THE EFFECTS OF HALOTHANE AND ETHER ON THE PULMONARY CIRCULATION IN THE INNERVATED PERFUSED CAT LUNG

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SUMMARY
The effects of halothane and diethyl ether on pulmonary vascular resistance and the pulmonary vasoconstrictor response to alveolar hypoxia were studied in the innervated perfused cat lung. Neither anaesthetic agent caused a significant change in pulmonary vascular resistance but both agents caused a depression of the pulmonary vasoconstrictor response to hypoxia.

Measurements of pulmonary vascular resistance are affected by changes in pulmonary blood flow, left atrial pressure and transpulmonary pressure. As a result, previous studies of the effects of volatile anaesthetic agents on the pulmonary vasculature have been performed in the isolated cat lung perfused at a constant flow (Sykes et al., 1973, 1975). These experiments showed that whereas halothane and methoxyflurane dilated pulmonary blood vessels, ether and trichloroethylene tended to constrict them. Furthermore, when these agents were administered in the inspired concentrations used in clinical practice, the pulmonary vasoconstrictror response to alveolar hypoxia was depressed or abolished. It was postulated therefore that inhalation anaesthetics might decrease homeostatic pulmonary vasoconstriction in areas of lung rendered hypoxic by regional under-ventilation and so increase the degree of arterial hypoxaemia present during anaesthesia.

The isolated lung is not a physiological preparation. Not only is it denervated effectively by the absence of a bronchial circulation (Allison, Daly and Waaler, 1961), but it is perfused with oxygenated blood and is separated from the humoral or other influences generated by the intact body. In order to overcome these objections and yet retain control of flow, transpulmonary pressure and left atrial pressure, we have investigated the actions of ether and halothane in an innervated perfused cat lung preparation in which the pulmonary and systemic circulations were perfused by separate pumps which created effectively a right and left heart bypass.

METHODS
The experiments were performed on 22 cats, weighing 2.5-5.2 kg. Nine preparations were abandoned because of technical faults or an inadequate pulmonary vasoconstrictror response to hypoxia at the beginning of the perfusion. The results of the remaining 13 successful perfusions are presented, seven animals being exposed to halothane and six to diethyl ether. Anaesthesia was induced with sodium pentobarbitone 30 mg/kg i.v. A tracheotomy was performed and the lungs were ventilated with air via a second-stage bellows device driven by a Cape ventilator set at a frequency of 20/min (fig. 1A). The tidal volume was adjusted to give an end-tidal carbon dioxide concentration between 4.0 and 5.0%. The lungs could be ventilated with air or an hypoxic gas mixture with or without the volatile anaesthetic agent. Halothane was administered from a Dräger Vapor vaporizer, and diethyl ether from a previously calibrated Blease Univap vaporizer. The expired gas passed through an underwater seal to maintain a positive end-expiratory pressure of 2-3 cm H$_2$O. The chest was opened by a median sternotomy and, after total body heparinization (2.5 mg/kg), the right and left atria were cannulated. Ligatures were passed round the roots of the aorta and pulmonary artery and purse string sutures inserted into the right ventricular wall near the pulmonary artery and around the apex of the left ventricle.

The perfusion circuits were primed with heparinized blood taken from a donor cat whose lungs were to be used in another experiment. Dextran 110 was added if there was insufficient blood to prime the circuit fully and the blood was circulated round the
system for a short time to remove air bubbles from the tubing. The perfusion system is shown in figure 1B. When the perfusion circuits were prepared the ventricles were fibrillated by applying a d.c. current to the myocardium from a 90-V battery. The aorta and pulmonary artery were cannulated through the purse-string sutures in the ventricles and the ligatures round the vessels tied. Any air bubbles remaining in the tubing were removed through T-pieces close to the cannulae. The perfusion pumps were started and, after a period of stabilization, the flows were adjusted to maintain a mean pulmonary artery pressure between 15 and 35 mm Hg. This usually required flows of 200–300 ml/min. The constant flow roller pumps were balanced carefully so that the flow through the pulmonary artery was equal to the flow through the aorta. Any further adjustments to match the flows during the perfusion were made by adjusting the aortic pump thus keeping the flow through the lungs constant.

Left atrial pressure was adjusted to produce zone 3 conditions throughout the lungs and was maintained
constant by keeping the distal end of the left atrial drain at a fixed level in relation to the atrium. Mean pulmonary artery pressure ($P_{PA}$), left atrial pressure ($P_{LA}$), and aortic pressure were recorded continuously using Consolidated Dynamics strain gauge transducers and a Devices four-channel heated stylus recorder. Airway pressure was recorded from a side arm of the tracheostomy tube, through which end-tidal carbon dioxide concentrations could also be checked with an infra-red analyser (Hartmann Braun: URAS 4). All transducers were calibrated repeatedly against a column of saline.

The perfusion pumps (Watson–Marlow) had been calibrated previously for flow and were known to be occlusive. Thermostatically controlled water jackets maintained the blood in the reservoirs at 37 °C.

After a steady mean pulmonary artery pressure had been achieved, left atrial reservoir blood was taken for measurement of pH. Usually the blood was excessively acid and sodium bicarbonate was added to the perfusate to bring the pH within the range 7.25–7.45. The lungs were then ventilated for 2 min with a mixture of 3% oxygen in nitrogen and the presence of an hypoxic pressor response was verified. The preparation was allowed to stabilize again for a period of 10 min and a second hypoxic response elicited. This was taken as the first control measurement. The lungs were then ventilated sequentially with increasing concentrations of the anaesthetic agent. Each concentration of anaesthetic agent was administered in air for 18 min, and then in 3% oxygen in nitrogen for 2 min; 1%, 2% and 3% halothane or 5%, 7% and 10% ether were used. When the anaesthetic sequence was over the lungs were ventilated with air alone for 20 min and a final 2-min hypoxic response was obtained as a second control measurement.

Left atrial blood pH was checked with an electrode (Radiometer) every 30 min and, if necessary, brought within the specified range with sodium bicarbonate and blood loss was replaced with Dextran 110 if the reservoir levels became dangerously low.

Pulmonary vascular resistance (PVR) was calculated by dividing mean pulmonary artery to left atrial pressure difference ($P_{PA} - P_{LA}$) by the flow ($Q$).

$$\text{PVR} = \frac{P_{PA} - P_{LA}}{Q} \times 100 \text{ mm Hg/dl min}^{-1}$$

**RESULTS**

There was no significant difference between the mean weights of the cats who received halothane (3.38 kg, SD 0.67) and those receiving diethyl ether (3.40 kg, SD 0.45), neither were there any statistically significant differences between the initial pulmonary artery or femoral artery pressures in the two groups. The relevant data from the 13 successful preparations are shown in table I.

The hypoxic pressor response is expressed as the maximum change in $P_{PA}$ (mm Hg) during hypoxia as a percentage of baseline value.

**Table I. Results of the halothane (n = 7) and ether (n = 6) groups of cats expressed as mean values ± 1 SD**

<table>
<thead>
<tr>
<th>Anaesthetic concentration (halothane)</th>
<th>Control 1</th>
<th>1%</th>
<th>2%</th>
<th>3%</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{PA}$</td>
<td>30.6 ± 6.4</td>
<td>28.6 ± 5.0</td>
<td>26.6 ± 5.0</td>
<td>27.3 ± 4.8</td>
<td>30.6 ± 6.6</td>
</tr>
<tr>
<td>$P_{PA}$ %</td>
<td>20.4 ± 7.9</td>
<td>20.5 ± 6.7</td>
<td>17.2 ± 8.2</td>
<td>8.3 ± 6.5*</td>
<td>23.4 ± 9.1</td>
</tr>
<tr>
<td>PVR</td>
<td>11.0 ± 4.0</td>
<td>9.9 ± 3.3</td>
<td>8.9 ± 2.7</td>
<td>9.3 ± 2.9</td>
<td>10.4 ± 2.8</td>
</tr>
<tr>
<td>$P_{PA}$</td>
<td>81.0 ± 20.8</td>
<td>70.3 ± 21.9</td>
<td>62.5 ± 12.4</td>
<td>60.2 ± 12.8</td>
<td>64.3 ± 11.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anaesthetic concentration (ether)</th>
<th>Control 1</th>
<th>5%</th>
<th>7%</th>
<th>10%</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{PA}$</td>
<td>26.3 ± 6.1</td>
<td>27.8 ± 5.8</td>
<td>28.0 ± 7.0</td>
<td>27.4 ± 5.7</td>
<td>28.5 ± 7.7</td>
</tr>
<tr>
<td>$P_{PA}$ %</td>
<td>40.4 ± 19.8</td>
<td>39.9 ± 7.6*</td>
<td>12.4 ± 7.1*</td>
<td>2.6 ± 3.1*</td>
<td>26.7 ± 8.8</td>
</tr>
<tr>
<td>PVR</td>
<td>8.3 ± 2.9</td>
<td>8.8 ± 3.0</td>
<td>8.9 ± 3.5</td>
<td>8.7 ± 3.2</td>
<td>9.1 ± 3.9</td>
</tr>
<tr>
<td>$P_{PA}$</td>
<td>75.8 ± 14.6</td>
<td>75.0 ± 13.4</td>
<td>75.0 ± 10.5</td>
<td>72.8 ± 14.3</td>
<td>75.3 ± 20.8</td>
</tr>
</tbody>
</table>

$P_{PA}$ = Mean pulmonary artery pressure (mm Hg); $\Delta P_{PA}$ % = percentage change in mean pulmonary artery pressure in response to hypoxia; PVR = pulmonary vascular resistance (mm Hg/dl.min$^{-1}$); $P_{PA}$ = femoral artery pressure (mm Hg).

* Results which show a statistically significant difference ($P < 0.05$) from the initial control value using a paired Student's $t$ test.
a percentage of $P_{PA}$ immediately before hypoxia. The statistical analysis was performed with Student's $t$ tests using paired data. Neither halothane nor ether produced any statistically significant changes in pulmonary vascular resistance although the mean values show a small decrease in PVR with halothane and a small increase with ether. There were no significant differences between the control values before and after the administration of the anaesthetic agents.

Increasing concentrations of halothane caused a progressive depression of the hypoxic pressor response (fig. 2A). However, the change was only significant with 3% halothane. On only one occasion with 3% halothane was the response abolished completely, the response returning to normal at the time of the second control measurement. Ether also caused a deterioration in the hypoxic pressor response which was significantly different from the initial control value at all three concentrations. In three of the six preparations 10% ether abolished the response completely but the responses returned after withdrawal of the anaesthetic so that there was no significant difference between the first and second control values (fig. 2B).

**DISCUSSION**

The results of the right and left heart bypass preparations are qualitatively similar to those of the isolated lung preparations in that both halothane and ether diminish the hypoxic pulmonary pressor response. They differ in the quantitative changes which occur with similar inspired anaesthetic concentrations. In the isolated lung preparations the hypoxic pressor response could be abolished frequently by 1.5% halothane or 7% ether (Sykes et al., 1973) and sometimes the response could be abolished permanently. In the present experiment it was difficult to abolish the response which always returned with alacrity when the anaesthetic was discontinued.

There are many differences in the two preparations which could account for the apparent persistence of the hypoxic pressor response in the heart bypass preparations. The lungs were maintained in better condition in the preparation used in the present study, and the bronchial circulation was perfused continuously. Although we had no method of testing the integrity of the neural innervation of the lung tissue, it is probable that the nerve supply was not destroyed by the aortic or pulmonary artery ligatures which were placed as near to the heart as possible. There was no sign that the hypoxic response deteriorated with time as in the isolated lung. Since the remainder of the animal tissue was being normally perfused also the pulmonary vasculature was subject to normal biochemical influences such as catecholamines and other hormones. Benumof and Wahrenbrock (1975a) have suggested that hypoxic pulmonary vasoconstriction is mediated by a local vasoconstrictor metabolite and that anaesthetic agents may cause the inactivation of such a metabolite or alter its production or release. Benumof, Mathers and Wahrenbrock (1975) demonstrated also that such a vasoactive substance was released into the lymph draining an hypoxic lung. One could speculate that a similar factor, which helps to maintain the hypoxic pressor response, is present and is replenished constantly in the bypass.
In the isolated lung the blood perfusing the lungs is well oxygenated. However, in the present preparation the lungs were perfused with venous blood. This may alter the behaviour of the lungs, but it is likely also that the two preparations will differ in the actual blood concentrations of anaesthetic attained for the same inspired concentrations. In the isolated lung, because there is a very small tissue compartment, the blood and alveolar anaesthetic concentrations will rapidly be equal to the inspired concentrations. With the bypass preparation there is an appreciable absorption of anaesthetic by the tissues of the cat and the alveolar and blood concentrations of anaesthetic agent will increase at a slower rate than in the isolated lung. Although the experimental protocol allowed a period of 18 min with each anaesthetic concentration before the hypoxic response was tested, and there was no washout period between concentrations, it is possible that there was insufficient time for equilibration with vessel-rich tissues and the alveolar concentrations could have been considerably less than the inspired concentrations. In addition, in the perfusion system there were two open reservoirs through which some loss of anaesthetic vapour could occur.

Therefore, it is not difficult to find an explanation for the relative resilience of the hypoxic pressor response in the heart bypass in cats compared with the isolated lung preparation. However, it is not clear which are the most important factors.

The concentrations of the anaesthetics were chosen to cover the clinical range of concentrations and ether appears to have a greater effect on the hypoxic pressor response than does halothane. The hypoxic pressor response varies with lung vascular pressures (Benumof and Wahrenbrock, 1975b), but in the present experiments there was no difference in mean pulmonary artery pressures in the two anaesthetic groups. It is possible also that systemic pressure could affect the pulmonary vascular response via some baroreceptor mechanism, but no significant difference in femoral artery pressure between the two groups was noted.

It is concluded from these experiments that clinically used concentrations of ether and halothane may depress the pulmonary vasoconstrictor response to alveolar hypoxia in the perfused lung.

Acknowledgement

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References


Effets de l'halothane et de l'ether sur la circulation pulmonaire d'un poumon de chat enerve et asperge

Resumé

On a étudié sur un poumon de chat énervé et aspergé les effets de l'halothane et de l'ether diéthyl sur la résistance vasculaire pulmonaire et sur la réaction vasoconstrictrice pulmonaire à l'hypoxie alvéolaire. On a utilisé une technique basée sur une dérivation gauche et droite du cœur pour permettre l'asperger à débit constant des poumons. Aucun des agents anesthésiques n'a provoqué de changement significatif dans la résistance vasculaire pulmonaire, mais les deux agents ont causé une dépression de la réaction vasoconstrictrice pulmonaire à l'hypoxie.

Die Wirkungen von Halothan und Äther auf den Lungenkreislauf in der innervierten, durchströmten Katzenlunge

Zusammenfassung

Es wurden die Wirkungen von Halothan und Diäthyläther auf den Lungengefäßwiderstand und die Vasokonstriktorreaktion auf Alveolenhypoxie in der innervierten, durchströmten Katzenlunge studiert. Ein Verfahren für die linke und rechte Herzüberbrückung wurde angewendet, um es zu gestatten, die Lungenflügel mit einem gleichbleibenden Fluss zu durchströmen. Keines der beiden Narkosemittel verursachte eine bedeutsame Veränderung im Lungengefäßwiderstand, beide Mittel jedoch bewirkten eine Reaktionsschwächung des Lungen-Vasokonstruktors auf die Hypoxie.
Los efectos de halotano y éter dietílico sobre la resistencia vascular pulmonar y la respuesta vasoconstrictora pulmonar a la hipoxia alveolar fueron estudiados en el pulmón felino inervado perfundido. Se utilizó una técnica de derivación cardiaca derecha e izquierda para permitir la perfusión de los pulmones a flujo constante. Ninguno de los agentes anestésicos causó un cambio significativo en la resistencia vascular pulmonar aunque ambos agentes provocaron una depresión de la respuesta vasoconstrictora pulmonar a la hipoxia.