

## LABORATORY INVESTIGATIONS

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# Direct In Vivo Visualization of Bronchodilation Induced by Inhalational Anesthesia Using High-resolution Computed Tomography

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**Background:** Volatile anesthetics are effective at preventing and reversing bronchospasm, but their effects on baseline airway tone are controversial. While tantalum bronchography has been used in the past to measure one-dimensional airway diameter changes, this method has inherent problems associated with the irritant effects of tantalum. Until recently, no other direct noninvasive *in vivo* method to assess airway caliber was available. The present investigation assesses the effects of the inhalation anesthetic halothane on individual unstimulated airways *in vivo*.

**Methods:** Ten studies were performed in seven dogs. All dogs were initially anesthetized with 15 mg/kg thiopental followed by a 10-mg·kg<sup>-1</sup>·h<sup>-1</sup> maintenance dose. Following tracheal intubation the lungs were mechanically ventilated (15 ml/kg, 15 beats/min). The dogs subsequently received increasing doses of halothane (range 0.5–1.5%). On a separate day, the dogs were pretreated with atropine (0.2 mg/kg) and the study was repeated. Fifty sequential high-resolution computed tomography scans were obtained using a 1-s scan time, 137 kVp, 220 mA, 2-mm slice thickness, and 1-mm table feed. Airway areas ranging in size from 3 to 22 mm in diameter were measured and analyzed by one way analysis of variance and Bonferroni pair-wise comparisons of means.

**Results:** Halothane in concentrations of 0.5%, 1.0%, and 1.5% showed significant dose-dependent dilation of the airways

(percent increase from control) that averaged 90 ± 19% (mean ± SEM), 128 ± 20%, and 182 ± 27%, respectively ( $P = .017$ ). Atropine pretreatment alone significantly dilated the airways to 151 ± 25% ( $P = .002$ ) of their baseline value. Halothane caused no further airway dilation in atropine pretreated dogs.

**Conclusions:** Halothane dilates baseline airways by blocking baseline vagal tone. Since baseline airway tone, airway wall thickness, and initial airway diameter are major determinants of airway reactivity, the observed dilation by halothane may be one of the mechanisms by which inhalational anesthetics decrease airway reactivity. (Key words: Airways; nerves; vagus. Anesthetics, volatile: halothane. Lungs, bronchi: dilation. Measurement technique: high-resolution computed tomography.)

VOLATILE inhalational anesthetics have been shown to be extremely effective at preventing and reversing bronchoconstriction.<sup>1,2</sup> Their ability to block airway reflexes is well established,<sup>3,4</sup> but their effects on the unstimulated airway have been controversial.

Pare *et al.* have shown that the airway wall areas of asthmatic subjects are larger over the entire range of airway sizes compared to control subjects.<sup>5</sup> This increased wall thickness leads to exaggerated airway narrowing after challenge. Therefore, bronchodilation of baseline airways may be one morphologic mechanism by which inhalational anesthetics prevent bronchoconstriction.

Assessment of changes in airway caliber classically has been performed with indirect methods such as airway resistance. Total pulmonary resistance ( $R_t$ ), calculated from pressure and flow signals, also is commonly used to estimate airway caliber. However,  $R_t$  is an insensitive measure of airway diameter and can give erroneous measures of airway caliber changes.<sup>6</sup> Total pulmonary resistance is a sum of airway resistance ( $R_{aw}$ ) and tissue resistance ( $R_{ti}$ ), and tissue resistance can account for as much as 77% of  $R_t$ .<sup>7</sup> At normal breathing frequencies, therefore, changes in  $R_{ti}$  may overwhelm changes in  $R_{aw}$ . A recent study showed that directly measured airway caliber changes were not always reflected by changes in  $R_t$ .<sup>6</sup> In precontracted airways, a

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deep inspiration decreased  $R_i$  but constricted the airways when airway caliber was measured directly.<sup>6</sup>

Although tantalum bronchography has been used in the past to measure one-dimensional airway diameter changes,<sup>8</sup> this method has inherent problems associated with the irritant effects of tantalum.<sup>9</sup> Until recently, no other direct noninvasive *in vivo* method to assess airway caliber was available. We can now resolve the controversy using high-resolution computed tomography (HRCT), which allows direct noninvasive *in vivo* measurements of airways as small as 1 mm.<sup>6</sup> Using HRCT, we demonstrated in this study unequivocally that halothane directly dilates unstimulated airways in their basal state, and one possible mechanism may be through inhibition of normal vagal tone.

## Methods

Our study protocol was approved by The Johns Hopkins Animal Care and Use Committee. Ten studies were performed in seven dogs (three dogs were in both groups). The dogs were anesthetized initially with thiopental (15-mg/kg induction dose followed by 10 mg · kg<sup>-1</sup> · h<sup>-1</sup> intravenous maintenance dose). After induction of anesthesia with thiopental, the dogs were paralyzed with 10 mg succinylcholine. The trachea of each dog was then intubated with an 8.5-mm internal diameter endotracheal tube, the dog was placed supine, and the lungs were ventilated with a volume-cycled ventilator (Harvard Apparatus, Millis, MA) with 100% oxygen at a tidal volume of 15 ml/kg and a rate of 18 breaths/min. End-tidal CO<sub>2</sub> was monitored by gas analysis (N-2500, Nellcor, Hayward, CA).

### *Imaging of Airway Area*

High-resolution computed tomography scans were obtained with a Somatom Plus scanner (Siemens, Iselin, NJ) using a 1-s scan time, 137 kVp, and 220 mA. Fifty contiguous sections were obtained starting approximately 3 mm above the take-off of the right upper lobe from the trachea proceeding caudally using 1-mm table feed and 2-mm slice thickness. The dogs were apneic and at functional residual capacity for the duration of the scans (30–45 s). Images were reconstructed with the use of a high spatial frequency (high-resolution) algorithm that enhances edge detection. The HRCT scans were photographed at a window level of -450 Hounsfield units (HU) and window widths of 1,300–1,350 HU. These settings have been shown to allow

optimal lung resolution.<sup>10</sup> A range of airway sizes were selected that could be visualized under all experimental conditions. For repeated image analysis within each experiment, parenchymal anatomic landmarks such as airway or vascular branching points were defined on the control state HRCT image. Following the change in concentration of halothane, the same airways in a given animal were then analyzed on images matched by these parenchymal landmarks. It was not possible to locate the original airways on the subsequent day's experiment in the three dogs that were studied under both sets of conditions. Therefore, a new set of control airways were determined, and these airways were measured after each change in halothane concentration.

### *Analysis of Airways*

The HRCT images were transferred as 16-bit data images to a UNIX-based work station and reduced to 8-bit images, which were then analyzed using the airway analysis module of the Volumetric Image and Display Analysis image analysis software package (Department of Radiology, Section of Cardiothoracic Imaging Research, University of Pennsylvania, Philadelphia, PA). An isocontour of the airway is drawn by the operator. The program automatically adjusts the isocontour by sending out rays in a spoke-wheel fashion to a pre-designated pixel intensity level that defines the luminal edge of the airway wall. All pixels within the adjusted isocontour are counted and represent the airway area. The value for the airway area is converted from the total number of pixels to millimeters squared by multiplying by the pixel dimensions in millimeters.

### *Protocol*

Control HRCT scans were performed while the dogs were anesthetized with thiopental as described above. During the experimental conditions, the thiopental infusion was stopped and halothane (Ayrest Laboratories, New York, NY) was added in cumulative doses to the breathing circuit until end-tidal anesthetic concentrations of 0.5%, 1.0%, and 1.5% as measured by gas analysis (N-2500, Nellcor, Hayward, CA) was attained. On a separate day, at least 2 weeks later, the dogs were studied following the same protocol except 0.2 mg/kg atropine (a dose shown to completely block vagal innervation<sup>11</sup>) was administered before control HRCT scan acquisition. Data were analyzed by one way analysis of variance and Bonferroni pair-wise comparisons of means with significance set at  $P < .05$ .

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## Results

Six to ten airways were measured in each dog, ranging in size from approximately 3 mm to 22 mm in diameter (fig. 1). The ranges of measured airways were comparable across dogs. After the thiopental was discontinued, the dogs received either halothane alone or atropine pretreatment and then halothane. In the dogs that received halothane alone, the majority of airways demonstrated dose-dependent dilation as illustrated by one set of individually measured airways in one representative dog (fig. 2, top). In the dogs that received atropine pretreatment and subsequent halothane, the majority of airways showed no further dilation, as illustrated by another set of individually measured airways in the same representative dog (fig. 2, bottom).

Dogs that received halothane alone in concentrations of 0.5%, 1.0%, 1.5% showed a significant dose-dependent dilation in the mean of all individual airway areas

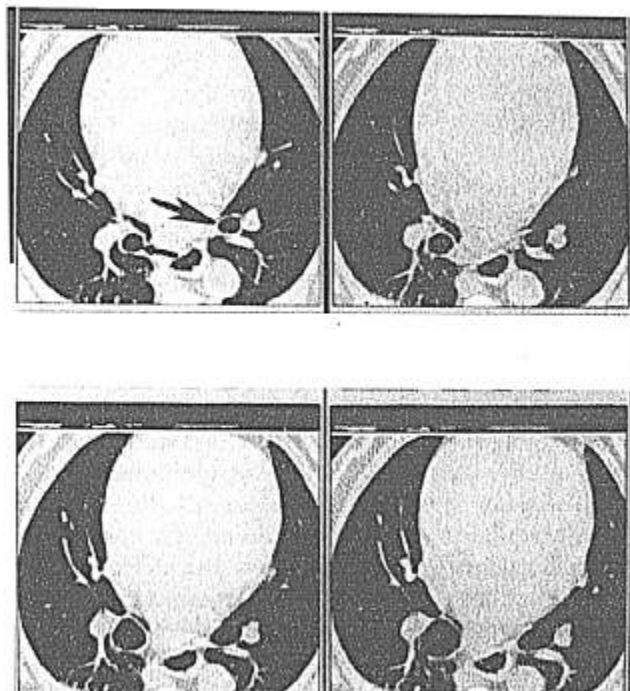


fig. 1. (Upper left) Control high-resolution computed tomography scan from one dog. Arrows indicate example airways (dark circles below tips of arrows). (Upper right) Same dog anesthetized with 0.5% halothane. Note the slight dilation of indicated airways from control. (Lower left) Same dog anesthetized with 1.0% halothane. Note the progressive dilation of indicated airways. (Lower right) Same dog anesthetized with 1.5% halothane. Note the marked dilation of indicated airways.

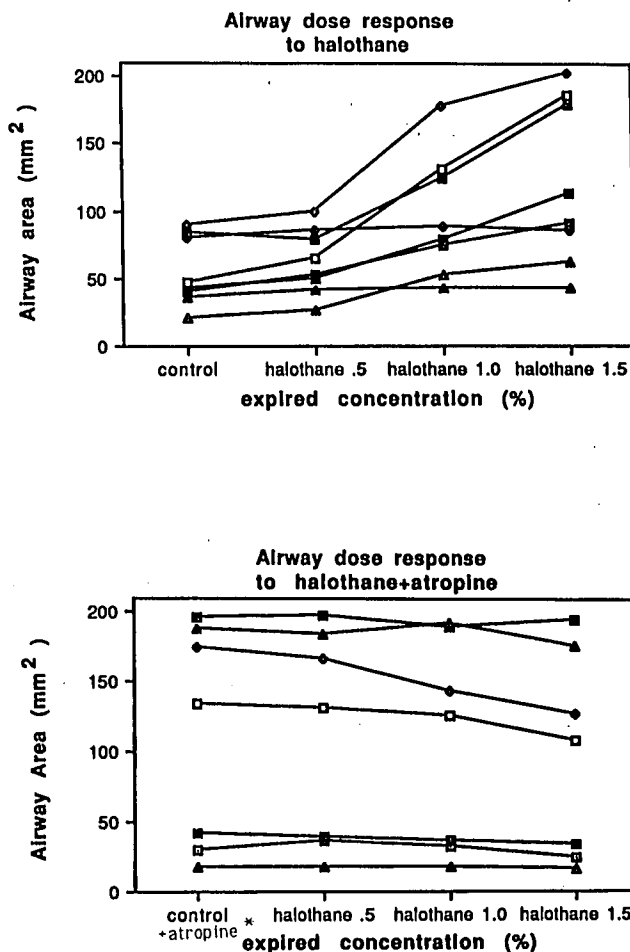


Fig. 2. The change in absolute size of all individual airways measured in one dog at control and increasing doses of halothane. (Top) Halothane alone. Increasing dilation of most individual airways occurred with increasing concentrations of halothane. (Bottom) Atropine pretreatment and halothane. No further dilation of individual airways to increasing concentrations of halothane occurred after pretreatment with atropine. Atropine pretreatment increases airway size (\* $P = .017$ ).

of  $90 \pm 19\%$  (mean  $\pm$  SEM),  $128 \pm 20\%$ , and  $182 \pm 27\%$ , respectively ( $P = .017$ ; fig. 3). Atropine alone caused a significant dilation in airways of  $151 \pm 25\%$  ( $P = .002$ ; fig. 2). When halothane was administered to the atropine-pretreated dogs, the airways showed no significant further dilation (fig. 3). Moreover, the airway dilation induced by the atropine pretreatment was not significantly different from the airway dilation induced by 1.5% halothane ( $P = .42$ ).

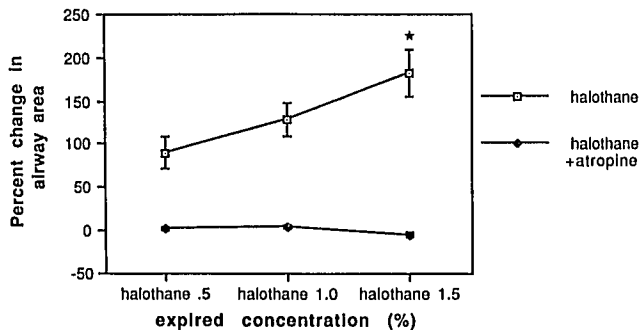


Fig. 3. The upper line represents the percent change in the mean of all individual airways measured from control to increasing doses of halothane, showing dose-dependent dilation. The lower line represents the percent change in the mean of all individual airways measured from control after pretreatment with atropine, showing the lack of further increase in atropine-pretreated airways. (\* $P = .002$ ).

## Discussion

We found that halothane dilated the unstimulated canine airway *in vivo* in a dose-dependent manner. Atropine also significantly dilated the unstimulated airways. The two agents, halothane and atropine, showed no additive effects, suggesting a common mechanism of action. Several studies in animals examined the effect of the inhalational anesthetic halothane on baseline airway tone. In dogs *in vivo*, no difference was found in  $R_L$  between the control state (thiobarbiturate anesthesia) and during halothane anesthesia.<sup>12,13</sup> Intravenous chloralose anesthesia as a control showed no difference in  $R_L$  compared to halothane-anesthetized dogs.<sup>6</sup> In horses, no statistical difference in specific airway conductance between intravenous thiopental anesthesia and inhalational anesthesia with halothane was shown, but there was a suggestion of bronchodilation using this more sensitive method of measurement<sup>14</sup> (see below). Likewise, in the rabbit, no difference in baseline tone between control state pentobarbital anesthesia and inhalational anesthesia with halothane was demonstrated.<sup>15</sup>

One study found increased lung compliance and bronchial distension during halothane anesthesia compared to pentobarbital anesthesia during spontaneous ventilation.<sup>16</sup> While another study found a decrease in  $R_L$  in dogs anesthetized deeply with halothane compared to dogs lightly anesthetized,<sup>17</sup> there was no control group and the concentrations of halothane administered were unknown. Moreover, in both studies, the

respiratory rate, the tidal volume, and the minute volume changed with the depth of anesthesia, making interpretation of their results difficult.

Airway resistance and tissue resistance, as components of total pulmonary resistance, have been measured separately in an attempt to increase the ability to differentiate the components that comprise total lung resistance, to measure changes in airway resistance more sensitively, and thus to make inferences about the associated changes in airway caliber.<sup>18</sup> One such study measured airway resistance and tissue resistance after vagotomy in dogs in intravenous urethan and chloralose (control) and halothane-anesthetized dogs.<sup>19</sup> They were unable to show any effect of halothane on either airway or tissue resistance in the baseline state. Another study from the same group used a similar protocol to look at direct and neurally mediated effects of halothane on pulmonary resistance *in vivo*.<sup>4</sup> This study too found no effect of halothane on baseline  $R_L$  compared to the control state, chloralose, and urethan anesthesia. However, Vettermann *et al.*<sup>20</sup> measured total lung resistance, airway resistance, and tissue resistance in isolated canine lobes during the control condition of no anesthetic that was compared to halothane 3%. At a ventilatory frequency of 15 breaths/min, they showed a decrease in total lung resistance from approximately 2.5 to 2.0  $\text{cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$ . This was associated with decreases in airway resistance from 0.8 to 0.6  $\text{cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$  and tissue resistance from 1.9 to 1.6  $\text{cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$  during halothane administration compared to control. These changes are small but consistent with a direct effect of halothane anesthesia at high concentrations on airway contractile elements.

Results of studies of the effects of volatile inhalational anesthetics on baseline airway tone in humans have been similarly inconclusive. In patients studied during cardiopulmonary bypass, nitrous oxide in oxygen and thiopental served as the control anesthetic, and halothane was administered either systemically through the pump oxygenator or directly into the airways while pulmonary resistance and compliance were measured.<sup>21</sup> The authors were unable to detect differences in dynamic compliance or pulmonary resistance between either systemically administered halothane or halothane administered to the airways and the control state. Gold and Helrich<sup>22</sup> measured pulmonary compliance ( $C_L$ ) in the same patients awake and anesthetized. In the control state, patients were premedicated with pentobarbital and scopolamine and breathed through a tight-fitting mask while in the sitting position

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The same patients were anesthetized with nitrous oxide and halothane and allowed to breathe spontaneously through an endotracheal tube in the supine position. The depth of anesthesia was assessed from changes in tidal volume, electroencephalogram, and clinical signs. The authors observed a decrease in  $C_i$  during halothane anesthesia compared to the awake state.

Calculation of specific airway conductance has been performed to control for the effects of lung volume on airway resistance measurements in an attempt to improve the sensitivity of the measurement of airway changes. Specific airway conductance also takes into account lung recoil pressure and changes in expiratory reserve volume. Lehane *et al.*<sup>23</sup> and Heneghan *et al.*<sup>24</sup> examined the effect of subsequent administration of 1.3% halothane on specific airway conductance in patients initially anesthetized with nitrous oxide in oxygen. Both studies found a significant decrease in specific airway conductance during halothane administration compared to the control condition.

The larger more central airways are innervated by parasympathetic fibers that run through the vagus nerve. Activation of the nerves mediates irritant-induced bronchoconstriction.<sup>2</sup> Interruption of vagal nerve impulses should attenuate neurally induced bronchoconstriction and eliminate resting tone. Vagal innervation can be blocked either surgically by transecting the nerve or chemically by treating the subject with atropine.<sup>11</sup>

We demonstrated previously the ability to directly visualize *in vivo* individual airways as small as 1 mm in diameter and to measure individual airway responses to various challenges using the recent advance of HRCT technology.<sup>9,6</sup> The responses of individual airways to an agonist challenge may not be reflected in and even may be discordant with the measurement of total lung resistance.<sup>6</sup>

The change in resistance in a simple tube model is proportional to the inverse of the radius of the tube raised to the fourth power with all other variables held constant. Therefore, a 50% constriction in the radius of the tube will lead to a 16-fold increase in the resistance through the tube, which is an easily detectable change. Conversely, a twofold increase in the radius of the tube (100% increase) will cause only a  $\frac{1}{16}$ -fold decrease in the resistance through the tube. Total lung resistance is comprised of airway resistance and tissue resistance. The former may be as little as one quarter of the total.<sup>7</sup> Therefore, while a twofold constriction of the airways can make a significant addition to the

total lung resistance, a twofold dilation of the airways would be obscured by the much greater tissue resistance and cause a relatively small change in total lung resistance and probably would be within the error of measurement of  $R_L$ .

With the use of HRCT, we have demonstrated for the first time dose-dependent dilation of individual conducting airways in the baseline (control) state during administration of halothane. Our finding that halothane had no further effect on the airways of dogs pretreated with atropine is consistent with the findings of other investigators<sup>3,12,25</sup> that a major effect of volatile inhalational anesthetics in clinically relevant concentrations is to block airway reflexes. It is possible that inhalational anesthetics have additional effects on airways.

In conclusion, the canine airway appears to have resting vagal tone. Halothane dilated the unstimulated airway by blocking the baseline (control state) vagal tone. As humans have greater resting tone than do dogs,<sup>26</sup> an even greater effect of halothane on the baseline human airway would be expected. Since baseline airway tone, airway wall thickness,<sup>5</sup> and initial internal airway diameter<sup>5</sup> are major determinants of airway reactivity, this observed airway dilation associated with a decrease in baseline airway tone by halothane may be one of the mechanisms by which inhalational anesthetics decrease airway reactivity.

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