Halothane, Tracheal Compliance and Upper-airway Mechanoreceptors

Susan K. Palmer, M.D.,* Edward J. Zuperku, Ph.D.,† Zeljko Bosnjak, B.S., Robert L. Coon, Ph.D.,‡ John P. Kampine, M.D., Ph.D.§

This study was designed to define the effects of halothane on the compliance of the trachea. An isolated in-vitro tracheal preparation was studied in 14 mongrel dogs anesthetized with pentobarbital. Compliance of the closed tracheal segment was measured with continuous intraluminal pressure recordings during repeated injections of known volumes of air. Slow-adapting neural activity observed in paratracheal branches of the recurrent laryngeal nerve accurately reflected pressure in the tracheal segment. Halothane at 0.5–4.0 per cent concentrations caused a significant (P < 0.001) average 10 per cent increase in the compliance of the trachea. Stimulation of the efferent vagus caused a significant (P < 0.001) average 8 per cent decrease in compliance of the trachea. After exposure to halothane, vagal stimulation still caused a significant decrease in compliance of the trachea. (Key words: Anesthetics, intravenous; pentobarbital. Anesthetics, volatile: halothane. Airway: mechanics. Lung: trachea.)

Previous studies in man1,2 and in animals3–8 have indicated that potent inhalational anesthetic agents may produce changes in pulmonary compliance and airway resistance. Although halothane has been studied most extensively, there is lack of agreement in the literature with respect to the exact effect of this agent on bronchomotor tone. The lack of uniformity in published results may be related to the problems of obtaining a standard baseline of bronchomotor tone. Without some pre-existing airway tone, it is impossible to demonstrate bronchodilator activity of any agent.7,8

Kilde and Aviando3 and Hickey et al.9 have reported that halothane decreases total pulmonary resistance in dogs. Colgan,9 however, could find no change in total pulmonary resistance in dogs given halothane to 2.5 per cent. McAslan10 has reported that halothane causes a decrease in pulmonary resistance in man during cardiopulmonary bypass. However, Brakensiek11 and co-workers could find no change in total pulmonary resistance in healthy patients given halothane as a general anesthetic. Conflicting results have also been found in studies of the action of halothane on airways previously constricted by histamine. Hickey9 reported that halothane attenuated the increase in total pulmonary resistance seen with histamine. Colgan’s3 group found no change in the histamine-induced decrease in pulmonary compliance.

Most previous studies have been done on lung in vivo or on in-vitro tracheal preparations. Fleish and Calkins5 point out that there is a lack of pharmacologic uniformity in reactions of tracheal versus bronchial smooth muscle. Histamine, for example, causes tracheal relaxation and bronchial contraction in their experiments in rabbits. Lung preparations in vivo offer gross compliance measurements, and may obscure offsetting compliance changes in large and small airways; or they may be unable to differentiate local from systemic effects of halothane. The purpose of this investigation was threefold: 1) to investigate the effects of halothane on compliance of the isolated upper tracheal segment in situ; 2) to study the effects of halothane on the decrease in upper tracheal segment compliance produced by stimulation of the vagus nerve; 3) to study the response of upper tracheal slowly-adapting stretch receptors to graded pressure stimuli.

Methods

Fourteen mongrel dogs, weighing 12–27 kg, were anesthetized with pentobarbital, 25 mg/kg, intravenously, with supplemental doses of 60 to 120 mg as necessary to maintain anesthesia. A femoral artery was cannulated with rigid polyethylene tubing. Lead II of the ECG was monitored using needle electrodes. Esophageal temperature was measured with a General Electric temperature monitor and maintained within normal limits by appropriate draping and use of a heating lamp.

The trachea and larynx were exposed through a midline neck incision from above the hyoid bone to the

*Assistant Professor, Chief, Section of Obstetric Anesthesia, Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, Wisconsin.
†Assistant Professor, Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, Wisconsin; Assistant Clinical Professor, Department of Biomedical Engineering, Marquette University, Milwaukee, Wisconsin.
‡Assistant Professor, Departments of Anesthesiology and Physiology, The Medical College of Wisconsin, Milwaukee, Wisconsin.
§Professor of Anesthesiology and Professor of Physiology, The Medical College of Wisconsin, Milwaukee; Associate Chief of Staff for Research, Veterans Administration Center, Wood (Milwaukee), Wisconsin.

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Address reprint requests to Dr. Palmer: St. Mary's Hospital, Department of Obstetric Anesthesia, 4th Floor, 2323 North Lake Drive, Milwaukee, Wisconsin 53211.
sternal notch. A tracheostomy was performed as low in the neck as possible; a right-angle cannula was placed and directed caudally to allow for ventilation. After the trachea was divided, a second cannula was placed in the upper tracheal segment and directed cranially. The top of the tracheal segment was sealed at the cricoid cartilage by a rigid cannula ligated in place. Using a flow-through system, the tracheal-segment lumen was exposed to halothane in oxygen for 30–300 seconds. Halothane was delivered from a calibrated Mark 2 Fluotec vaporizer on an anesthesia machine. Care was taken to identify and preserve the tracheal nerves and blood supply.

The left recurrent laryngeal nerve or one of its para-tracheal branches was located and freed of connective tissue. Using a Zeiss operating microscope, the nerve was dissected and desheathed carefully under warm mineral oil. After removal of the nerve sheath, a slip of nerve was placed on fine tungsten recording electrodes. Single- and multi-fiber nerve filaments were held in position by a micromanipulator. The bipolar electrodes were connected to a high-impedance preamplifier and filter system with photoelectric coupling. A Faraday cage was used to minimize 60-Hz interference. The moving time-average of neural activity was shown on the polygraph. Single- or few-fiber neural activity was chosen for study when the activity was responsive to tracheal-segment pressure stimuli and displayed a slowly-adapting pattern. Some rapidly-adapting neural activity was observed but not studied. Stretch receptors with a high basal firing rate, which were responsive to graded pressure changes within the trachea, were chosen for study only when they could not also be excited by probing the extratracheal adventitial or esophageal tissues. At the end of each study, the trachea was opened and the receptive field of the single- or few-fiber group was located by direct probing.

Square-wave tracheal-segment pressure stimuli were produced by rapid syringe injection of air, or by turning a three-way valve that exposed the segment to pressure from a weighted spirometer that maintained a prolonged constant-pressure stimulus.

The right vagus was carefully located and sectioned at the level of the cricoid cartilage, and the distal end was placed on stimulating electrodes. Supramaximal stimulation strengths were used with a constant-current stimulation at 2–6 mA, with 0.5-msec spike duration, and frequencies of 2–40 Hz. A bell-type water-seal microspirometer was attached to the tracheal segment in a closed system to detect small volume changes of the segment during vagal stimulation. Movement of the spirometer bell was monitored with a photoelectric system coupled to a Grass Model 7 Polygraph channel for permanent recording of the volume changes.

Compliance measurements were made by repeatedly injecting known volumes (1–12 ml) of air into the isolated tracheal segment and measuring the changes in segment pressure produced. Pressure changes were measured after the initial stress—relaxation curve caused by the rapid change in pressure. When necessary, small leaks in the tracheal segment could be corrected for by projecting the stable-plateau-phase slope back to the point of injection.

Femoral arterial blood pressure was monitored with a Statham transducer. Arterial blood-gas values were analyzed using a Radiometer multiple-electrode blood-gas machine. Pressure inside the isolated tracheal segment was measured with a Statham low-pressure transducer. Electrocardiogram, blood pressure, ventilation, tracheal-segment pressure, and averaged neural activity were amplified and recorded on a Grass Model 7 Polygraph. The neural activity was displayed on a Tektronix type 5103N storage oscilloscope and monitored with a loudspeaker. Neural activity, tidal volume, tracheal-segment pressure, and blood pressure or voiced information were recorded on a Tandberg series 100 FM tape recorder for later analysis.

Comparisons between compliance measurements were made by use of Student's t test for paired data. The method of least-squares linear regression was used to determine the slope and y intercept of representative pressure—volume curves. Analysis of variance was used to compare the slopes (compliance) and y intercepts of these curves.

Results

When increments of air (1–12 ml) were added to the closed tracheal segment the average neural activity of a para-tracheal branch of the recurrent laryngeal nerve showed: 1) an initial overshoot, which reflected the pressure stress—relaxation overshoot; 2) a plateau, illustrating the slow adapting nature of the receptors studied; 3) momentary suppression to below baseline levels when the pressure was released to zero (fig. 1). Stimulation of the efferent right vagus produced the following changes: 1) heart rate decreases; 2) blood pressure decreases; 3) ventilatory pattern changes, which were probably mediated through the intact left vagus; 4) slight increases in pressure in the closed tracheal segment in response to the initiation of vagal stimulation; 5) brief increases in neural activity when vagal stimulation ceased (fig. 2). The immediate increase in frequency of breathing with vagal stimulation (fig. 2) could be explained by reflex mechanisms. Right efferent vagal stimulation caused airway con-
striction and a decrease in compliance, which changed slowly-adapting receptor discharge and increased irritant receptor discharge through the intact left vagal afferents. This increase in afferent activity may have caused a centrally-mediated reflex increase in ventilatory frequency. Or, right efferent vagal stimulation may also have caused bradycardia and a concomitant decrease in blood pressure, which resulted in decreased cerebral perfusion pressure and chemoreceptor ischemia. Carotid chemoreceptor ischemia is known to cause reflex increases in ventilation.

The neural activity studied was excited by slight deformation of a small area (<1 cm diameter) of the posterior tracheal wall. The areas immediately ad-

Fig. 1. Changes in average neural activity resulting from tracheal pressure changes in tracheal segment in situ. BP = systemic blood pressure; AF = air flow; TRACH SEG = tracheal segment; AV = average.

Fig. 2. Changes in tracheal-segment pressure and average neural activity during stimulation of the contralateral vagus nerve.
FIG. 3. Tracheal volume decreases produced by trachealis muscle contraction, plotted as a function of the frequency of the constant-current stimulation applied to the right vagus.

Adjacent to the open ends of the tracheal C-rings were the most frequent sites of receptor activity. It was possible by direct stretching of the posterior tracheal wall with forceps to reproduce the increases in neural activity caused by increasing the intraluminal pressure in the intact trachea. Transverse stretching was usually more effective than longitudinal stretching in producing increased receptor discharge.

Direct observation of the open tracheal during electrical stimulation of the vagus showed progressive folding of the posterior wall as the transverse distance between the open ends of the tracheal C-rings was shortened. A stimulation frequency of 30 Hz was chosen; this yielded maximal decreases in tracheal volume (fig. 3) with reasonable recovery times after repeated stimulations.

FIG. 4. Relationship of the changes in tracheal segment pressure to the volume of air injected. The slopes differ from each other at the $P < 0.005$ level of confidence.
Table 1. Tracheal-segment Compliance Differences with Local Halothane Exposures and Vagal Stimulation

<table>
<thead>
<tr>
<th>Compliance Conditions Compared</th>
<th>Number of Pairs</th>
<th>Average Compliance Difference*</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control–halothane, 0.5–4 per cent</td>
<td>62</td>
<td>+0.027 ml/torr</td>
<td>0.007</td>
</tr>
<tr>
<td>Control–vagal stimulation after halothane, 0.5–4 per cent</td>
<td>83</td>
<td>−0.047 ml/torr</td>
<td>0.007</td>
</tr>
<tr>
<td>Control–vagal stimulation after halothane, 0.5–4 per cent</td>
<td>48</td>
<td>−0.055 ml/torr</td>
<td>0.007</td>
</tr>
<tr>
<td>Control–vagal stimulation after halothane, 0.5–1 per cent</td>
<td>13</td>
<td>−0.031 ml/torr</td>
<td>0.008</td>
</tr>
<tr>
<td>Control–vagal stimulation after halothane, 2 per cent</td>
<td>15</td>
<td>−0.073 ml/torr</td>
<td>0.014</td>
</tr>
<tr>
<td>Control–vagal stimulation after halothane, 3–4 per cent</td>
<td>20</td>
<td>−0.058 ml/torr</td>
<td>0.011</td>
</tr>
</tbody>
</table>

* P < 0.01 for all differences; all comparisons were made by use of the t test for paired data.

Compliance measurements showed that pressure changes were a nearly linear function of the volume changes when 1–12 ml were injected (fig. 4). When larger volumes were injected, the increments of pressure increases became smaller as a flatter portion of the compliance curve was approached. During vagal stimulation, tracheal compliance decreased, as illustrated by the slopes of the pressure–volume curves in figure 4, which are significantly different from each other (P < 0.005). Control compliances varied widely (0.104–1.075 ml/torr) because tracheal-segment dimensions varied with animal size and preparation. Tracheal-segment volumes, calculated from tracheal diameter and length measurements, assuming a perfect cylindrical shape, ranged from 15 to 110 ml. Regardless of the segment volume, the addition of halothane consistently produced increases in compliance, ranging from 4 to 25 per cent. In 62 paired compliance measurements, halothane caused increases in compliance of the tracheal segment, the average increase being 0.027 ml/torr (table 1). In 85 pairs of compliance measurements, vagal stimulation caused an average 0.047 ml/torr decrease in compliance of the isolated tracheal segment. Exposure to halothane in low or high concentrations did not prevent the decrease in compliance caused by vagal stimulation.

Discussion

Compliance of the intact, canine trachea in situ was increased after exposure to halothane. This finding agrees with and extends the work of Fletcher et al.6 who reported relaxation of the in-vitro guinea pig tracheal chain preparation by halothane. Colgan5 reported that inhalation of halothane increased bronchial diameter in dogs. However, his studies were complicated by an increase in ventilatory rate, which would have independently caused airway dilation.

The mechanism of the increase in tracheal compliance by halothane is not clear. Halothane has been found to antagonize contraction of bronchial smooth muscle caused by histamine,5,6 or by hypcapnia.4 Klide and Aviado5 have postulated that halothane causes airway dilation by stimulation of beta receptors in smooth muscle. However, Fletcher et al.6 reported that β-blockade did not prevent halothane-induced relaxation of the tracheal-chain preparation, and Coon et al.4 showed that β-blockade did not inhibit halothane-induced relaxation of hypoxic bronchoconstriction. Direct electrical stimulation of the efferent vagus was still effective in producing a decrease in tracheal compliance after exposures to halothane, 0.5–4 per cent, in our study. Halothane probably did not increase tracheal compliance by direct or competitive blockade of the neuroeffector junction in the trachealis muscle.

This study confirms the findings reported by others13–16 that slowly-adapting receptors are located in the trachea17 and monitor precisely the positive intraluminal pressure in the physiologic range of 0.5–15 torr. Stein and Widdicombe18 have suggested that airway receptors may monitor and aid in the control of airway caliber. Precise control of airway caliber is necessary to minimize the work of breathing, since large airways offer minimal resistance but increased deadspace. Slowly-adapting tracheal receptors may provide some of the constant feedback information necessary for continual readjustments of the glottis needed for control of normal expiratory air flow or expiratory period,19 normal speech or singing, or physiologic maneuvers such as a cough or Valsalva maneuver.

In this study halothane has been shown to cause an increase in compliance of the canine trachea in situ. Halothane did not block the decrease in compliance caused by the efferent vagal stimulation.

References