The Effects of Halothane on the Pulmonary Vascular Bed of the Dog

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The effects of 0.5 and 1.5 per cent (end-tidal) halothane on the pulmonary circulation in the anesthetized dog were studied by measurement of left atrial pressure, pulmonary arterial pressure, and total pulmonary blood flow. Halothane, 1.5 per cent, decreased pulmonary arterial pressure and flow, while computed pulmonary vascular resistance remained unchanged. In order to establish whether halothane has a direct effect on the pulmonary vascular bed, the left diaphragmatic lobe was isolated from the pulmonary circulation and perfused at a constant rate with blood from an external oxygenating circuit. When halothane was added to the external circuit a sustained decrease in perfusion pressure occurred, indicating that pulmonary vascular resistance had decreased. In the same experiments when halothane was administered to the dog by inhalation no change in perfusion pressure occurred in the lobe. Thus, by a direct action on pulmonary vascular smooth muscle, halothane is capable of producing vasodilatation, which is masked in the intact animal by the decrease in pulmonary arterial pressure and/or the action of a circulating vasoconstrictor substance. (Key words: Halothane; Pulmonary vascular resistance; Pulmonary vascular tension; Isolated diaphragmatic lobe; Autoperfused lobe.)

The effects of halothane (Fluothane) on the general circulation have been studied extensively since its introduction as a volatile anesthetic 14 years ago.1-6 Despite the fundamental importance of the pulmonary circulation in the transfer and elimination of the anesthetic, relatively little is known about the effects of halothane on pulmonary vascular smooth muscle. Price et al.7 reported that halothane does not alter pulmonary vascular resistance in man, while Wyant et al.8 reported an increase in pulmonary arterial pressure following induction with the anesthetic, an effect which was interpreted by the authors as representing increased pulmonary vascular resistance. Buckley and co-workers9 suggested that halothane may possess a pulmonary vasodilator effect since pulmonary vasoconstriction associated with hypoxia was antagonized in the presence of the anesthetic. The present investigation was undertaken to define the effect of halothane on the pulmonary circulation per se and to clarify the effect of halothane on pulmonary vascular smooth muscle.

Methods

Ten dogs of either sex were anesthetized with pentobarbital sodium, 30 mg/kg. Decamethonium (Strycholine), 0.25 mg/kg, was used to permit controlled pulmonary ventilation. The lungs were ventilated through a tracheal cannula at a fixed rate of 16/min and a tidal volume determined from a nomogram to maintain P\textsubscript{CO\textsubscript{2}} within normal limits (see table 1). Inspired oxygen concentration was 40 per cent. Systemic blood pressure was monitored from a brachial artery. Right atrial pressure was measured via a cannula passed into the right atrium from right external jugular vein. Measurement of pulmonary arterial pressure was accomplished by passing a catheter via the jugular vein and through the right heart into the pulmonary artery. A left thoracotomy was performed, through which an electromag-
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Table 1. pII and Blood-Gas Status of Animals Exposed to Halothane by Inhalation and Ventilated with 40 Per Cent O₂

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Halothane</th>
<th>Mean Difference ± SE</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>Halothane, 0.5 per cent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial P&lt;sub&gt;0₂&lt;/sub&gt;</td>
<td>146</td>
<td>139</td>
<td>7 ± 4</td>
<td>NS*</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.36</td>
<td>7.37</td>
<td>0.01 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial P&lt;sub&gt;CO₂&lt;/sub&gt;</td>
<td>37.8</td>
<td>34.5</td>
<td>3.3 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Mixed venous P&lt;sub&gt;0₂&lt;/sub&gt;</td>
<td>39.5</td>
<td>36.2</td>
<td>3.3 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Mixed venous pH</td>
<td>7.35</td>
<td>7.33</td>
<td>0.02 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Mixed venous P&lt;sub&gt;CO₂&lt;/sub&gt;</td>
<td>43.2</td>
<td>41.9</td>
<td>1.3 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Halothane, 1.5 per cent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial P&lt;sub&gt;0₂&lt;/sub&gt;</td>
<td>144</td>
<td>141</td>
<td>3 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.39</td>
<td>7.38</td>
<td>0.01 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial P&lt;sub&gt;CO₂&lt;/sub&gt;</td>
<td>36.1</td>
<td>33.2</td>
<td>2.9 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Mixed venous P&lt;sub&gt;0₂&lt;/sub&gt;</td>
<td>37.3</td>
<td>25.3</td>
<td>12 ± 1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mixed venous pH</td>
<td>7.34</td>
<td>7.27</td>
<td>0.07 ± 0.03</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mixed venous P&lt;sub&gt;CO₂&lt;/sub&gt;</td>
<td>41.9</td>
<td>47.3</td>
<td>5.4 ± 2.3</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

* NS = not significant.

In addition to the variables measured directly, four values were computed. Left ventricular stroke volume was found by dividing total pulmonary blood flow by heart rate. Left ventricular stroke work was defined as the product of left ventricular stroke volume and mean systemic blood pressure. Total peripheral resistance was calculated as the difference between mean systemic blood pressure and right atrial pressure, divided by total pulmonary blood flow. Pulmonary vascular resistance was computed by taking the difference between pulmonary arterial pressure and left atrial pressure and dividing by total pulmonary blood flow.

Isolated Lobe Perfusion

Thirteen dogs ranging in weight from 24 to 29 kg were anesthetized basally with pentobarbital sodium, 30 mg/kg, and paralyzed with decamethonium, 0.25 mg/kg. A left thoracotomy was performed, the artery and vein of the left diaphragmatic lobe were carefully dissected, and after anticoagulation with heparin sodium, 5 mg/kg, were cannulated with 5-mm (i.d.) elbow-shaped catheters. The incision was covered with Vi-Drape self-adhering surgical film and the thoracic cavity evacuated of air. The lobe was perfused from an extracorporeal circuit (fig. 1) previously...
primed with blood obtained from a donor dog. Blow flow to the lobe was set to give a perfusion pressure comparable to that of pulmonary arterial pressure in intact animals. Lobar venous blood was allowed to drain by gravity into a reservoir. The blood was then pumped from the reservoir by a Mark roller pump (model SH-51) to a modified Lillehei-Dewall bubble oxygenator. The blood was defoamed and pumped at a constant rate through a heat exchanger to the artery of the isolated lobe. Carbon dioxide, nitrogen, and air were admitted to the oxygenator column in amounts sufficient to produce gas tensions equivalent to those found in mixed venous blood. The bronchus of the autoperfused lobe remained intact and was ventilated along with the non-isolated lobes at a fixed rate and volume with 40 per cent $\text{O}_2$. Peak inflation and intrathoracic pressures were monitored using Statham pneumatic transducers.

Halothane, 1.5 per cent, was administered to the perfused lobe with a Fluotec vaporizer placed in series with the gas-delivery system of the bubble oxygenator. Gas exhaust from the oxygenator was analyzed for halothane content as described above. Following the administration of halothane to the blood perfusate, ten of the 13 dogs used in this study received the same concentration of halothane by inhalation after basal conditions of the lobe had been re-established. The duration of halothane administration by either method was ten minutes after the onset of a response, as interpreted by a change in perfusion pressure in the lobe.

As a test of the functional status of the perfused lobe, pulmonary arterial and venous samples were obtained and analyzed for $P_{O_2}$, $P_{CO_2}$, and $pH$ just prior to halothane administration.

Statistical analyses were performed using paired $t$ tests. A probability level of 0.05 or less was used as the criterion for statistical significance.

Results

Halothane Administered by Inhalation to the Intact Dog

Both high and low end-tidal concentrations of halothane produced significant decreases in systolic, mean, and diastolic blood pressures (fig. 2). The response to the high concentration of halothane was significantly different from the response to the low concentration after four minutes. This dose-related depressant effect of halothane on systemic blood pressure has been reported previously.

Figure 3 illustrates changes in right atrial pressure, left ventricular stroke work, left ven
tricular stroke volume, and total peripheral resistance produced by 0.5 and 1.5 per cent end-tidal halothane. Right atrial pressure was not altered significantly by either the high or the low concentration. Left ventricular stroke work was significantly depressed by both concentrations of the anesthetic. Left ventricular stroke volume was not affected significantly by halothane. Total peripheral resistance was reduced significantly by both concentrations.

Figure 4 illustrates changes in pulmonary arterial pressure, left atrial pressure, total pulmonary blood flow, and pulmonary vascular resistance. Pulmonary arterial pressure was decreased significantly by the high dose of halothane. The peak decrease represents a 20 per cent reduction of pulmonary arterial pressure. The increases in left atrial pressure were significant at both 0.5 and 1.5 per cent end-tidal halothane. Total pulmonary blood

![Graph showing blood pressure changes](image)

### Table 2. Comparison of the Effects of Halothane Administered in the Perfusate of the Lobe and by Inhalation

<table>
<thead>
<tr>
<th></th>
<th>Perfusion, N = 13</th>
<th>Inhalation, N = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Halothane</td>
</tr>
<tr>
<td>Lobar blood flow (ml/min)</td>
<td>106</td>
<td>106</td>
</tr>
<tr>
<td>Lobar perfusion pressure (mm Hg)</td>
<td>18.3</td>
<td>16.8</td>
</tr>
<tr>
<td>Systemic blood pressure (mm Hg)</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>Peak inflation pressure (cm H₂O)</td>
<td>12.5</td>
<td>12.2</td>
</tr>
<tr>
<td>Thoracic pressure (cm H₂O)</td>
<td>-3 to -5</td>
<td>-3 to -5</td>
</tr>
</tbody>
</table>

*Significant difference from control, P < 0.001.
Fig. 3. The changes in right atrial pressure, left ventricular stroke work, left ventricular stroke volume, and total peripheral resistance produced by administration of 0.5 and 1.5 per cent halothane to ten dogs. The arrows indicate the duration of halothane administration. Right atrial pressure was not significantly altered. Left ventricular stroke work was reduced after two minutes of halothane administration ($P < 0.05$), and after six minutes the difference between the high and low doses was significant ($P < 0.01$). Left ventricular stroke volume was not significantly altered by either the high or the low dose. Total peripheral resistance was significantly reduced by both doses after two minutes ($P < 0.05$), and the differences between the doses were significant after four minutes.

Flow was reduced by both concentrations of halothane, but not significantly. Calculated pulmonary vascular resistance was not significantly altered by the administration of either the high or the low dose.

Changes in heart rate induced by halothane were extremely variable, and no significant effects were noted.

The 0.5 per cent end-tidal concentration of halothane produced no significant changes in either arterial or mixed venous pH, $P_{O_2}$ or $P_{CO_2}$. Arterial pH and blood gases were unaltered by 1.5 per cent halothane; however, mixed venous samples showed a significant decrease in $P_{O_2}$ and pH and an increase in $P_{CO_2}$. Data summarizing the effects of the two concentrations of halothane on pH and blood gases are found in table 1.

**Halothane Administered to the Isolated Lobe**

Halothane equilibrated in the blood perfusing the isolated lobe produced a slight but significant decrease in lobar perfusion pressure. The onset of the response was slow, the average time being about four minutes. The decrease in perfusion pressure produced by halothane administered in this fashion was of long duration, on the average requiring 12 minutes to return to control levels after the anesthetic was discontinued. Halothane administered by inhalation in the same concentration to ten of the 13 dogs in the lobe-perfusion study produced no significant change in perfusion pressure, though systemic effects such as lowered arterial pressure were noted.
Peak inflation and intrathoracic pressures were unaltered by halothane administered to the perfusate or by inhalation. A comparison of the effects of halothane administered by equilibration in the perfusate and by inhalation is found in table 2.

Pulmonary arterial and venous blood gases were determined as an index of the functional status of the perfused lobe prior to halothane administration. Averaged arterial pH, $P_{O_2}$, and $P_{CO_2}$ values were 7.38, 47 mm Hg, and 47 mm Hg, respectively; corresponding venous samples averaged 7.45, 154 mm Hg, and 36 mm Hg.

**Discussion**

Halothane administered to the intact dog produced generalized cardiovascular depression, a condition long known to be associated with use of the anesthetic. Since pulmonary blood flow and arterial pressure decreased in parallel, no significant change in pulmonary vascular resistance was detected in this study. These findings are in agreement with the work of Price et al. However, despite the fact that halothane did not produce a significant change in pulmonary vascular resistance, the present results suggest that a pulmonary vascular smooth-muscle-depressant effect of halothane exists. If the overall radii of the vessels remained the same in face of a decrease in vascular distending pressure, the product of these variables, tension, probably was reduced. Theoretically, the reduction in pulmonary vascular tension could be the result of a withdrawal of neurogenically mediated tone since halothane has been demonstrated to possess sympathetic ganglionic and...
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peripheral and central vasomotor depressant properties.\textsuperscript{6,11,12} The results of the present investigation suggest, however, that the pulmonary vascular depressant effect of halothane is the result of a direct effect of the anesthetic on the pulmonary vessels, since halothane in blood perfusing the isolated diaphragmatic lobe produced a significant decrease in perfusion pressure. The decrease in perfusion pressure occurred at a time when there was no change in peak inflation or intrathoracic pressure.

When halothane was administered by inhalation to the same dogs, thus confining the anesthetic to the intact animal and essentially denying halothane access to vessels of the perfused lobe, no changes in perfusion pressure occurred. Thus, during halothane-induced systemic hypotension, a condition which would be expected to increase, by reflex means, neurogenic pulmonary vasoconstrictor activity,\textsuperscript{12} no pulmonary vascular adjustments were noted. It may be assumed from these data that the neural pathways associated with reflex regulation of pulmonary vascular resistance probably were depressed by the peripheral and central neural depressant actions of the anesthetic.

Since reflex pulmonary vasoconstriction did not occur in the isolated lobe during halothane-induced systemic hypotension, and the direct effect of halothane on pulmonary vessels was demonstrated to be vasodilating, the failure of pulmonary vascular resistance to decrease in the intact animal still requires explanation.

One explanation has already been alluded to. If active tension in pulmonary vascular smooth muscle is depressed by halothane, vasodilatation should ensue. If, however, pulmonary arterial pressure falls concomitantly, vascular caliber may remain unchanged. Thus, the demonstrated direct depressant effect of halothane on pulmonary vascular smooth muscle might not be translatable, in the intact animal, to a decrease in pulmonary vascular resistance.

It is also possible that the direct pulmonary vasodilatation produced by halothane is overridden by vasoconstriction produced indirectly as a consequence of the action of a circulating vasoconstrictor substance. Antidiuretic hormone (vasopressin) has been shown to be released from the hypothalamus in the dog upon inhalation or intracarotid injection of halothane.\textsuperscript{14} This or other substances with pulmonary vasoconstrictor properties could well be involved in masking the pulmonary vasodilator effect of halothane.

References