The Effect of Isoflurane, Halothane, Sevoflurane, and Thiopental/Nitrous Oxide on Respiratory System Resistance after Tracheal Intubation

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Background: After tracheal intubation, lung resistance and therefore respiratory system resistance (Rrs) routinely increase, sometimes to the point of clinical bronchospasm. Volatile anesthetics generally have been considered to be effective bronchodilators, although there are few human data comparing the efficacy of available agents. This study compared the bronchodilating efficacy of four anesthetic maintenance regimens: 1.1 minimum alveolar concentration (MAC) end-tidal sevoflurane, isoflurane or halothane, and thiopental/nitrous oxide.

Methods: Sixty-six patients underwent tracheal intubation after administration of 2 µg/kg fentanyl, 5 mg/kg thiopental, and 1 mg/kg succinylcholine. Vecuronium or pancuronium (0.1 mg/kg) was then given to ensure paralysis during the rest of the study. Postintubation Rrs was measured using the isovolume technique. Maintenance anesthesia was then randomized to thiopental 0.25 mg·kg⁻¹·min⁻¹ plus 50% nitrous oxide, or 1.1 MAC end-tidal isoflurane, halothane, or sevoflurane. The Rrs was measured after 5 and 10 min of maintenance anesthesia. Data were expressed as means ± SD.

Results: Maintenance with thiopental/nitrous oxide failed to decrease Rrs, whereas all three volatile anesthetics significantly decreased Rrs at 5 min with little further improvement at 10 min. Sevoflurane decreased Rrs more than either halothane or isoflurane (P < 0.05; 58 ± 14% of the postintubation Rrs, vs. 69 ± 20% and 75 ± 13%, respectively).

Conclusions: After tracheal intubation in persons without asthma, sevoflurane decreased Rrs as much or more than isoflurane or halothane did during a 10-min exposure at 1.1 MAC. (Key words: Anesthetics, volatile; halothane; isoflurane; sevoflurane. Intubation: intratracheal. Lungs: bronchial hyperreactivity.)

BRONCHOSPASM is a feared complication of anesthesia,¹ but fortunately it occurs only rarely.² Even audible wheezing occurs relatively infrequently, in approximately 0.17% of general anesthetics.³ The low incidence of adverse outcomes may be partially attributed to good anesthetic management, care that often includes the use of potent inhalational anesthetics to prevent and manage bronchospasm. Although halothane is often recommended as the agent of choice in such situations, there is little evidence in humans that halothane is more effective than other volatile agents.⁴ Sevoflurane compares favorably with halothane as less noxious to human airways than either isoflurane or enflurane.⁵ In dog bronchospasm models, sevoflurane has not proved to be better than halothane or even isoflurane,⁶ but the bronchodilatory properties of sevoflurane have not been examined in humans.

It is difficult to study the relative efficacy of the volatile anesthetics during bronchospasm in humans because it occurs so rarely. One potential alternative is to examine the ability of volatile agents to block the effects of intubation. Besides being a common trigger for intraoperative bronchospasm,⁷ tracheal intubation causes some degree of bronchoconstriction in most patients. In awake volunteers given topical anesthesia, tracheal intubation was associated with a 40% increase in airway resistance.⁸ Additional indirect evidence for intubation-induced bronchoconstriction comes from measurements made exclusively after intubation. The respiratory resistance present after tracheal intubation decreases after bronchodilator therapy,¹² and different induction agents are associated with different degrees of postintubation resistance.¹³ Tracheal intubation can therefore serve as a stimulus to increase lung resistance and permit comparison of the bronchodilating ability of various anesthetics.
VOLATILE AGENT BRONCHODILATION AFTER INTUBATION

This study compared the degree of bronchodilation achieved with halothane, isoflurane, and sevoflurane maintenance anesthesia subsequent to the bronchoconstriction associated with standardized induction and intubation. A fourth group consisting of maintenance with a thiopental infusion plus nitrous oxide anesthesia served as a time control.

Methods

After we received approval of our study by the Human Subjects Committees of the University of Washington School of Medicine and the Veterans Affairs Puget Sound Health Care System, we obtained written informed consent from 66 persons. We excluded potential participants if they were being treated with a β2-adrenergic agonist inhaler, an anticholinergic inhaler, corticosteroids, or theophylline. Baseline lung function before administration of any anesthetic drugs was assessed by measuring peak expiratory flow (PEF; Assess Peak Flow Meter; Healthscan, Cedar Grove, NJ) with the participant awake in a sitting position.14 With the participant lying supine, we induced anesthesia with 2 μg/kg fentanyl, 5 mg/kg thiopental, and 1 mg/kg succinylcholine. The trachea was intubated with auffed endotracheal tube (inner diameter, 7.5–8.0 mm). Immediately after intubation and without waiting for the effects of succinylcholine to subside, 0.1 mg/kg of vecuronium or pancuronium (depending on the expected case duration) was administered to ensure paralysis for the rest of the study. Controlled ventilation was set (Narkomed 2A; North American Drager, Telford, PA) at 8 breaths per minute, with a tidal volume of 10 ml/kg, an inspiratory flow rate of 36 l/min, and an inspiratory-expiratory ratio of 1.3 or less if more time was necessary to deliver the desired tidal volume at the 36 l/min flow rate. Fresh gas flow was 3 l/min.

Measurement of respiratory system resistance (Rs) began within 2 min after intubation, as soon as mechanical ventilation was established with the preceding guidelines. At completion of the measurement (less than 30 s), patients were given one of four anesthetic maintenance options chosen by random drawing: 1) thiopental infusion at 0.25 mg·kg⁻¹·min⁻¹ plus 50% nitrous oxide in oxygen; 2) 1.4% isoflurane in oxygen; 3) 0.85% halothane in oxygen; or 4) 2.3% sevoflurane in oxygen. Volatile anesthetic concentrations were chosen to approximate 1.1 minimum alveolar concentration (MAC). Approximately 20 μg/ml thiopental plasma concentration is necessary for 0.6 MAC of thiopental alone.16 Given the pharmacokinetics of thiopental, plasma levels probably were at that level during the study.17 Overpressure was used to achieve the desired end-tidal concentrations as rapidly as possible. Thereafter, the fresh gas concentration was adjusted continually to maintain a constant end-tidal concentration throughout the rest of the study. The Rs was measured 5 min and 10 min after the maintenance anesthetic was begun. Boluses of 50–100 μg phenylephrine were administered intravenously by the patient’s anesthesia team if the patient was judged to be hypotensive.

The Rs was measured in centimeters of water per liter per second using the isovolume method after correcting for the resistance of the endotracheal tube.13,18 The isovolume method of resistance measurement is a technique applicable to mechanically ventilated patients and is based on measuring airway pressure and flow at identical volumes during inspiration and exhalation. Before each study the pneumotachograph (Capnomac Ultima; Datex, Tewksbury, MA) was calibrated in air for volume (integrated flow measurements) using a 1-1 syringe (Hans Rudolph Inc., Kansas City, MO). Correction for flow and volume measurements in the presence of 50% nitrous oxide was achieved by comparing integrated flow using air versus a mixture of 50% nitrous oxide and 50% oxygen. No correction between air and oxygen was necessary. Using the pneumotachograph and a personal computer, the ventilatory flow and pressure curves were sampled at 10-ms intervals, and the volume curve was determined by integration of the flow curve. The pressure decrease across the endotracheal tube was excluded by constructing a pressure-flow curve for the 7.5-mm and 8-mm endotracheal tubes. The expected pressure decrease across the tube for the observed flow was subtracted from the actual pressure measurement during inspiration and was added to the measured pressure during expiration to yield the pressure at the tip of the endotracheal tube. These corrected pressures were used to calculate Rs as follows:

\[ P_i = C/V + R \times F_i \]

\[ P_e = C/V - R \times F_e \]

where \( P_i \) = inspiratory pressure, \( P_e \) = expiratory pressure, \( C \) = compliance, \( F_i \) = inspiratory flow, \( F_e \) = expiratory flow, and \( V \) = lung volume above functional residual capacity. Subtracting these two equations yields:

\[ P_i - P_e = R(F_i + F_e) \text{ or } R = (P_i - P_e)/(F_i + F_e). \]

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Table 1. Demographic Information

<table>
<thead>
<tr>
<th></th>
<th>Thiopental-N₂O</th>
<th>Isoflurane</th>
<th>Halothane</th>
<th>Sevoflurane</th>
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<tbody>
<tr>
<td>Male/female (no.)</td>
<td>6/1</td>
<td>19/1</td>
<td>17/3</td>
<td>18/1</td>
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<tr>
<td>Age (yr)</td>
<td>44 ± 13</td>
<td>59 ± 13</td>
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<td>55 ± 13</td>
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<td>Height (cm)</td>
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<td>175 ± 9</td>
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<td>Weight (kg)</td>
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<td>90 ± 20</td>
<td>86 ± 16</td>
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<td>3/13/4</td>
<td>2/16/2</td>
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<tr>
<td>Smokers/nonsmokers (no.)</td>
<td>5/2</td>
<td>17/3</td>
<td>14/6</td>
<td>15/4</td>
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<tr>
<td>Pack-years (of smokers)</td>
<td>14 ± 11</td>
<td>40 ± 31</td>
<td>26 ± 18</td>
<td>36 ± 20</td>
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<tr>
<td>Peak expiratory flow (% of predicted value)</td>
<td>85.5 ± 20.1</td>
<td>84.3 ± 31.6</td>
<td>80.8 ± 17.1</td>
<td>87.0 ± 22.7</td>
</tr>
</tbody>
</table>

With the isovolume method, inspiratory and expiratory resistance contribute to the measurement of $R_n$.

Measurements of inhalation anesthetic end-tidal concentrations were made using a Datex Capnomac Ultima. Peak expiratory flow was expressed as a percentage of the expected value for peak flow as based on patient height and age.¹⁰

Continuous variables are expressed as means ± SD, except in the figures where SEM is used. Comparisons within and between treatment groups for continuous variables were done with analysis of variance and the Student-Newman-Keuls post hoc test for multiple comparisons. Comparisons among categorical variables were done with the chi-square statistic. Because the measurements of $R_n$ at 5 min and 10 min were important for their change from $R_n$ immediately after intubation, the 5-min and 10-min measurements were expressed as a percentage of the $R_n$ after intubation. Statistical significance was defined at the 0.05 level.

Results

There were no differences among the groups with respect to sex, age, height, weight, American Society of Anesthesiologists classification, percentage of smokers and their smoking history, and peak expiratory flow as a percentage of expected peak flow (table 1). Only seven patients were included in the thiopental group because after the first 30 persons were studied, it became apparent that the response to thiopental was dramatically different from the response with the inhalational agents. Thereafter, the patients were randomized among the three inhalational agents only.

After intubation but before the commencement of maintenance anesthesia, $R_n$ was not significantly different among the four study groups (thiopental, 9.9 ± 2.9 cmH₂O·L⁻¹·s⁻¹; isoflurane, 11.3 ± 4.4 cmH₂O·L⁻¹·s⁻¹; halothane, 10.9 ± 5.5 cmH₂O·L⁻¹·s⁻¹; sevoflurane, 10.8 ± 4.1 cmH₂O·L⁻¹·s⁻¹; $P = 0.92$ by analysis of variance). At 5 and 10 min of maintenance anesthesia, $R_n$ had decreased significantly for the three volatile anesthetic groups but not for the patients who received thiopental and nitrous oxide (fig. 1). The $R_n$ was lower for sevoflurane than for either isoflurane or halothane ($P < 0.05$; at 10 min, sevoflurane was 58 ± 14%, isoflurane was 75 ± 13%, and halothane was 69 ± 20%), whereas the difference between halothane and isoflurane was not significant.

![Respiratory System Resistance (Percent of Baseline)](image)

Fig. 1. The percentage change (mean ± SE) in respiratory system resistance ($R_n$) is shown after 5 and 10 min of maintenance anesthesia with 0.25 mg·kg⁻¹·min⁻¹ thiopental plus 50% nitrous oxide (n = 7); 1.1 MAC isoflurane (n = 20); 1.1 MAC halothane (n = 20); or 1.1 MAC sevoflurane (n = 19). All three volatile anesthetics decreased $R_n$ significantly below the $R_n$ present after intubation and below the response to thiopental/nitrous oxide ($P < 0.05$). Sevoflurane decreased $R_n$ more than either halothane and isoflurane at 5 and 10 min ($P < 0.05$), although the difference between halothane and sevoflurane was no longer significant when a single outlier in the halothane group was removed. The differences between halothane and isoflurane were not significant. The 10-min response was significantly lower ($P < 0.05$ by paired t test) than the 5-min response for halothane and isoflurane, but not for sevoflurane.

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Fig. 2. The individual responses in respiratory system resistance are shown after 10 min of maintenance anesthesia with 0.25 mg kg⁻¹ min⁻¹ thiopental plus 50% nitrous oxide; 1.1 MAC isoflurane; 1.1 MAC halothane; or 1.1 MAC sevoflurane. There was considerable variability among the individual responses.

ane did not achieve statistical significance (P = 0.26). For all three volatile anesthetic groups, of the total change in Rₚ from immediately after intubation to 10 min of 1.1 MAC of anesthesia, at least 86% of that decrease was achieved by 5 min of the volatile anesthesia. For the halothane and isoflurane groups, the change from the 5-min to the 10-min result was significant (P < 0.05), although not for sevoflurane (P = 0.15).

The individual responses varied for all treatment groups (fig. 2). In particular, there was one participant in the halothane group that showed an increase in Rₚ in contrast to the decrease exhibited by all the other participants. If this outlier is removed, the response to halothane improved to -66 ± 17% (10-min response), and the halothane responses at 5 and 10 min were no longer significantly different from the sevoflurane responses.

Discussion

In this study of human Rₚ after tracheal intubation, all three volatile anesthetics significantly reduced resistance within 5 min, whereas resistance remained unchanged during thiopental/nitrous oxide maintenance. The surprising result was that sevoflurane decreased Rₚ more than isoflurane did and performed at least as well as halothane during the 10-min exposure to the 1.1 MAC end-tidal anesthetic level. Sevoflurane has been postulated to be potentially better than other inhalational agents because it produces the least amount of airway irritation.⁶⁻⁸ Theoretical considerations notwithstanding, studies performed on dogs showed that halothane is superior to sevoflurane and isoflurane is equal to sevoflurane.⁹⁻¹⁰ These animal studies may not apply to humans, not only because of species differences but because the bronchospasm was induced with either intravenous histamine or ascariis anaphylaxis and thus may not mimic the mechanism of postintubation bronchospasm in humans.

Sevoflurane possesses a theoretical advantage over the other volatile anesthetics because its lower solubility would permit more rapid tissue equilibration. This advantage was minimized by using high inspiratory concentrations to maintain end-tidal gas (and presumably arterial) concentrations at a constant 1.1 MAC for all agents. Nevertheless, end-organ anesthetic concentrations were not likely to have equilibrated after 10 min of exposure, so the responses to the volatile anesthetics could have converged with more prolonged exposure. However, the results do suggest a significant response after a 5-min exposure, and sevoflurane performed as well or better than isoflurane and halothane in this time period.

Clinical tradition states that halothane is better at reversing clinical bronchospasm than isoflurane. Unfortunately, scientific evidence for this assertion in humans is lacking. Even animal studies show only mixed support for the superiority of halothane over isoflurane.⁸⁻¹⁰,¹²⁻¹³ In our study, halothane was not significantly better than isoflurane at reducing Rₚ. The inability of the current study to demonstrate a significant difference between the effects of halothane and isoflurane may have been a result of the low power of this study. More than 60 participants per group would have been required to achieve statistical significance using the observed means and SDs for halothane and isoflurane.

The relative efficacy of the volatile anesthetics that we observed may have been influenced by the choice of 1.1 MAC end-tidal concentration and by the mechanism used to stimulate bronchoconstriction. Halothane is a more effective bronchodilator than isoflurane in dogs at 0.6 MAC but not at 1.7 MAC.¹⁰ When ascariis anaphylaxis was used to induce bronchoconstriction in dogs, sevoflurane was not more effective than isoflurane at blocking the bronchoconstriction.⁹ In our study, an end-
tidal concentration of 1.1 MAC was chosen as a dose that would be tolerated by most patients, and the stimulus of endotracheal intubation was selected because it is a common mechanism of bronchoconstriction during anesthesia.

Pancuronium may potentiate vagally mediated bronchoconstriction. In this study, pancuronium was administered to only one person in the halothane group, two in the isoflurane group, four in the sevoflurane group, and to none in the thiopental-nitrous oxide group. The conclusion that sevoflurane is as effective a bronchodilator as halothane therefore is not likely to have been inadvertently biased by using pancuronium.

The effect of anesthesia on functional residual capacity could have influenced the results of this study. The decrease in functional residual capacity with induction of anesthesia decreases airway size and increases airway resistance. This phenomenon is thought to be responsible for the increase in airway resistance after induction with isoflurane. Because all subjects in our study had identical inductions, the four groups should have had similar changes in functional residual capacity before the maintenance anesthetic. All four groups had similar Rₐ after intubation but before maintenance anesthesia. Because there is no evidence that volatile anesthetics increase functional residual capacity, the observed decreases in respiratory resistance speak for a bronchodilatory property in the three volatile anesthetics. It is possible that some of the differences in resistance among the volatile anesthetics could be caused by agent-specific differences in functional residual capacity, but the use of paralyzing agents should have minimized any such differences.

We studied a patient population with a high incidence of lung disease primarily because of smoking. Only 18 of the 66 participants had a peak expiratory flow equal to or greater than expected. Nevertheless, the patients did not have clinical asthma, were not in respiratory distress before operation, and did not develop clinically apparent bronchospasm. We did not believe we were justified in withholding chronic bronchodilator therapy from patients; consequently, the study population does not reflect the subset of patients at highest risk. However, many cases of severe intraoperative bronchospasm occur in patients not considered to be at risk. Although this study suggests that any of the volatile agents could be used to manage intraoperative bronchospasm, it is possible that the responses to the volatile agents could be different in higher risk patients or in patients who develop more severe bronchoconstriction than our participants did.

The Rₐ, as measured in this study using the isovolume technique, includes airway resistance, chest wall resistance, and tissue viscosity. In this study, chest wall resistance should have been constant and the changes in Rₐ representative of changes in lung resistance because the patients were paralyzed. This close relation between Rₐ and lung resistance has been confirmed in anesthetized, paralyzed animals. The contribution of changes in tissue viscosity to changes in Rₐ cannot be separated from the changes in airway resistance in this study, although it appears that both sources contribute approximately equally to changes in lung resistance caused by airway stimuli. Nevertheless, Rₐ represents the overall resistance to gas flow that has to be overcome either by the patient or the ventilator.

In conclusion, in middle-aged adults with mild-to-moderate chronic lung disease, 1.1 MAC end-tidal concentrations of halothane, isoflurane, and sevoflurane decreased the respiratory system resistance present after induction and intubation, in contrast to no change when anesthesia was maintained with a thiopental infusion plus nitrous oxide. More specifically, sevoflurane may be a worthwhile alternative to the traditional choice of halothane as an adjunct to prevent and manage intraoperative bronchospasm.

References

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