REDUCTION OF HYPOXIC PULMONARY VASOCONSTRICTION DURING DIETHYL ETHER ANAESTHESIA IN THE DOG

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SUMMARY

The activity of the pulmonary vasoconstrictor response to alveolar hypoxia was assessed by measuring the redistribution of pulmonary blood flow in response to the ventilation of one lung with nitrogen. The vasoconstrictor response was depressed during the administration of 5% diethyl ether but returned when the ether was withdrawn. It is suggested that depression of the hypoxic vasoconstrictor mechanism may be one cause of the increased alveolar–arterial \( \Delta P_{O_2} \) difference noted during ether anaesthesia.

It has now been established clearly that there is an increase in venous admixture during anaesthesia. This results in arterial hypoxaemia unless the patient inspires oxygen-enriched gas mixtures. It is generally believed that the major factor producing this change in lung function is an increase in dependent airway closure secondary to a reduction in functional residual capacity (Rehder, Sessler and Marsh, 1975). However, it has been suggested also that inhalation anaesthetic agents may produce a further increase in venous admixture effect by depressing the pulmonary vasoconstrictor response to regional alveolar hypoxia, thus increasing the blood flow through underventilated areas of lung (Sykes et al., 1972). In support of this hypothesis it has been shown that concentrations of inhalation anaesthetic agents used in clinical practice depress reversibly the pulmonary vasoconstrictor response to generalized alveolar hypoxia in both the denervated and the innervated cat lung preparation (Sykes et al., 1973, 1976; Gibbs, Sykes and Tait, 1974; Hurtig et al., 1977; Loh, Sykes and Chakrabarti, 1977). Further experiments in the intact dog have demonstrated that 1% trichloroethylene abolishes the pulmonary vasoconstrictor response to unilateral alveolar hypoxia produced by ventilating one lung with nitrogen. The response returns when the anaesthetic is withdrawn and is only depressed partially by 0.75% trichloroethylene (Sykes et al., 1975).

Unfortunately, experiments in the intact animal are often complicated by the effects of the anaesthetic drugs on the cardiovascular system. In the trichloroethylene experiments, it was observed that there was a marked increase in left atrial pressure during the administration of the drug and that the pressure increased still further when unilateral hypoxia was induced. Since an increase in left atrial pressure has been shown to blunt the hypoxic response (Benumof and Wahrenbrock, 1975), it was felt that further experiments should be performed with agents which do not produce an increase in left atrial pressure.

A further complicating factor in this type of experiment is that the intensity of the hypoxic vasoconstrictor response appears to decrease with time (Malik and Kidd, 1973). In our previous experiments with trichloroethylene we measured the diversion of blood flow at fixed time intervals after the onset of unilateral hypoxia but we had no visual record of the pattern of onset and disappearance of the vasoconstrictor response.

For these reasons we have developed a method which enables us to make a continuous record of the distribution of pulmonary blood flow throughout the experiment (Sykes et al., 1977a). This paper describes the application of this method to studies designed to assess the effect of diethyl ether on hypoxic pulmonary vasoconstriction in the dog.

METHODS

Preparations

The experiments were performed on eight dogs of various breed weighing 25–35 kg. The animals were anaesthetized with thiopentone 20–30 mg/kg i.v. followed by pentobarbitone i.v. or further increments of thiopentone. A cuffed endotracheal tube was inserted and ventilation was controlled with a Cape volume preset ventilator at a frequency of 15 b.p.m. and a tidal volume which produced an end-tidal
carbon dioxide concentration of 4–4.5%. The dogs were in the supine position. Cannulae were inserted into the right femoral artery and vein for dye dilution cardiac output measurements and into the left femoral artery for pressure recording and blood sampling. A catheter was passed into the inferior vena cava through the left femoral vein for xenon infusion and two other catheters were floated through the external jugular veins to permit continuous recording of pulmonary artery and pulmonary artery wedge pressures. All pressures were recorded with Consolidated Electrodymanics strain gauges and a Devices M19 heated stylus recorder, the transducers being calibrated repeatedly against a saline column.

**Ventilation system**

When these preparations had been completed a low tracheotomy was performed and a tracheal divider inserted (Seed and Sykes, 1972). Each limb of the divider was connected to one of a pair of matched non-rebreathing valves (Sykes, 1969) and the valves were then connected by a Y-piece to the patient connection port on the ventilator tubing. The airway pressure on each side was monitored continuously by strain gauges and the position of the tracheal divider checked by measuring the expired volumes and by pressurizing each side to +30 cm H₂O whilst the other side was connected to a tube dipping under water. After these manoeuvres both lungs were inflated simultaneously to +30 cm H₂O to centralize the mediastinum. Further checks on the position of the divider were obtained by measuring the arterial PO₂ when both sides were ventilated with air and with 100% oxygen and by examining the ventilation of each lobe at autopsy.

When the tube had been positioned correctly the non-rebreathing valves were connected to the second-stage (bellows-in-bottle) systems (shown in figure 1 of Sykes et al., 1977b*). The gases used to ventilate the lungs were accumulated in reservoir bags and were aspirated into the bellows during the expiratory phase. The anaesthetic agent could be added to these gases by switching in previously calibrated Blease Univap vaporizers. The expansion of each bellows was limited by a stop which determined the tidal volume. The bellows were compressed synchronously by the Cape ventilator which was adjusted to produce a pressure of 60 cm H₂O in each bottle so that there was a period of zero flow at the end of each inspiration. The expired gas from each non-rebreathing valve was directed to a 1.5-litre chamber, where mixing was achieved with a rotary fan, and then to a 55-ml glass chamber situated within the collimator of a scintillation detector. Each detector was linked to a counting system and the counts recorded on a two-channel pen recorder running at a paper speed of 1 cm/min. The time constant of the counting system was 10 s.

**Experimental protocol**

Both lungs were first ventilated with oxygen and the tidal volume on each side adjusted to produce an end-tidal carbon dioxide concentration close to 4%. Ten millilitre of the ¹³³xenon solution (containing 1 mCi/ml) was then diluted with 40 ml of saline, and infused at a rate of 6–12 ml/h into the inferior vena cava. At the slowest infusion rate this provided count rates of between 150 and 300 ct/s on each channel. When the count rates had become steady mean arterial, pulmonary artery, pulmonary artery wedge and dynamic airway pressures were recorded and 5-ml artery and pulmonary artery blood samples were obtained for blood-gas analysis. Each set of measurements was completed by duplicate or triplicate determinations of cardiac output using indocyanine green as the indicator.

When the measurements had been completed the ventilating gas to one lung was changed to nitrogen. The time course of the diversion of blood flow to the oxygenated lung was followed by observing the xenon counts on the recorder (fig. 1) and a second set of measurements was initiated 5-10 min later when the diversion had reached a peak. Both lungs were then ventilated with oxygen and 5% diethyl ether for 30 min. A third set of measurements was recorded and the magnitude of the diversion tested again by replacing the oxygen on one side by nitrogen, the administration of ether to both sides being continued throughout this period. The fourth set of measurements was started 5–10 min later when the diversion was at a peak. Both lungs were then ventilated with oxygen and 5% diethyl ether for 30 min. A third set of measurements was recorded and the magnitude of the diversion tested again by replacing the oxygen on one side by nitrogen, the administration of ether to both sides being continued throughout this period. The fourth set of measurements was started 5–10 min later when the diversion was at a peak and immediately afterwards the ether and nitrogen mixture was discontinued and ventilation of both lungs was continued with oxygen. Thirty to forty-five minutes later the fifth set of measurements was made. The sixth set of measurements was made 5–10 min after diversion had been tested again by ventilating one lung with nitrogen.

In two animals, which showed little change in the hypoxic response during 5% diethyl ether, the animal was returned to bilateral oxygen and 10% ether was administered for 15 min before the response was...
EFFECT OF ETHER ON HYPOXIC PULMONARY VASOCONSTRICTION

tested again. The ether was withdrawn and the final response tested in the usual way.

Calculations
Since tidal volume was unchanged, the mixed expired xenon concentration was proportional to the blood flow in each lung. Nitrogen was always administered to the left lung in these experiments so that the distribution of blood flow was expressed in terms of the right/left (R/L) ratio of xenon counts. Diversion of blood flow to the right lung in response to pulmonary vasoconstriction in the left lung ventilated with nitrogen thus increased the R/L ratio.

Duplicate blood samples were analysed for pH, P_{\text{CO}_2} and P_{\text{O}_2} on two different electrode systems, the Radiometer ABL 1 automated blood-gas analyser (Selman and Tait, 1976) and the standard Radiometer electrode system (Sykes et al., 1970). All blood-gas tensions were expressed as at body temperature using the correction factors of Kelman and Nunn (1966).

Cardiac output was calculated from a formula derived by Simons and White (1976). As a check, the area of a number of dye dilution curves was determined by planimetry and cardiac output was calculated by standard formulae.

RESULTS
Figure 1 shows the record of xenon counts from a typical experiment and figure 2 shows the results of another experiment replotted to show the distribution of pulmonary blood flow in terms of the right-to-left (R/L) ratios of blood flow. It can be seen that there was a marked diversion of blood flow to the opposite lung when unilateral hypoxia was induced and that the response to hypoxia was diminished during the administration of 5% diethyl ether. Thirty minutes after discontinuing the ether the response to hypoxia was slightly greater than that present at the beginning of the experiment. This marked depression of the hypoxic vasoconstrictor response was seen in six of the eight dogs. In the remaining two dogs the response was little affected by 5% diethyl ether but was depressed by the administration of 10% ether for a further 10-15 min (fig. 3). When the results from the eight dogs were submitted to statistical analysis, using the
TABLE I. Right-to-left (R/L) ratios of blood flow at each stage of the experiment. The high R/L ratios on $O_2/O_2$ in the second dog were found at autopsy to be a result of a collapsed lobe

<table>
<thead>
<tr>
<th>Gases R/L</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
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<th>G</th>
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<td>0</td>
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<tr>
<td>Dog No. 1</td>
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<td>2.91</td>
<td>0.89</td>
<td>2.78</td>
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<td>1.0</td>
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<td>3.22</td>
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<tr>
<td>3</td>
<td>0.93</td>
<td>4.27</td>
<td>0.91</td>
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<td>1.36</td>
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<td>1.86</td>
<td>1.12</td>
<td>2.86</td>
<td>1.12</td>
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Statistical comparisons:
B v. D, $P<0.01$; B v. H, n.s.; D v. H, $P<0.05$; A v. C v. G, n.s.

Wilcoxon signed rank test for paired data, there was a significant difference between the diversion of blood flow during the administration of 5% diethyl ether and the diversions obtained at the beginning and end of the experiment (fig. 4 and table I).

There were no significant differences in tidal volume and airway pressure between any of the phases of the experiment.

The other measurements are summarized in table II. Mean arterial pressure ($P_{Aa}$) was unchanged throughout the experiment. Mean pulmonary artery pressure ($P_{PA}$) increased significantly in response to unilateral hypoxia during each phase of the study, but the mean pressure was increased markedly during the administration of ether and remained increased until the end of the experiment. Mean pulmonary artery wedge pressure ($P_{Lw}$) increased slightly during
unilateral hypoxia but was approximately doubled during the administration of 5% diethyl ether. Cardiac output (\(\dot{Q}\)) changes were small but there was a tendency for the output to increase when one lung was made hypoxic. There was a significant increase in cardiac output after discontinuing ether when these values are compared with the \(O_2/O_2\) values before or during the administration of ether.

\(PaO_2\) decreased during unilateral hypoxia and although most of the values were reduced during oxygen/nitrogen/ether compared with before or after the administration of ether, the difference between the means was not significant (\(n = 7\)). Mixed venous \(Po_2 (PvO_2)\) with \(O_2/O_2\) increased during the experiment but there were no significant differences between the means of the \(PvO_2\) values during the three phases of unilateral hypoxia. Mixed venous and arterial \(Pco_2 (Pvco_2\) and \(PaCO_2\) increased progressively during the experiment as did hydrogen ion concentration \([H^+]\). The haemoglobin concentration (Hb) reached a peak at the end of the period of ether administration.

### DISCUSSION

These studies show that 5% diethyl ether produces a significant reduction in the magnitude of the pulmonary vasoconstrictor response to unilateral alveolar hypoxia resulting from the ventilation of one lung with nitrogen. Although \(PaO_2\) was reduced markedly in the majority of animals when unilateral hypoxia was induced during the administration of 5% diethyl ether compared with unilateral hypoxia without ether anaesthesia, there were only seven comparisons and the differences were not statistically significant.

The two main questions raised by these results are:

1. Is the reduction in hypoxic vasoconstriction a result of the administration of the inhalation agent or of some other cause?
2. Would such a reduction in hypoxic vasoconstriction cause arterial hypoxaemia?

Mechanical factors which might oppose the effects of unilateral alveolar hypoxia during anaesthesia are an increase in cardiac output or left atrial pressure (Benumof and Wahrenbrock, 1975), or an increase in transpulmonary pressure in the oxygenated lung. There was a small increase in cardiac output when
unilateral hypoxia was induced, but the magnitude of this change was similar in each phase of the study. The mean pulmonary artery wedge pressure was increased significantly during the administration of the ether but the wedge pressure increased less than 5 mm Hg in three dogs with a marked reduction in the diversion of blood flow. Furthermore, in a number of animals, dextran infusion to achieve wedge pressures of 25–30 mm Hg failed to obviate the hypoxic response.

With the constant-volume ventilation system employed in these studies changes in airway resistance or lung compliance are reflected in changes in the airway pressure trace. Transient increases in the airway resistance on the oxygenated side occurred sometimes during unilateral hypoxia but otherwise there were no changes in airway pressure. Therefore it seems reasonable to conclude that the changes in hypoxic response.

The finding that ether depresses the vasoconstrictor response to alveolar hypoxia in the intact animal confirms the observations of Sykes and others (1973) and Loh and others (1977) that ether depresses the hypoxic vasoconstrictor response in the denervated and innervated perfused cat lung. Since the earlier studies showed that the hypoxic vasoconstrictor response could be elicited in the isolated perfused lung and that clinical concentrations of inhalation anaesthetic agents depressed this response reversibly, it is reasonable to assume that the anaesthetic is also acting directly on the vasoconstrictor mechanism in the intact animal. However, it is possible that autonomic activity or circulating catecholamines may modify the response in the latter situation.

When one lung is made hypoxic it contributes venous blood to the circulation. If the blood leaving the lung had the same composition as mixed venous blood the resultant shunt would be proportional to the blood flow so that $P_{A\text{O}_2}$ would be expected to be greater when blood flow was diverted maximally by the unilateral hypoxia than when the diversion was depressed by diethyl ether. This supposition is borne out by the experimental results which showed that the dogs with the most marked depression of the hypoxic response also had the greatest reduction of $P_{A\text{O}_2}$ during ether. However, during inhalation of nitrogen, the alveolar $P_{\text{O}_2}$ is less than mixed venous $P_{\text{O}_2}$ so that oxygen is extracted into the alveoli. Under these conditions the end-pulmonary capillary $P_{\text{O}_2}$ depends on the ventilation/perfusion ratio, the end-pulmonary capillary $P_{\text{O}_2}$ being less when blood flow is reduced than when it is not. Hence during maximal diversion the small shunt flow will have a low $P_{\text{O}_2}$ whilst depression of the vasoconstrictor response will result in both a greater blood flow and a greater end-pulmonary capillary $P_{\text{O}_2}$. Therefore this mechanism will tend to minimize the changes in $P_{A\text{O}_2}$ produced by unilateral hypoxia in this experimental model, but will not be active in the human situation where the end-pulmonary capillary $P_{\text{O}_2}$ cannot decrease to less than mixed venous $P_{\text{O}_2}$.

It is known that there is a significant increase in right-to-left shunt during anaesthesia in humans (Marshall et al., 1969; Price et al., 1969; Føeø, Meloche and Prys-Roberts, 1971) and it seems reasonable to believe that this mechanism may contribute to the increase in alveolar arterial oxygen tension difference noted during ether anaesthesia by Marshall and Grange (1966). Confirmatory evidence that a similar depression of the pulmonary vasoconstrictor response occurs during ether anaesthesia in humans has been provided recently by Bjertnaes and others (1976).


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**REDUCTION DE LA VASOCONSTRICTION PULMONAIRE HYPOXIQUE PENDANT UNE ANESTHESIE A L’ETHER DIETHYL SUR LE CHIEN**

**RESUME**

On a évalué l’activité de la réaction vasoconstrictrice pulmonaire à l’hypoxie alvéolaire en mesurant la redistribution du débit sanguin pulmonaire en réponse à la ventilation d’un poumon à l’aide d’azote. Le réaction vasoconstrictrice a été modérée pendant l’administration de 5% d’ether diéthyl, mais elle est revenue normale lorsqu’on a supprimé l’ether. On suggère que la dépression du mécanisme vasoconstricteur hypoxique peut être l’une des causes de l’augmentation de la différence alvéolaire artérielle de $P_O_2$ remarquée pendant l’anesthésie à l’ether.

**HERABSETZUNG DER HYPOXISCHEN LUNGENGEFÄSSVERENGUNG WAHREND DER DIATHYLÄTHERNARKOSE IM HUND**

**ZUSAMMENFASSUNG**

Es wurde die Tätigkeit der Vasokonstriktorreaktion auf Alveolenhypoxie beurteilt, indem die Neuverteilung des Lungenblutflusses als Reaktion auf die Ventilation eines Lungenflügels mit Stickstoff gemessen wurde. Die Vasokonstriktorreaktion wurde während der Verabreichung von 5% Diathyläther abgeschwächt, kehrte aber nach Entziehung des Äthers wieder zurück. Es liegt nahe, dass die Herabsetzung des hypoxischen Vasokonstriktor-Mechanismusses eine der Ursachen für den erhöhten Unterschied im alveolären–arteriellen Sauerstoffdruck $P_O_2$ sein kann, der während der Äthernarkose beobachtet wurde.

**REDUCCION DE VASOCONSTRICCIÓN PULMONAR HIPOXICA DURANTE ANESTESIA CANINA CON ÉTER DIETILICO**

**SUMARIO**

La actividad de la respuesta vasoconstrictora pulmonar a la hipoxia alveolar fue evaluada midiendo la redistribución del flujo sanguíneo pulmonar en respuesta a la ventilación de un pulmón con nitrogénico. La respuesta vasoconstrictora fue depredizada durante la administración de 5% éter dietilico, pero volvió al suspenderse el éter. Se sugiere que la depresión del mecanismo vasoconstrictor hipóxico pudiera ser una de las causas da la diferencia aumentada de $P_O_2$ alveolar – arterial observada durante la anestesia con éter.