Extent and Localization of Changes in Upper Airway Caliber with Varying Concentrations of Sevoflurane in Children

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Background: Previous studies in humans suggest that inhibition of upper airway muscle activity is independent of the dose of inhalational anesthesia. Whether a dose-independent relation applies to changes in airway caliber is unknown. The authors sought to evaluate the configurational changes that lead to upper airway narrowing during inhalational anesthesia with sevoflurane and to determine whether these changes are dose dependent within a clinically relevant dose range.

Methods: Fifteen children undergoing elective magnetic resonance imaging of the brain were studied. Magnetic resonance images of the upper airway were acquired at sevoflurane concentrations of 0.5, 1.0, and 1.5 minimum alveolar concentration (MAC), administered in random sequence. At least 15 min was allowed for equilibration of inspired and alveolar partial pressures of sevoflurane. Images were acquired in early expiration at the level of the soft palate, base of the tongue, and tip of the epiglottis. Airway cross-sectional area (CSA), anteroposterior, and transverse dimension were determined using image-analysis software.

Results: At each anatomical level, pharyngeal CSA decreased progressively with increasing depth of sevoflurane anesthesia (P < 0.001). Increasing the sevoflurane concentration from 0.5 to 1.0 MAC reduced airway CSA by 13–18%, and a further increase to 1.5 MAC resulted in an overall 28–34% reduction in CSA. The reduction in CSA was predominantly due to a decrease in anteroposterior dimension.

Conclusions: Increasing the depth of sevoflurane anesthesia resulted in a relatively uniform reduction in pharyngeal caliber at each anatomical level studied. The effect of sevoflurane on upper airway caliber is dose dependent.

The patency of the upper airway is dependent in part on the activity of its intrinsic muscles. General anesthetics inhibit upper airway muscle and neural activity by central and direct effects. It is generally believed that this inhibition causes narrowing of the upper airway, thereby rendering the airway vulnerable to obstruction in spontaneously breathing patients. A dose-dependent relation between depth of anesthesia and upper airway muscle activity has been demonstrated for some intravenous anesthetics in humans. For example, thiopentone and propofol both decrease genioglossus muscle activity in a dose-dependent manner, and increasing the depth of propofol anesthesia was associated with a reduction in airway caliber. Studies in animals suggest that inhalational anesthetics also exhibit dose-dependent effects on the upper airway. In contrast, inhibition of upper airway muscle activity by isoflurane was independent of dose in adults. Little is known about the dose-related effects of inhalational anesthetics on upper airway caliber in humans. The aim of this study was to evaluate the degree to which changes in sevoflurane concentration affect the caliber of the upper airway and to assess the configurational changes that lead to upper airway narrowing during sevoflurane anesthesia. Our null hypothesis was that the effect of clinically relevant concentrations of sevoflurane on upper airway caliber is independent of dose. We tested this hypothesis in spontaneously breathing children undergoing elective magnetic resonance imaging (MRI) of the brain.

Materials and Methods

The study was approved by the Research Ethics Board (Hospital for Sick Children, Toronto, Ontario, Canada), and parents or legal guardians gave written consent. Fifteen unpremedicated children with American Society of Anesthesiology physical status I or II, aged 2–8 yr, scheduled to undergo elective MRI of the brain were studied. Children were excluded if they had obstructive sleep apnea, pathology of the upper airway, craniofacial anomalies, gastroesophageal reflux, or increased intracranial pressure or weighed more than 130% of ideal body weight. In addition, failure to maintain a patent airway (defined as the presence of stridor, paradoxical chest wall motion, oxygen desaturation, or other clinical evidence of airway obstruction) was considered an exclusion criterion during the study.

General anesthesia was induced with 8% sevoflurane in oxygen. After loss of the eyelash reflex, a 22-gauge intravenous catheter was inserted, and 10 µg/kg glycopyrrolate was administered. Anesthesia was maintained with sevoflurane in an oxygen–air mixture (fractional inspired oxygen, 0.5) administered via a Jackson Rees modification of the Ayres T-piece breathing circuit (fresh...
flow gas rate, 6 l/min) and a transparent facemask that was kept in position using a head strap. Arterial oxygen saturation, exhaled carbon dioxide tension, respiratory rate, heart rate, and noninvasive arterial blood pressure were monitored using an MRI-compatible device. In addition, a respiratory bellows was placed around the chest to obtain a waveform of the respiratory cycle, as previously described.5 No continuous positive airway pressure was applied. All patients were studied in the supine position with the head position standardized such that the angle between the horizontal plane of the MRI table and a line connecting the tragus of the ear and the lateral corner of the eye was 110°.9 The mouth, visualized through the facemask, was seen to be closed in all patients. Care was taken to ensure that application of the facemask and head strap caused no posterior mandibular displacement.

Magnetic resonance images were acquired using a GE 1.5-T MRI scanner with maximal gradient strength of 4 G/cm (CV/i system; General Electric Medical Systems, Milwaukee, WI) and a quadrature head coil. A sagittal localizer image (echo time 1.6 ms; repetition time = 4.5 ms; 30° flip angle; 5-mm slice thickness; number of excitations = 1; 5 slices/plane; and 256 × 128 matrix) was performed to identify the midline and allow selection of subsequent upper airway images. A single-shot fast spin echo pulse sequence (echo time = 30 ms; variable repetition time; 3-mm slice thickness; number of excitations = 0.5; field of view = 16 × 9.6 cm; echo train length = 16; and 192 × 192 matrix) was used to acquire images orthogonal to the airway at the level of the soft palate, base of the tongue, and tip of the epi-glottis. Image acquisition was triggered manually by a single investigator in early expiration. The waveform generated by the respiratory bellows was used to identify the expiratory phase of the respiratory cycle. The acquisition time was approximately 0.5 s for each image.

Magnetic resonance images of the upper airway were acquired at each of three inspired concentrations of sevoflurane, 1.25%, 2.50%, or 3.75% (corresponding to 0.5, 1.0, or 1.5 age-adjusted minimum alveolar concentration [MAC], respectively), administered in random sequence using a random number table. The first concentration in the randomized sequence was administered immediately after induction of anesthesia, and diagnostic imaging of the brain was begun. For each inspired concentration, approximately 15 min was allowed for equilibration of inspired and alveolar partial pressures of sevoflurane before acquisition of airway images. Diagnostic imaging of the brain was continued during the equilibration period. Immediately after acquisition of airway images, the inspired concentration of sevoflurane was changed to the next in the randomized sequence, until the final set of airway images was obtained. Thereafter, the inspired concentration of sevoflurane was titrated at the discretion of the anesthesiologist until completion of diagnostic brain imaging, at which time sevoflurane was discontinued and oxygen administered until the patient recovered. All airway images were stored on computer and were subsequently analyzed by a blinded investigator. Blinding was achieved by assigning a code number to each image and presenting the images for analysis in random order. After image magnification (×3), upper airway cross-sectional area, anteroposterior dimension, and transverse dimension were determined using image-analysis software (Advantage Workstation 4.2; General Electric Medical Systems). Measurements were performed in triplicate, and average values were calculated.

**Statistical Analysis**

For the estimation of sample size, we assumed an effect size similar to that reported in our previous study evaluating the airway dimensional changes occurring with propofol anesthesia.9 For a two-tailed α of 0.05 and a β of 0.2 (power = 80%), we estimated that 15 patients would be required to demonstrate a 25% difference in cross-sectional area with increasing depth of sevoflurane anesthesia. Airway cross-sectional area and dimensions were analyzed using one-way repeated-measures analysis of variance and the Student-Newman-Keuls *post hoc* test. Data are presented as mean ± SD. A significance level of *P* < 0.05 was assumed.

**Results**

Demographic data, randomized MAC sequences, and diagnoses are presented in table 1. Mean age and weight were 5.3 ± 2.2 yr and 19.9 ± 5.5 kg, respectively. The inspired concentration of sevoflurane remained stable at each target level throughout the acquisition of airway images. Because diagnostic imaging of the brain required 60–90 min, acquisition of airway images was completed within the time allotted for diagnostic imagining. Image acquisition at any given inspired concentration took less than 2 min, and thus airway imaging prolonged the total anesthetic time by no more than approximately 6 min.

High-resolution representations of upper airway anatomy were obtained in all subjects. The cross-sectional area of the entire pharyngeal area decreased progressively with increasing depth of sevoflurane anesthesia (fig. 1). At the level of the soft palate, increasing the sevoflurane concentration from 0.5 to 1.0 MAC decreased mean airway cross-sectional area by 13% (−11.9 mm²), although this difference did not achieve statistical significance. A further increase from 1.0 to 1.5 MAC resulted in an overall reduction in mean cross-sectional area of 30% (−27.3 mm²) (*P* < 0.001).

At the base of the tongue, increasing the sevoflurane concentration from 0.5 to 1.0 MAC decreased mean airway cross-sectional area by 18% (−29.5 mm²) (*P* <
0.001), and a further increase to 1.5 MAC resulted in an overall reduction in mean cross-sectional area of 34% (56.1 mm²) (P < 0.001). These changes were comparable in magnitude to those occurring at the tip of epiglottis, where increasing the sevoflurane concentration from 0.5 to 1.0 MAC decreased mean airway cross-sectional area by 16% (31.3 mm²) (P < 0.001), and a further increase to 1.5 MAC resulted in an overall reduction in mean cross-sectional area of 28% (55.4 mm²) (P < 0.001). At each anatomical level, the reduction in caliber was due predominantly to a reduction in anteroposterior dimension (figs. 2 and 3). Changes in airway cross-sectional area are depicted in representative images from one patient (fig. 4). Airway cross-sectional area was least at the level of the soft palate in 14 of 15 children irrespective of the depth of anesthesia. There were no complications, and no child demonstrated stridor, paradoxical chest wall motion, oxygen desaturation, or other clinical evidence of airway obstruction during the study.

Discussion

The current study evaluated the extent and localization of changes in upper airway caliber and configuration that occur with increasing depth of sevoflurane anesthesia in spontaneously breathing children. The results show a progressive reduction in the caliber of the pharyngeal airway across all anatomical levels studied. Increasing the concentration of sevoflurane from 0.5 to 1.0 MAC resulted in a reduction in airway cross-sectional area ranging from 13% to 18%, and a further increase to

Table 1. Demographics, Randomized MAC Sequences, and Diagnoses

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Randomized MAC Sequence</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>8.4</td>
<td>26.0</td>
<td>0.5, 1.0, 1.5</td>
<td>Autism</td>
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<tr>
<td>2</td>
<td>F</td>
<td>7.2</td>
<td>23.9</td>
<td>0.5, 1.0, 1.5</td>
<td>Seizure disorder</td>
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<tr>
<td>3</td>
<td>M</td>
<td>3.2</td>
<td>14.3</td>
<td>1.0, 0.5, 1.5</td>
<td>Ganglioneurona, postresection</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>8.1</td>
<td>23.2</td>
<td>1.0, 0.5, 1.5</td>
<td>Mild developmental delay</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>8.7</td>
<td>29.8</td>
<td>1.5, 0.5, 1.0</td>
<td>Glioma, postresection</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>2.3</td>
<td>10.0</td>
<td>1.0, 1.5, 0.5</td>
<td>Mild developmental delay</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>4.3</td>
<td>26.0</td>
<td>0.5, 1.0, 1.5</td>
<td>Headaches</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>4.3</td>
<td>21.1</td>
<td>0.5, 1.0, 1.5</td>
<td>Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>6.5</td>
<td>19.9</td>
<td>1.0, 1.5, 0.5</td>
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</tr>
<tr>
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<td>M</td>
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<td>1.0, 1.0, 0.5</td>
<td>Spina bifida</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
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<td>17.1</td>
<td>1.0, 0.5, 1.5</td>
<td>Medulloblastoma, postresection</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>3.0</td>
<td>17.0</td>
<td>1.5, 0.5, 1.0</td>
<td>Neuroblastoma, postresection</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
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<td>1.5, 1.0, 0.5</td>
<td>Intraventricular hemorrhage</td>
</tr>
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<td>M</td>
<td>5.3</td>
<td>20.3</td>
<td>1.5, 0.5, 1.0</td>
<td>Glioma, postresection</td>
</tr>
</tbody>
</table>

MAC = minimum alveolar concentration.

Fig. 1. Dose-related effect of sevoflurane on upper airway cross-sectional area. Data are mean ± SD. * P < 0.001 versus 0.5 minimum alveolar concentration (MAC) and P < 0.05 versus 1.0 MAC. † P < 0.001 versus 0.5 MAC. †† P < 0.001 versus 0.5 MAC and P < 0.01 versus 1.0 MAC.

Fig. 2. Dose-related effect of sevoflurane on upper airway anteroposterior dimension. Data are mean ± SD. * P < 0.05 versus 0.5 MAC and P < 0.05 versus 1.0 MAC. † P < 0.001 versus 0.5 MAC and P < 0.01 versus 1.0 MAC. †† P < 0.001 versus 0.5 MAC and P < 0.05 versus 1.0 MAC. # P < 0.001 versus 0.5 MAC and P < 0.05 versus 1.0 MAC.
1.5 MAC resulted in an overall reduction of 28–34% (fig. 1). These findings refute the hypothesis that the effect of sevoflurane on upper airway caliber is independent of dose.

The mechanism underlying the dose-dependent reduction in airway caliber is speculative. Upper airway caliber is determined by a balance of forces.1 Outward dilating forces result from tonic and phasic neurogenic activity in airway muscles such as the genioglossus, posterior cricoarytenoid, and muscles of the hyoid bone. Longitudinal forces within the upper airway wall act to stabilize the airway and oppose collapse. An inward collapsing force results from subatmospheric intraluminal pressure during inspiration. In the current study, restrictions imposed by the MRI environment precluded us from obtaining simultaneous measurements of upper airway muscle activity, which limits a mechanistic interpretation of our data. Given the results of previous studies in animals,6,7 it is reasonable to hypothesize that a dose-dependent reduction in upper airway muscle activity is responsible for the observed airway narrowing. In humans, however, even subanesthetic concentrations of isoflurane totally abolished genioglossus activity, and evidence of a dose-dependent relation is lacking.8 Extrapolation of those data to the conditions of the current study is tenuous, however, given age-related and methodologic differences between the studies.

Another mechanistic factor to be considered is the effect of lung volume on upper airway caliber. Lung volume modulates upper airway wall tension and thereby airway caliber through lung–airway interdependence.10,11 In animal studies, a decrease in lung volume causes rostral tracheal displacement and an increase in upper airway resistance,12 whereas caudal traction of the upper airway, as occurs with increasing lung volume, decreases its collapsibility.13,14 Accordingly, it is possible that sevoflurane-induced reductions in lung volume might explain the reduction in airway caliber. In support of this notion, evidence from studies in humans suggests that lung volume changes in a dose-related fashion as the depth of anesthesia changes.8,15 That upper airway muscle activity might be of lesser importance in this regard is supported by Drummond’s failure to demonstrate a relation between pharyngeal patency and genioglossus activity in thiopentone-anesthetized humans.5

Alternatively, it is possible that an anesthesia-induced increase in the activity of pharyngeal constrictor muscles, such as the superior, middle, and inferior constrictor, might have contributed to the observed upper airway narrowing. Given that little is currently known about the effect of anesthesia on the activity of pharyngeal constrictor muscles in humans, further studies are needed to test this hypothesis.

Other physiologic factors determining upper airway caliber include body position, head and neck position, and the degree of mouth opening.15,16,17 To control for these factors in the current study, subjects were supine, a standard head position was used, and the mouth was closed in all patients. In addition, because any systematic variation in the respiratory effects of sevoflurane over time could introduce bias, we randomized the order in which sevoflurane concentrations were administered. A limitation of the study is the lack of control measurements of airway caliber in the awake state. Most children in the age group studied are reluctant to lie motionless inside the magnetic resonance scanner, making it impractical to obtain control measurements in the awake state. Accordingly, our data likely underestimate the true magnitude of sevoflurane-induced changes because they were referenced to measurements obtained during 0.5 MAC anesthesia.

The current findings are clinically important because they imply that the vulnerability of the upper airway to collapse increases dose-dependently with increasing depth of sevoflurane anesthesia. A narrow airway is vulnerable to collapse for several reasons.1 In accordance with Laplace’s law, a narrow radius of curvature requires a greater transmural pressure to maintain sufficient wall tension to oppose collapse. In addition, the greater resistance of the narrow airway requires a more negative intraluminal pressure during inspiration, which increases its tendency to collapse. Nonetheless, the structural and functional characteristics of the pediatric airway render it more resistant to collapse than that of the adult.18

In the current study, the retropalatal region was the narrowest part of the airway in the majority of children irrespective of the depth of anesthesia. This region is also the most common site of airway collapse during

**Fig. 3. Dose-related effect of sevoflurane on upper airway transverse dimension.** Data are mean ± SD. *P < 0.01 versus 0.5 MAC. †P < 0.001 versus 0.5 MAC and P < 0.05 versus 1.0 MAC.
anesthesia and in some patients with obstructive sleep apnea.\textsuperscript{8,19–21} In a previous study evaluating the effect of propofol anesthesia on upper airway caliber in children, we showed that the magnitude of airway narrowing with propofol was least at the level of the soft palate and greatest in hypopharynx at the level of the epiglottis.\textsuperscript{5} Although the lack of a specific measure of depth of anesthesia makes it difficult to compare equipotent anesthetic concentrations in the two studies, it is notable that for comparable reductions in hypopharyngeal caliber, sevoflurane seems to cause a greater percent reduction in caliber at the level of the soft palate compared with propofol. The clinical implication of these findings—that inhalational anesthesia with sevoflurane may be associated with a greater propensity for airway obstruction at the level of the soft palate compared with equipotent propofol anesthesia—remains to be established. Of interest, as the depth of anesthesia increases, the increase in airway collapsibility seems to be more linear for propofol than for isoflurane.\textsuperscript{4,8}

We evaluated the relative contributions of anteroposterior and lateral dimensional changes to the observed

\textbf{Fig. 4.} Representative magnetic resonance images at the level of the soft palate (SP), base of the tongue (BT), and tip of the epiglottis (TE) in early expiration demonstrating a progressive reduction in cross-sectional area with increasing concentration of sevoflurane (0.5, 1.0, 1.5 minimum alveolar concentration). The arrows show the site of the collapsible pharyngeal airway.
reduction in cross-sectional area. By acquiring airway images at a fixed point in the respiratory cycle, we controlled for the normal variation in airway caliber that occurs during the respiratory cycle in anesthetized children primarily as a result of changes in the anteroposterior dimension. At any given anatomical level, we found that the reduction in airway caliber was due predominantly to a decrease in anteroposterior dimension, which is consistent with previous studies evaluating airway dimensional changes occurring during propofol anesthesia. These findings likely represent a gravitational effect unmasked by reduced upper airway muscle activity, wall tension, or their combination.

In summary, the effect of sevoflurane on pharyngeal airway caliber is dose dependent in spontaneously breathing children, implying that the vulnerability of the pharyngeal airway to collapse increases dose-dependently with increasing depth of sevoflurane anesthesia.

References

4. Eastwood PR, Platt PR, Shepherd K, Maddison K, Hillman DR. Collapsibility of the upper airway at different concentrations of propofol anesthesia. Anesthesiology 2005; 103:470–7