obtained after 30 minutes. The readings on air were meaned and compared with the readings obtained during the administration of the anaesthetic agent.

Dog isolated lung perfusion.

In these preparations the lungs were isolated from their nerve supply and ventilated by intermittent positive pressure applied to the trachea. They were then perfused at constant flow with deoxygenated blood (fig. 2), the gas flows to the oxygenator being

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*Various methods of cleaning were used but they did not appear to have any consistent effect on the results. Agents used included chromic acid, chlorhexidine, hydrogen peroxide and sodium bicarbonate. The final wash sequence was always water, distilled water and saline.
adjusted to provide blood with normal mixed venous oxygen and carbon dioxide tensions.

The initial preparations were similar to those outlined in the previous section but the lungs were perfused with blood which had been deoxygenated in an adult size Temptrol disposable oxygenator (DeWall, Najafi and Roden, 1966; Kalke, Castaneda and Lillehei, 1969). In the earlier experiments in this series the animal was bled directly into the pump reservoir and the heart and lungs were then excised. Pulmonary arterial and left atrial perfusion cannulae were inserted and the lung suspended vertically in a Perspex box which was continuously flushed with moist air at 37°C. Lungs suspended in this manner tended to develop pulmonary oedema at the bases so that a horizontal form of suspension was used in later experiments. However the ischaemia time (from circulatory arrest to establishment of perfusion) could not be reduced below 10–15 minutes and so an in situ technique was adopted for the final perfusions in this series. In these experiments the lungs were not physically isolated from their nerve supply. However, it has been shown that if the bronchial arteries are not perfused autonomic activity rapidly disappears (Allison, Daly and Waaler, 1961). When using the in situ preparation it was possible to position the cannulae in the pulmonary artery and left atrium whilst the heart was still beating. The animal was then bled into the reservoir from the left atrium, the tape round the pulmonary artery was tightened and perfusion commenced. This greatly shortened the ischaemia time. Furthermore there were no problems with the suspension of the lung.

The measurements made during perfusion were carried out in a similar manner to the right and left heart bypass experiments.
**Left lower lobe preparations.**

This type of preparation was utilized to provide a constant flow of desaturated blood to a denervated lobe. It was used in 8 greyhounds (20–30 kg body weight) and 2 cats† (2.5–3.5 kg body weight). Although the lobe was perfused in situ, it is probable that most of its nerve supply was destroyed by the ligatures round the pulmonary artery and bronchus (Hebb and Daly, 1966).

The dogs were anaesthetized with an intravenous injection of pentobarbitone (60 mg/kg body weight) and the cats were given a similar dose by the intraperitoneal route. Tracheostomy was performed and the lungs ventilated with air from a Cape ventilator at a frequency of 10 b.p.m., the tidal volume being adjusted to give an end-tidal CO$_2$ concentration of 4 to 6 per cent. A pressure-operated collect valve was used as described above and an end-expiratory pressure was applied to maintain expansion of the lungs when the chest was open. A screw clip on the inlet to the collect valve could be adjusted to provide a high pressure in the inspiratory tube of the ventilator so that adequate pressure was available to drive the paediatric attachment used to ventilate the left lower lobe (fig. 3).

A catheter in the femoral artery was connected to a pressure transducer and a femoral vein was cannulated to permit the infusion of fluid and drugs. Access to the pedicle of the left lower lobe was obtained via the fourth left interspace in dogs and by a median sternotomy in cats. The lobar bronchus and artery were identified and exposed and the bronchus was then cannulated and connected to the Cape paediatric attachment (Adams and Fox, 1967). The latter was driven by pressure from the inspiratory tube of the Cape ventilator and was used as a volume pre-set device. The ventilation of the lobe and rest of the lungs could thus be controlled independently but phase relationships were unchanged.

After cannulation of the bronchus, heparin (10 mg/kg) was injected and blood was withdrawn from a cannula in the right atrium to prime the circuit. In the cats 50 ml of dextran* was simultaneously infused into the femoral vein to prevent hypotension. The lobar pulmonary artery was then cannulated with a metal cannula. The cannula contained a fine pressure recording line which extended to its tip. Cannulation of the artery took 7 to 10 minutes, perfusion being commenced as soon as it was certain that there were no air bubbles in the circuit. A pressure recording line was then inserted into the left atrium via its appendage and flow increased until a mean lobar artery pressure of 20–25 mm Hg was obtained. Ventilation of the lobe and the rest of the lungs was then adjusted to produce end-tidal CO$_2$ concentrations close to 5 per cent and the activity of the lobar vasculature was assessed by measuring the pressor response resulting from the ventilation of the lobe with 3–5% oxygen in nitrogen for 3-4 minutes.

When the lobar artery pressure was once again stable the anaesthetic agent was added to the air delivered to the bellows of the paediatric attachment. The agents used were halothane 5 per cent, ether 15 per cent, methoxyflurane 2 per cent and trichlorethylene 1.5 per cent. Nitrous oxide was given as a 79 per cent mixture in oxygen. Since only qualitative results were being sought, high concentrations of the agents were given and the agent was discontinued as soon as a definite change in lobar arterial pressure occurred. The activity of the hypoxic pressor response was then assessed at 10 to 15 minute intervals after removal of the drug. If the response returned another agent was tested.

The concentration of the agents delivered to the lobe was measured by a previously calibrated re-

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*This is a very difficult preparation in small cats and accordingly was used only in cats weighing 3–3.5 kg.

†Dextran 110 injection BP in 0.9 per cent sodium chloride. Fisons Pharmaceuticals Ltd.
fractometer* (Hulands and Nunn, 1970) and the pump flow rate was obtained from a separate calibration.

Cat isolated perfused lung preparations.

Anaesthesia was induced in the animals with intraperitoneal pentobarbitone (60 mg/kg), tracheostomy was performed and the lungs ventilated with a Cape ventilator and paediatric attachment at a rate of 10 b.p.m. The paediatric attachment delivered air at a constant tidal volume which was adjusted to produce an end-tidal CO$_2$ concentration of 4 to 6 per cent.

The heart was exposed through a median sternotomy and after heparin (10 mg/kg) had been injected, the animal was bled into the perfusion system via a right atrial cannula. 10–20 ml of dextran was added to the prime in some experiments. When the heart had stopped, a “bulldog” clip was placed on the main pulmonary artery close to its bifurcation and a cannula passed into the pulmonary artery through an incision in the right ventricle. The cannula was fixed in place with a tape tied around the aorta and pulmonary arteries. The cannula was then filled with blood and all the air bubbles were removed. The left atrium was cannulated through the left ventricle and a tape tied round both ventricles to prevent leakage from the left atrium. The pulmonary artery clip was then removed and, after a final check for air bubbles, the perfusion was commenced. A left atrial pressure recording line was then inserted. Blood from the left atrium drained into the reservoir and was pumped by a previously-calibrated occlusive roller pump to the heat exchanger, and so to the pulmonary artery (fig. 4). The damping provided by the volume of air in the heat exchanger and the screw clip on the pulmonary artery line ensured that flow was non-pulsatile. The cat and atrial reservoir were kept warm by a heated mat and all perfusions were performed at 34–37°C. Flow rates were adjusted initially to maintain pulmonary arterial pressures between 15 and 25 mm Hg when left atrial pressures were 0–10 mm Hg. The resulting flows were usually between 50 and 75 ml/kg body weight/minute.

The metabolic acidosis present in the blood at the beginning of perfusion was corrected by the addition of 4.2 per cent sodium bicarbonate and a normal respiratory acid-base status was maintained by ventilating the lungs with 5 per cent CO$_2$ in air during perfusion. Anaesthetic agents were added to this gas mixture by a Blease universal vaporizer. The hypoxic gas mixture used for assessing the pressor response contained 3–5% O$_2$ and 5 per cent CO$_2$ in N$_2$ and was administered for 3 minutes.

The anaesthetic agents were administered in random order in the same concentrations as in the previous experiments.

**MEASUREMENTS**

Measurements of pulmonary vascular resistance (PVR) were made in all the experiments, PVR being calculated from the formula:

$$PVR = \frac{PAP-LAP}{\text{Flow (l./min)}}$$

where $PAP$ = Pulmonary artery pressure (mm Hg)

$\text{LAP} =$ Left atrial pressure (mm Hg)

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Additional measurements were made in the dog right and left heart bypass and dog isolated lung perfusions. In these experiments the measurements included tidal volume, physiological deadspace, deadspace/tidal volume ratio, arterial-alveolar \( P_{\text{CO}_2} \) difference, \( \text{CO}_2 \) output, \( O_2 \) consumption, alveolar-arterial \( P_{\text{O}_2} \) difference, total venous admixture, arterio-venous oxygen content difference, haemoglobin concentration, perfusion flow rate, airway, pulmonary arterial and left atrial pressures.

A full set of cardiorespiratory measurements was made on air after the perfusion had been stabilized for at least 30 minutes and a second set of measurements was made after 30 minutes inhalation of the agent under test. A further set of measurements was then made 30–45 minutes after discontinuing the agent. If the lungs were in good condition another agent was then studied.

The cardiorespiratory measurements were made by standard techniques (Sykes et al., 1970), appropriate corrections having been made for gas analysis in the presence of anaesthetic agents. Pressures were recorded with Bell and Howell transducers on a Devices heated-stylus 4-channel recorder. All transducers were hydrostatically zeroed with the left atrial appendage.

**RESULTS**

**Right and left heart bypass.**

Successful perfusions were achieved in 21 of 24 dogs. The mean lung ischaemia time was 4.4 min (range 1–12) and the mean duration of perfusion was 2 hr 50 min (range 25 min to 3 hr 45 min). A pressor response to alveolar hypoxia could only be elicited in two of the preparations. The number of technically satisfactory measurements obtained with each agent was: halothane 9, trichloroethylene 6, ether 2, nitrous oxide 8.

The measurements on air before and after the administration of the anaesthetic agents were compared with the measurements obtained during anaesthesia using paired \( t \)-tests. The results were compared with the measurements obtained during anaesthesia using paired \( t \)-tests. The only statistically significant differences were a fall in \( O_2 \) consumption and \( \text{CO}_2 \) output with trichloroethylene and halothane.

**Dog perfused lower lobe.**

In these animals a brisk pressor response to hypoxia was obtained in 4 of the 8 preparations used. After applying the criteria detailed below for cats, there were 7 satisfactory readings (table II).

**Cat perfused lower lobe.**

The results in 2 successful perfusions were similar to those obtained in the cat isolated perfused lung preparations. The results have therefore been included in the next section.

**Cat isolated perfused lungs.**

Twenty-two successful perfusions were achieved in 24 cats and all of these initially displayed a pressor response to hypoxia of 5–10 mm Hg. The hypoxic pressor response invariably decreased or disappeared after the administration of the anaesthetic agent, even if this was very brief (fig. 5). In some of the animals exposed to anaesthetic agents, hypoxia subsequently produced a fall in pulmonary artery pressure. When the exposure time had been short (1–3 minutes) the pressor response often re-
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FIG. 5. Hypoxic pressor response (HYP) before and after 5 per cent halothane (HAL) for 5 minutes. Halothane produced a fall in mean pulmonary artery pressure (MPA)

AP = airway pressure
MLA = mean left atrial pressure
Pressures in mm Hg. Time marker (below AP) in minutes.

appeared. However, in some animals it did not return until 30 to 60 min after the anaesthetic had been stopped and in other animals the response never reappeared despite a further period of perfusion of 2 to 3 hr.

During the course of the perfusions there were sometimes changes in airway pressure associated with the development of small areas of collapse in the lung, pulmonary oedema or the administration of an anaesthetic agent. In the lower lobe perfusions left atrial pressure varied from time to time as a result of blood loss or cardiac depression produced by the anaesthetic drugs. Since both these factors affect the measured pulmonary vascular resistance the comparison of pulmonary vascular resistance before and after the administration of an anaesthetic agent was limited to those occasions on which:

(1) There was an active pressor response to hypoxia immediately before the administration of the agent.

(2) There was a steady pulmonary artery pressure for three to four minutes before the administration of the anaesthetic.

(3) There was no change in left atrial pressure.

(4) There was no change in peak or end-expiratory airway pressure during the test (and hence no change in lung volume, compliance or airway resistance).

With ether airway pressure often fell slightly during the test. Since this change would have tended to lower the pulmonary vascular resistance and ether normally caused a rise in resistance, this effect was ignored for this agent.

The results shown in table III and figure 6 were selected on the basis of these four criteria and only represent the direction of change with each agent, for the drug was turned off as soon as a definite change in pulmonary artery pressure was observed. Despite this, statistically significant mean changes were observed with every agent except methoxyflurane. It may be seen that 5 per cent halothane appears to dilate the pulmonary vascular bed whilst 1.5 per cent trichloroethylene, 15 per cent ether and 79 per cent nitrous oxide appear to cause pulmonary vasoconstriction.

Fifteen per cent ether in air results in an inspired O₂ concentration of 17.8 per cent. To ensure that the vasoconstriction observed was not due to the lowered inspired oxygen concentration 2 further experiments were performed in which the inspired oxygen was increased to 21 per cent. Vasoconstriction was observed in both these experiments.

Fig. 6. Effect of inhalational anaesthetic agents on pulmonary vascular resistance. The triangles were results obtained in the 2 isolated cat lower lobe preparations whilst the rest of the results were obtained in isolated cat lung perfusions.

ΔPVR = change in pulmonary vascular resistance.

DISCUSSION

Drugs acting on the pulmonary circulation may produce their effects by a direct action on the blood vessels or by an alteration in autonomic activity. They may also affect the heart or systemic circula-
tion, the resulting changes in cardiac output, pulmonary arterial or left atrial pressures leading to secondary effects on the pulmonary circulation. Many vasoactive drugs also act on the bronchial smooth muscle. Such drugs may alter pulmonary blood flow by changing the transpulmonary pressure gradient or by altering bronchial blood flow.

### Table III.

**Halothane 5%.**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Flow (l/min)</th>
<th>PVR (mm Hg/L/min)</th>
<th>Before</th>
<th>After</th>
<th>Change</th>
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<tbody>
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<td>Mean</td>
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<td>175</td>
<td>-33</td>
<td>0.005&gt;P&gt;0.001</td>
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</table>

**Trichloroethylene 1.5%.**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Flow (l/min)</th>
<th>PVR (mm Hg/L/min)</th>
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<th>After</th>
<th>Change</th>
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<td>Mean</td>
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<td>229</td>
<td>248</td>
<td>+17</td>
<td>0.05&gt;P&gt;0.025</td>
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**Nitrous oxide 79%.**

<table>
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<tr>
<th>Preparation</th>
<th>Flow (l/min)</th>
<th>PVR (mm Hg/L/min)</th>
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<th>After</th>
<th>Change</th>
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<tr>
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<td>147</td>
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<td>270</td>
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<tr>
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<td>450</td>
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</tr>
<tr>
<td>Mean</td>
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<td>240</td>
<td>254</td>
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<td>0.05&gt;P&gt;0.025</td>
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</table>

### Ether 15\%.

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<th>PVR (mm Hg/L/min)</th>
<th>Before</th>
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</tr>
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</tr>
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</tr>
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<td>-6</td>
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</tr>
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</tr>
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<td>230</td>
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<td>0.01&gt;P&gt;0.005</td>
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</table>

**Methoxyflurane 5\%.**

<table>
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<th>Flow (l/min)</th>
<th>PVR (mm Hg/L/min)</th>
<th>Before</th>
<th>After</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLL</td>
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<td>323</td>
<td>323</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ILP</td>
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<td>133</td>
<td>133</td>
<td>+5</td>
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</tr>
<tr>
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<td>75</td>
<td>-8</td>
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</tr>
<tr>
<td>ILP</td>
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<td>200</td>
<td>187</td>
<td>-13</td>
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</tr>
<tr>
<td>ILP</td>
<td>0.100</td>
<td>112</td>
<td>102</td>
<td>-10</td>
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<tr>
<td>ILP</td>
<td>0.080</td>
<td>149</td>
<td>139</td>
<td>-10</td>
<td></td>
</tr>
<tr>
<td>ILP</td>
<td>0.055</td>
<td>232</td>
<td>242</td>
<td>+10</td>
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</tr>
<tr>
<td>ILP</td>
<td>0.055</td>
<td>272</td>
<td>255</td>
<td>-17</td>
<td></td>
</tr>
<tr>
<td>ILP</td>
<td>0.030</td>
<td>300</td>
<td>283</td>
<td>-17</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.105</td>
<td>185</td>
<td>177.5</td>
<td>-7.5</td>
<td>0.10&gt;P&gt;0.05</td>
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</table>

Values of pulmonary vascular resistance (mm Hg/L/min) before and after the administration of anaesthetic agents in 22 cat preparations, for criteria of selection of results see text.

LLL = Left lower lobe preparation
ILP = isolated lung perfusion preparation

The mean and P values only refer to the ILP studies
+ sign = Increase in PVR
- sign = Decrease in PVR

It is apparent, therefore, that it is extremely difficult to assess the effects of pulmonary vasoactive drugs in the intact organism. For this reason the authors attempted to study the pulmonary vascular effects of inhalation agents in three types of preparation.

1. The isolated lung (to assess the direct action on pulmonary blood vessels).
2. The right and left heart bypass preparation (to assess the effects mediated by autonomic activity).
3. The intact animal (to observe the modifications produced by the other cardiovascular effects of the drugs).
The first problem was to maintain a state of unconsciousness in the animal without the use of drugs. Various methods of decerebration were used but all produced respiratory or cardiovascular changes which rendered the preparation unacceptable. Electrical anaesthesia was also tried but this proved too uncertain for prolonged use. Finally, it was decided to utilize chloralose. This drug has been used to anaesthetize animals for experiments where unilateral alveolar hypoxia was shown to cause diversion of blood to the opposite lung (Atwell et al., 1951; Peters and Roos, 1952; Borst et al., 1957), and it has been widely used in experimental work on circulatory reflexes.

However, without premedication, induction with chloralose is slow and uncertain: for this reason anaesthesia was induced with nitrous oxide-oxygen-chloralose and then maintained with chloralose, a period of 1–2 hours being allowed after withdrawal of the halothane before perfusion was commenced.

Despite this precaution only 4 of 43 dogs anaesthetized in this manner displayed a pulmonary arterial pressor response to alveolar hypoxia during the perfusion. On the other hand a pressor response was obtained in 4 of the 8 dogs anaesthetized with pentobarbitone and in all of the successful cat preparations. In view of the later results obtained in the cat perfusions it would seem reasonable to conclude that halothane had obtunded the hypoxic pressor response in the dog experiments and that this response did not return before perfusion was commenced.

Although most of the dog preparations showed no response to hypoxia a number showed a pressor response to the inhalation of 10% CO₂. Furthermore, many of the preparations showed pressure changes with drugs such as isoprenaline or phenylephrine when these were given at the end of the perfusion. It is therefore difficult to understand why the right and left heart bypass and dog isolated lung preparations failed to show any changes in pulmonary vascular resistance after the inhalation of anaesthetic agents.

It was initially believed that this was due to poor surgical technique and prolonged ischaemia. However, the later developments in the technique of right and left heart bypass and the use of the in situ isolated lung preparation permitted very short ischaemia times with minimal handling of the lung. Another possibility was that the blood might have been damaged by passage through the Temptrol oxygenator. Gas flows of up to 12 L/min were necessary to de-oxygenate the blood and this caused marked haemolysis of the blood, plasma haemoglobin levels of 500–600 mg/100 ml being recorded on occasion. To obviate this problem some lungs were perfused without the oxygenator in the circuit: however there was still no response to hypoxia or anaesthetic drugs. Furthermore there was no response to hypoxia in three isolated lungs which were perfused with desaturated blood from a homologous lung. For this reason we abandoned attempts to make full measurements of lung function and turned to the lower lobe preparations, at first in the dog and later, more successfully, in the cat.

In isolated lung perfusions in cats in which no inhalational anaesthetic agent was administered we have found that the hypoxic response can usually be elicited at 30 minute intervals for periods of three to five hours. In some cats the response remains brisk throughout the perfusion but in others there is a gradual reduction in the response until it becomes zero or even negative. Since most of the results reported here were obtained during the first two to three hours of perfusion it seems unlikely that the disappearance of the hypoxic response after the administration of an inhalational agent was related to deterioration of the preparation. Furthermore, in a number of preparations the pressor response returned when the anaesthetic agent was discontinued, and in some perfusions it returned after the exhibition of a second or even a third agent.

There therefore seems to be no doubt that in the concentrations used, inhalational agents can abolish this response in the cat. Whether the administration of the agents in the more commonly used anaesthetic concentrations will have the same effect remains to be seen, but preliminary experiments suggest that the response disappears during the administration of halothane in a concentration of 0.5–1.0 per cent and trichloroethylene in a concentration of 0.75 per cent. Suggestive evidence that halothane in a concentration of 1 per cent will abolish the hypoxic pressor response has also been obtained in intact dogs by Buckley and associates (1964) but in their experiments many other factors could have influenced the results.

There have been very few animal studies on the effects of inhalational anaesthetics on pulmonary vascular resistance and most of those that have been made are inconclusive. However Heitz and associates (1971) made measurements in the left diaphragmatic lobe of the dog and showed that if halothane was added to the blood perfusing the lobe at constant
flow it produced a drop in pulmonary vascular resistance. Whether these results can be confirmed in species other than the dog and cat remains to be seen.

Early studies in the human were also inconclusive. Johnson (1951) studied 43 patients, 14 of whom were given ether, and found an increase in pulmonary artery pressure, a decrease in pulmonary blood volume but little change in cardiac output. Wyant, Donaldson and Merriman (1961) and Wyant, Chang and Merriman (1962) found similar changes. Wyant and associates (1958) found a slight elevation of pulmonary artery pressure during the early stages of anaesthesia with thiopentone with 3 per cent halothane and Wyant and associates (1960) found that the halothane-ether azo trope produced similar, though not such marked, results.

None of these studies included measurements of left atrial or wedged pulmonary artery pressures and it is therefore impossible to know whether the changes followed changes in pulmonary vascular resistance or whether they occurred passively in response to changes in left atrial pressure. Price and associates (1969), however, found that halothane produced no significant changes in pulmonary arterial pressure, pulmonary wedge pressure or pulmonary vascular resistance, whilst cyclopropane caused a marked increase in pulmonary arterial and wedge pressures with a calculated increase in pulmonary vascular resistance.

In conclusion, it appears from these preliminary studies that both hypotheses proposed earlier could be responsible for hypoxaemia during anaesthesia. The abolition of the hypoxic pressor response could result in an increased blood flow to hypoxic areas of lung and so could increase both shunt and ventilation/perfusion inequality. An agent such as halothane produced generalized pulmonary vasodilatation might produce a similar effect. On the other hand, agents which produce pulmonary vasoconstriction would be unlikely to increase shunting unless they preferentially vasoconstricted well-oxygenated areas of lung and thereby diverted the blood to hypoxic areas of lung. It is probable that the effect of anaesthetic drugs will depend on many factors, including the respiratory and metabolic acid-base status of the blood. There are also likely to be species differences. Nevertheless it appears that the hypotheses put forward are worthy of further investigation.

ACKNOWLEDGEMENT
This work was supported by the Medical Research Council.


--- L'EFFET DES ANESTHESIQUES PAR

--- INHALATION SUR LA VASOCOCONSTRICTION

--- PULMONAIRE HYPOXIQUE ET LA RESISTANCE

--- VASCULAIRE PULMONAIRE DANS LE POUMON

--- DU CHIEN ET CHAT

--- SOMMAIRE

--- L’hypoxie alvéolaire causait une augmentation de la résistance vasculaire pulmonaire dans des poumons ou lobes isolés de chats et chiens, perfusés à flux constant. Cette réaction fut éliminée durant des laps de temps variés par l’administration de concentrations élevées d’agents anesthésiques inhalatoires. 5 pourcent d’halothane dans ces préparations causait une vasodilatation pulmonaire tandis que 15 pourcent d’ether, 1,5 pourcent de trichloroéthylène et 79 pourcent de protoxyde d’azote provoquèrent une vasoconstriction. 2 pourcent de méthoxyflurane ne causa pas de modification significative de la résistance vasculaire pulmonaire. Il est supposé que l’élimination de la réaction vasoconstrictrice pulmonaire à l’hypoxie pourrait augmenter la proportion de sang passant par des shunts ou des régions du poumon à rapport ventilation/perfusion bas et pourrait ainsi contribuer à une réduction de la pression oxygénique artérielle durant l’anesthésie. La vasodilatation ou vasoconstriction pulmonaire, causé par les agents inhalatoires peut intensifier cet effet.

--- DIE WIRKUNG VON

--- INHALATIONSANAESTHETIKER AUF DIE

--- PULMONALE VASOKONSTRIKTIION UND DEN

--- PULMONALEN GEFASSWIDERSTAND

--- DURCHFLUTETER LUNGEN BEI HUND UND

--- KATZE

--- ZUSAMMENFASSUNG

--- Alveoläre Hypoxie verursachte einen Anstieg des pulmonalen Gefäßwiderstandes bei isolierten Katzen- und Hundelungen oder -lungenlappen, die mit gleichbleibender Stärke durchflutet wurden. Diese Reaktion wurde für unterschiedliche Zeitabschnitte durch Anwendung von Inhalationsanästhetika in hohen Konzentrationen unterbunden. Bei Anwendung dieser Anästhetika bewirkte Halothan in einer Konzentration von 5% eine pulmonale Vasodilatation, während 5% Aether, 1,5% Trichloräthylen und 79% Lachgas eine Vasokonstriktion bewirkten. Methoxyfluran in einer Konzentration von 2% verursachte keine bedeutende Änderung des pulmonalen Gefäßwiderstandes. Es wird angenommen, dass durch den Wegfall der reaktiven pulmonalen Vasokonstriktion auf Hypoxie die Menge des Blutes, das durch

EL EFECTO DE LOS ANESTESICOS POR INHALACION SOBRE LA VASOCONSTRICCION PULMONAR HIPOXICA Y LA RESISTENCIA VASCULAR PULMONAR EN PULMONES PERFUNDIDOS DEL PERRO Y DEL GATO

RESUMEN
La hipoxia alveolar produjo un aumento de la resistencia vascular pulmonar en pulmones o lóbulos pulmonares aislados de gatos y perros perfundidos con un flujo constante. Esta respuesta fue abolida durante periodos variables de tiempo mediante la administración de concentraciones elevadas de agentes anestésicos por inhalación. El halotano al 5 por ciento causó vasodilatación pulmonar, mientras que el éter al 15 por ciento, tricloroetileno al 1,5 por ciento y óxido nitroso al 79 por ciento provocaron vasoconstricción. El metohoflurano al 2 por ciento no causo un cambio significativo en la resistencia vascular pulmonar. Se postula que la abolición de la respuesta vasoconstrictora pulmonar a la hipoxia pudiera incrementar la proporción de sangre que fluye por los shunts o zonas del pulmón con un bajo cociente de ventilación/perfusión, pudiendo así contribuir a una disminución de la tensión arterial de oxígeno durante la anestesia. La vasoconstricción o vasodilatación pulmonar producida por los agentes por inhalación pudiera aumentar este efecto.

CONTROVERSIAL THOUGHTS IN MODERN ANESTHESIOLOGY

Symposium
Saturday, October 28, 1972
9.30—17.30
To be held in:
Department of Anesthesiology, Academic Hospital, University of Ghent (Belgium).
Proceedings will be conducted in English.

Dr D. Langrehr (Bremen) Ketamine—indications and limitation of its use.
Prof. G. Bull (Kaapstad) Malignant hyperthermia.
Prof. R. Simpson (London) Anaesthesia and postoperative jaundice.
Dr M. J. Halsey (Middlesex) The metabolic breakdown of inhalation anaesthetics and their clinical implications.
Prof. J. Spierdijk (Leiden) Dangers of chronic exposure to inhalation anaesthetics—preventive measures.
Prof. M. Hanquet (Liège) Éthrane—an advance in anaesthesia?

Round Table: Present place of inhalation anaesthesia.

Participants: Prof. Bull (Kaapstad), Prof. Hanquet (Liège), Dr Halsey (Middlesex), Dr Jewell (Manchester), Dr Langrehr (Bremen), Prof. Simpson (London), Prof. Spierdijk (Leiden), Prof. Rolly (Ghent).

Information can be obtained from Prof. Dr G. Rolly, Department of Anesthesiology, Academic Hospital, De Pintelaan 135, 9000 Ghent, (Belgium).