The Effects of Halothane and Atropine on Total Respiratory Resistance in Anesthetized Man

Allan L. Brakensiek, M.D.,* Norman A. Bergman, M.D.†

Halothane failed to decrease respiratory resistance in 11 of 13 subjects anesthetized with oxygen and nitrous oxide, curarized, and mechanically ventilated. Atropine failed to decrease respiratory resistance in 12 of the 13 subjects. Two subjects, each with chronic bronchopulmonary disease and high respiratory resistance, had small decreases in resistance following halothane, and one of these had a further small decline following atropine. We conclude that in healthy individuals, halothane and atropine do not have primary effects upon bronchial tone. The decreased resistance in the two patients seems best explained on the basis of blockade of reflex pathways, rather than direct effects upon bronchiolar tone. (Key words: Respiratory mechanics during anesthesia; Respiratory resistance; Bronchomotor tone; Halothane; Atropine.)

Clinical studies suggest that halothane (Fluothane) is a useful agent for asthmatic patients requiring general anesthesia. Shneider and Papper reported that the incidence of wheezing during halothane anesthesia was relatively low and that halothane was particularly effective in terminating asthmatic episodes occurring during anesthesia.1 Abajian credited halothane with improving the ventilatory status of patients exhibiting signs of asthma during anesthesia.2 Brown commented on the relaxed appearance of bronchi visualized during bronchoscopic examination with halothane anesthesia.3 These reports suggest a possible bronchodilating action of halothane in man. In addition, studies of dogs4 and isolated tracheal smooth muscle5 indicate a relaxant effect of halothane on respiratory tract musculature. On the other hand, Patterson and his associates failed to demonstrate decreases in pulmonary resistance produced by administration of halothane either directly to the lung or to the systemic circulation during total cardiopulmonary bypass.6 Atropine, administered to conscious subjects, produces a small decrease in airway resistance.7 The present study was undertaken to measure respiratory resistance in man undergoing general anesthesia with halothane under usual clinical conditions.

Methods
Subjects of the study were male hospital patients scheduled for elective surgical operations under general anesthesia. Their ages ranged from 34 to 76 years. Operations included herniorrhaphy and various procedures on the extremities. Signs of pulmonary disease consisted of abnormal physical or radiographic findings. Symptoms were cough, dyspnea, or wheezing. Each subject was premedicated with pentobarbital (Nembutal), 100 to 200 mg intramuscularly, approximately an hour before anesthesia. Anesthesia was induced with small intravenous increments of thiopental (Pentothal), utilizing loss of lid reflex as the end-point. The total doses of thiopental varied from 275 to 525 mg. Following loss of the lid reflex, d-tubocurarine (0.4 mg/lb body weight) was administered. This dose of d-tubocurarine was adequate for endotracheal intubation and prevented movement and spontaneous respiratory effort during the subsequent study. A #38 cuffed rubber endotracheal tube 25 cm in length was inserted and the cuff inflated to provide an airtight seal. Anesthesia initially was maintained with nitrous oxide, 60 per cent, and oxygen, 40 per cent, plus small supplemental doses of thiopental. Controlled ventilation with a minute volume of approximately 8 l/min was used, utilizing a nonrebreathing circuit and a Manley Ventilator (Blease Anaes-
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Table 1. Preanaesthetic Pulmonary Status and Respiratory Resistance (cm H₂O/l/sec) of Patients in Group A

<table>
<thead>
<tr>
<th>Pulmonary Disease</th>
<th>Signs</th>
<th>Symptoms</th>
<th>Initial Condition (Thiopental, Nitrous Oxide and d-Tubocurarine)</th>
<th>Initial Condition + Halothane</th>
<th>Initial Condition + Halothane + Atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>-</td>
<td>-</td>
<td>2.7</td>
<td>2.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Patient 2</td>
<td>-</td>
<td>-</td>
<td>3.7</td>
<td>3.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Patient 3</td>
<td>-</td>
<td>-</td>
<td>4.3</td>
<td>4.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Patient 4</td>
<td>-</td>
<td>-</td>
<td>4.7</td>
<td>5.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Patient 5</td>
<td>-</td>
<td>-</td>
<td>5.8</td>
<td>5.4</td>
<td>5.0</td>
</tr>
<tr>
<td>Patient 6</td>
<td>-</td>
<td>+</td>
<td>8.6</td>
<td>6.3</td>
<td>6.3</td>
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<tr>
<td>Patient 7</td>
<td>+</td>
<td>-</td>
<td>10.2</td>
<td>11.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Patient 8</td>
<td>+</td>
<td>+</td>
<td>11.9</td>
<td>10.4†</td>
<td>9.7†</td>
</tr>
<tr>
<td>Patient 9</td>
<td>+</td>
<td>+</td>
<td>12.7</td>
<td>10.4†</td>
<td>9.5</td>
</tr>
<tr>
<td>Patient 10</td>
<td>+</td>
<td>+</td>
<td>26.5</td>
<td>23.5</td>
<td>20.8</td>
</tr>
</tbody>
</table>

* Tabular values are means of four to six determinations made during each experimental period.
† Significant change from the preceding period (p < 0.05).

The preanesthetic equipment Ltd., England). Respiratory rates varied from 12 to 16/min, tidal volumes from 650 to 800 ml. End-expiratory P_{CO₂} was monitored throughout the study with a Beckman LB-1 infrared analyzer. Rates and tidal volumes were adjusted to maintain end-expiratory P_{CO₂} values in a range from 32 to 33 mm Hg.

When the conditions appeared relatively stable several control measurements of respiratory resistance were made. During the subsequent experimental period patients were treated in one of two ways. Group A received 0.5–1.0 per cent halothane for the experimental period of 45 to 50 minutes. Halothane was vaporized in 60 per cent nitrous oxide and 40 per cent oxygen at the above flow rate using a Fluotec vaporizer. Approximately halfway through the experimental period 0.8 mg atropine was administered intravenously. Group B received 0.8 mg atropine initially and administration of halothane was begun about 20 to 25 minutes later and continued for an additional 20 to 25 minutes. In all subjects, the doses of halothane administered were sufficient to decrease pulse rate and/or blood pressure compared with the control values. Operations were begun at various times in this sequence. Occasionally, operation was initiated during the control period. The incision did not produce pupillary or circulatory changes suggestive of light planes of anesthesia. In no instance did operation necessitate deepening anesthesia.

Measurements were made during the control period and at five-minute intervals throughout the experimental period. Total respiratory resistance was calculated from data obtained during passive exhalations, using an apparatus described in a previous publication. The thorax was inflated with 1,000 ml of the anesthetic gas mixture, using a giant syringe. Thoracic inflation was maintained for approximately three seconds; then passive exhalation into a 10-liter waterless spirometer (Wedge Spirometer, Med-Science Electronics, St. Louis, Mo.) occurred. Pressure in the endotracheal tube relative to atmospheric pressure during sustained thoracic inflation was measured with a Statham PM5TC pressure transducer. Exhaled volume and flow during the subsequent passive exhalation were measured by means of the volume and flow transducers of the spirometer. Pressure, volume, and flow signals were recorded using a Minneapolis-Honeywell Viscoorder. Between measurements artificial ventilation was provided with the Manley Ventilator.

Total respiratory compliance was calculated from transthoracic pressure recorded during the period of static thoracic inflation and from the volume subsequently exhaled. Respiratory resistance at a flow of 0.5 l/sec was calculated by dividing lung volume at the instant when expiratory flow rate was 0.5 l/sec by total respiratory compliance. This gives transthoracic pressure required to sustain a flow of 0.5 l/sec by definition, respiratory resistance.
at this flow. Resistance of the apparatus, including endotracheal tube, was subtracted from observed values to obtain the true resistance.

Significance of changes in respiratory resistance following administration of halothane or atropine was estimated using the Mann-Whitney U test. A double-tailed test was utilized and P values of 0.050 or less were considered significant.

Results

Mean values for respiratory resistance and preanesthetic pulmonary status of subjects in Group A are presented in Table 1. Of the ten subjects in this group, one had a significant reduction in respiratory resistance following halothane and a further decrease following atropine administration. Halothane produced a significant reduction in resistance in a second subject but subsequent atropine administration had no effect upon respiratory resistance. Both of these subjects had signs and symptoms of chronic obstructive airway disease and high initial resistance. In these two individuals, no change in resistance or compliance was clinically detectable during the course of the anesthesia. Results for subjects in Group B are presented in Table 2. No significant change in respiratory resistance occurred during any portion of the study in any subject.

End-expiratory P CO 2 values remained within desired limits, not varying more than 1.5 mm Hg throughout the study in any subject.

Discussion

Values for respiratory resistance in the present study are in good agreement with those previously reported for anesthetized, curarized subjects, and confirm the conclusion that the magnitude of respiratory resistance during anesthesia is similar to that anticipated in comparable conscious individuals. The stable end-expiratory P CO 2 eliminates this variable from further consideration as a factor contributing to the results of the present study.

Daly, Ross, and Behnke demonstrated a small but significant decrease in airway resistance, as well as an increase in deadspace, following administration of atropine to conscious man. Severinghaus and Stupfel reported an increase in deadspace following administration of atropine to both dogs and conscious human subjects. The increase in deadspace was attributed to dilatation of larger bronchi. In the present study, atropine failed to cause a significant change in respiratory resistance in 12 of 13 anesthetized subjects. The magnitude of change in airway resistance reported by Daly et al., although significant, was less than 0.4 cm H 2 O/l/sec. Such a change could be obscured in measurements of total respiratory resistance. Our results do not substantiate the findings of Don and Robson, who reported decreases in respiratory resistance following intravenous administration of atropine to subjects anesthetized with nitrous oxide. Their atropine dosage was comparable to that used in the present study.

Relaxation of bronchial smooth muscle attributable to halothane has been demonstrated in laboratory animals and in animal tissues. In the present study, addition of halothane to thiopental–nitrous oxide–curare anesthesia failed to produce a demonstrable change in respiratory resistance in 11 of 13 subjects. These findings are in agreement with those of Patterson and associates, who did not observe changes in pulmonary resistance following administration of halothane.

Table 2. Preanesthetic Pulmonary Status and Respiratory Resistance (cm H 2 O/l/sec) of Patients in Group B*

<table>
<thead>
<tr>
<th>Pulmonary Disease</th>
<th>Initial Condition (Thiopental, Nitrous Oxide and d-Tubocurarine)</th>
<th>Initial Condition + Atropine</th>
<th>Initial Condition + Halothane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs</td>
<td>Symptoms</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Patient 11</td>
<td>–</td>
<td>2.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Patient 12</td>
<td>–</td>
<td>5.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Patient 13</td>
<td>–</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*There were no significant changes in respiratory resistance throughout the study in this group.
during cardiopulmonary bypass. This lack of response in man could represent a species difference between man and the dog and guinea pig used in laboratory experiments. All subjects in the present study had decreased pulse rates and/or blood pressures and did not respond to surgical stimulation. Hickey et al. found no change in pulmonary resistance in dogs when inspired halothane concentration increased from 0.5 to 2.4 MAC (minimum anesthetic concentration). It seems unlikely that inadequate depth of anesthesia was a factor contributing to the results observed.

Administration of the potent bronchodilator isoproterenol as an aerosol to healthy individuals with normal airway resistance does not produce a remarkable decrease in airway resistance. It is possible, therefore, that only minimal bronchial smooth muscle tone exists during thiopental-nitrous oxide anesthesia also and further bronchial relaxation does not occur in response to halothane.

Decreases in respiratory resistance occurred in two subjects following administration of halothane, and one of them experienced a further decrease with atropine. Both subjects had signs and symptoms of pulmonary disease and high initial resistance. A portion of this elevated resistance could have been caused by reflex response to the presence of an endotracheal tube during a light plane of anesthesia. The subsequent decrease in resistance with halothane administration probably represents depression of such a reflex pathway, rather than direct action upon bronchial smooth muscle. Hickey et al. showed that in the dog both halothane and cyclopropane block bronchoconstriction caused by stimulation of the vagus nerve or administration of histamine. The subsequent response to atropine is one of the subjects also suggests that the mechanism for the decrease in respiratory resistance was blockage of a reflex pathway.

On the basis of clinical experience, halothane has generally been recognized as useful in the management of bronchospasm associated with anesthesia. Results of the present study suggest that previously reported beneficial effects of halothane in preventing and treating bronchospastic episodes probably are related to the anesthetic actions of halothane in blocking reflex responses to stimuli which elicit bronchospasm in susceptible individuals. A direct effect of halothane on respiratory resistance in man during usual clinical conditions could not be demonstrated.

References