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Comparison of Low Concentrations of Halothane and Isoflurane as Bronchodilators

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Background: Although high concentrations of all currently used inhalational anesthetics are thought to be good bronchodilators, studies using traditional measures of airway tone fail to show differences in airway responsiveness during halothane, enflurance, and isoflurane use. Using a more sensitive technique, the authors compared the ability of halothane and isoflurane to dilate histamine-constricted airways at equivalent MAC concentrations.

Methods: Responses of histamine-constricted individual airways to increasing doses of halothane and isoflurane were directly measured using high-resolution computed tomography (HRCT). Fifteen studies were performed in five dogs. All dogs were initially anesthetized with thiopental 15 mg/kg followed by a 10-mg · kg^{-1} · h^{-1} maintenance dose. Following tracheal intubation, the lungs were mechanically ventilated (15 ml/kg, 15 bpm). The airways were constricted with intravenous histamine 200 μg/min. On alternate days, the dogs subsequently received increasing concentrations of either halothane or isoflurane (0.6, 1.1, and 1.7 MAC). On a separate day, the dogs received atropine 0.2 mg/kg after the histamine infusion and the study was repeated.

Results: Histamine decreased airway area 34 ± 2.5% (mean ± SEM). All preconstricted airways showed a significant dose-dependent dilation to halothane and isoflurane at concentrations of 0.6, 1.1, and 1.7 MAC. Halothane significantly dilated airways to a greater extent than isoflurane at 0.6 and 1.1 MAC ($P < 0.001$). This effect was most pronounced in airways less than 3 mm in diameter. At 1.7 MAC, there was no significant difference between the two agents ($P = 0.42$). Atropine (0.2 mg/kg) reversed the airway constriction elicited by intravenous histamine. The histamine-preconstricted airways area increased 370 ± 34% ($P < 0.0001$) after atropine.

Conclusions: Halothane and isoflurane dilate histamine-constricted airways in a dose-dependent manner. However, at low concentrations, halothane was a more effective bronchodilator than isoflurane at equivalent MAC doses. (Key words: Anesthetics, volatile: halothane; isoflurane. Constriction, airways. Dilation. Histamine. Lungs, bronchi. Measurement techniques: high-resolution computed tomography.)

ALTHOUGH high concentrations of all currently used inhalational anesthetics are thought to be good bronchodilators, studies using traditional measures of airway tone fail to show differences in airway responsiveness during halothane, enflurane, and isoflurane use.[1–3] The three agents have differing effects with regard to their abilities at blocking airway reflexes, especially at low anesthetic concentrations.[4] Therefore, it is possible that different inhalational agents may have differential effects on airways whose caliber is regulated by nerves, but that the methods previously used to evaluate these effects have not been adequately sensitive.

Airway diameter changes are commonly assessed by the indirect measurements of changes in lung resistance (R_L) or, more specifically, changes in airway resistance (R_{aw}). Both of these indices measure pressure and flow to calculate resistance. These methods are not sensitive enough to detect changes in the caliber of conducting airways.[5,6]

Several recent studies demonstrate that high-resolution computed tomography (HRCT) detects changes in airway caliber that are not reflected in the measurement of lung resistance.[5,6] High-resolution computed tomography allows noninvasive measurements of individual airway caliber changes in airways as small as 1 mm in diameter.[5,7] Using HRCT, we recently showed that halothane directly dilated the unconstricted airways of the dog.[6] Similar studies using R_L showed no change.[8–12]

To determine whether differences exist in the dose-response relationships to halothane and isoflurane using

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this more sensitive technique, we compared the effects of 0.6, 1.1, and 1.7 minimum alveolar concentration (MAC) of the two agents with regard to their bronchodilatory effects in histamine-constricted airways. These data confirm the clinical impression that, at low agent concentrations, halothane is a significantly better bronchodilator than isoflurane, and this effect was most pronounced in the smallest airways measured.

Materials and Methods

Our study protocol was approved by The Johns Hopkins Animal Care and Use Committee. Fifteen studies were performed on five dogs. The dogs were initially anesthetized with thiopental (15 mg/kg induction dose followed by a 10-mg·kg^{-1}·h^{-1} intravenous maintenance dose). After induction of anesthesia with thiopental, the dogs were paralyzed with 10 mg succinylcholine. Following tracheal intubation with an 8.5-mm ID endotracheal tube, the dogs were placed supine and their 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.

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 and proceeding caudal using 1-mm table feed and 2-mm slice thickness. The dogs were apneic and at FRC for the duration of the scans. Images were reconstructed with the use of a high-spatial frequency (resolution) algorithm that enhances edge detection, and at a window level of −450 Hounsfield units (HU) and window widths of 1,300–1,350 HU. These window settings have been previously shown to allow optimal lung resolution.[13] A range of airway sizes were selected that could be visualized under all experimental conditions. For repeated image analysis within each experiment and across experiments on different days, parenchymal anatomic landmarks, such as airway or vascular branching points, were defined on the control-state HRCT image. Following the histamine challenge or change in inhalational anesthetic concentration, the same airways in a given animal were then analyzed on images matched by these parenchymal landmarks.

Analysis of Airways

The HRCT images were transferred as 16-bit data images to a UNIX-based workstation and reduced to 8-bit images, which were then analyzed using the airway analysis module of the Volumetric Image and Display Analysis (VIDA) image analysis software package (Department of Radiology, Section of Cardiothoracic Imaging Research, University of Pennsylvania, Philadelphia, PA). This package works as follows: 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 predesignated 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 squared.

Protocol

Control HRCT scans were performed while the dogs were anesthetized with thiopental as described above. Subsequently, the airways were contricted by the administration of intravenous histamine (200 μg/min.). The dose of histamine was selected based on our preliminary work in these animals, demonstrating that this dose constricted the airways by approximately 50%. A steady state was achieved within 10 min. Each histamine-constricted airway was used as its own control for calculating the percent increase in airway area with the subsequent administration of inhalational anesthetics.

As the thiopental infusion was stopped and its effects allowed to wear off, either halothane (Ayrest Laboratories, New York, NY), or isoflurane (Anaquest, Madison, WI) was administered. In dogs, MAC is 0.87% for halothane and 1.48% for isoflurane.[14,15] The concentrations of the inhalational anesthetics were matched on the basis of equivalent MAC doses of 0.6, 1.1, and 1.7, and were added in cumulative doses to the breathing circuit until steady state end-tidal anesthetic concentrations were attained (approximately 20 min) as measured by gas analysis (N-2500; Nellcor, Hayward, CA). On a separate day, after preconstriction of the airways with histamine, atropine 0.2 mg/kg was administered. We examined the data as a whole and also divided the data into subsets according to initial airway size: less than 3 mm in diameter, 3–7 mm in diameter, and greater than 7 mm in diameter. These sizes were chosen to represent small, medium, and large con-

ducting airways. Data were analyzed by one-way analysis of variance and Bonferroni pairwise comparisons of means with significance considered to be $P < 0.05$.

Results

Thirteen to 15 airways were measured in each of the five dogs in each of the 15 studies. The airways measured ranged in size from approximately 1.7 mm in diameter to 17.8 mm in diameter. The same airways were matched and measured in each dog under all experimental conditions. Under the control condition, the diameters of the individual airways did not vary significantly when measured on the different days ($P = .84$). The mean airway constrictor response to intravenous histamine (200 μg/min) for all airways among the five dogs and in the same dog on the different days were not significantly different. Histamine decreased airway area 34 ± 2.5%. All airways preconstricted with histamine showed a significant dose-dependent dilation to halothane and isoflurane at MAC doses of 0.6, 1.1, and 1.7. (fig. 1). There was a significant difference between the agents at the low anesthetic concentrations. Halothane significantly dilated airways to a greater extent than isoflurane at 0.6 and 1.1 MAC ($P < 0.001$, fig. 1). At 1.7 MAC, there was no significant difference between the two agents ($P = 0.42$).

In the airways less than 3 mm and 3–7 mm in diameter, halothane significantly dilated these histamine-constricted airways to a greater extent than isoflurane at 0.6 and 1.1 MAC ($P < 0.05$, fig. 2). In airways greater than 7 mm, the halothane dilation of the histamine-constricted airways was not significantly greater than that caused by isoflurane (fig. 2).

Atropine (0.2 mg/kg) reversed the airway constriction elicited by intravenous histamine, indicating that this concentration of histamine given by this route produced airway constriction by reflex mechanisms. The area of histamine-preconstricted airways increased 370 ± 34% ($P < 0.0001$) after atropine.

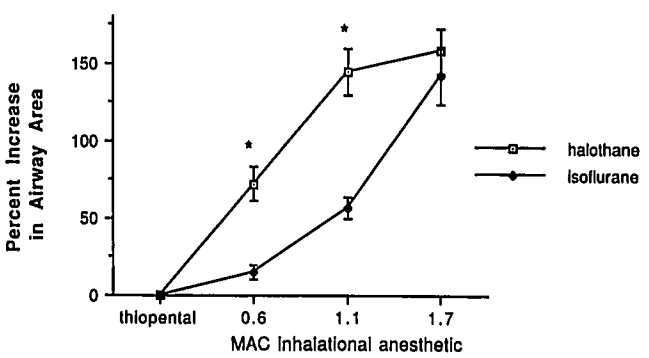

Fig. 1. The dose-response dilation of histamine-preconstricted airways to increasing concentrations of halothane (upper line, open boxes) and isoflurane (lower line, closed diamonds). The airways were significantly more dilated at the lower concentrations of anesthetic by halothane than by isoflurane (*$P < 0.001$). At the higher concentration, there was no difference in the amount of dilation in the airways between halothane and isoflurane.

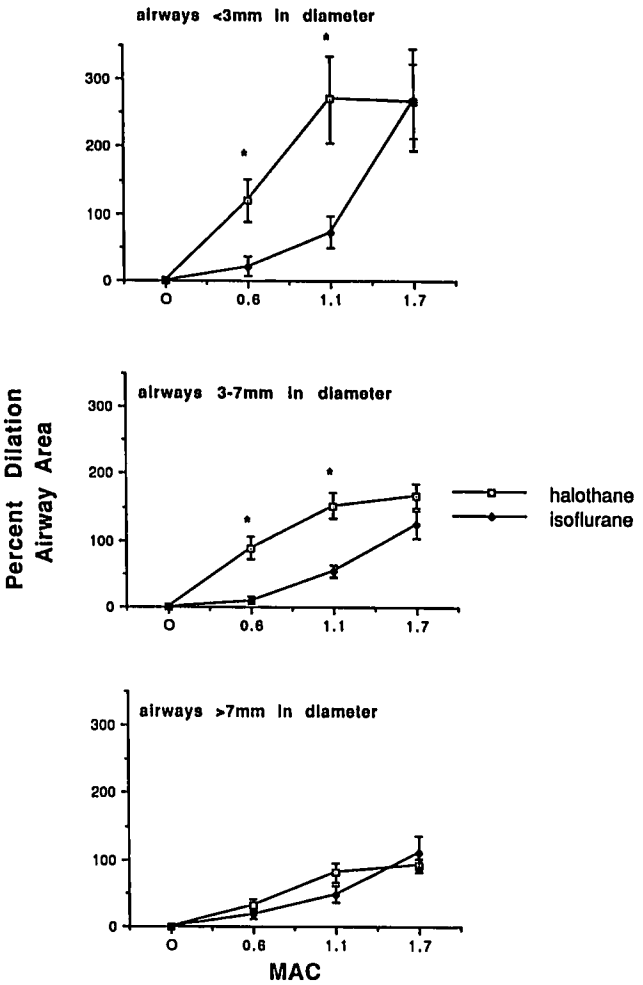

Fig. 2. The dose-response dilation of the histamine-preconstricted airways to halothane and isoflurane according to the initial airway size. *Upper*, small airways, less than 3 mm in diameter; *middle*, medium-size airways, 3–7 mm in diameter; and, *bottom*, large airway, greater than 7 mm in diameter. Halothane dilated small and medium-size airways significantly more than isoflurane at lower concentrations (*$P < 0.01$). In the larger airways, there was no significant difference between halothane and isoflurane.

Discussion

This study confirms that both halothane and isoflurane dose-dependently dilate histamine-preconstricted conducting airways. However, this is the first demonstration of the fact that low concentrations of halothane are more effective bronchodilators than isoflurane at equivalent concentrations.

Histamine receptors are located on airway smooth muscle and on airway nerve endings.[16] The afferent impulses run in the vagus in dogs, as well as in humans.[16] The cholinergic efferent impulses also run in the vagus. Therefore, histamine receptor stimulation results in constriction of the airways, both directly and indirectly. Severance of the vagus nerve or atropine pretreatment abolishes the indirect reflex component of airway constriction by blocking these afferent and efferent impulses.[17] The complete reversal or prevention of histamine-induced airway constriction by atropine, which blocks this reflex component,[18] indicates that intravenously administered histamine constricts the airways measured in our study largely or entirely by reflex-induced mechanisms with little or no direct effects.

Several studies using conventional techniques of R_L have examined the effects of halothane on airways of animals preconstricted with a variety of agonists. Halothane at 1 and 1.5 MAC and aerosol atropine pretreatment significantly attenuated the increase in R_L provoked by an aerosol histamine challenge.[11] Although the atropine pretreatment showed a larger attenuation than halothane, this was not statistically different. The authors concluded that the major action of halothane on airways was indirect and represented inhibition of airway reflexes. Using vagal nerve stimulation to elicit bronchoconstriction, Warner *et al.* and Joyner *et al.* showed a dose-dependent attenuation of 27–50% in R_{aw} by halothane at concentrations of 1.2–2.0 MAC during vagal nerve stimulation.[19–21]

Several *in vitro* studies have examined the effects of halothane on constricted airways. Halothane attenuated vagally induced contraction by electrical field stimulation of isolated canine trachealis muscle.[22] The authors proposed that this occurred at several sites along the peripheral vagal motor pathway, as demonstrated by a reduction of the contractile response to dimethyphenyl-piperazinium (DMPP), which stimulates postsynaptic nicotinic cholinergic receptors; electrical field stimulation (EFS), which stimulates postganglionic fibers; and acetylcholine, which stimulates M_3 muscarinic receptors. Only at concentrations greater than 1.7 MAC did halothane depress postganglionic fiber function, while a concentration as high as 2.4 MAC halothane only attenuated a direct constriction by 25%.

Korenaga *et al.* demonstrated that halothane suppressed the tracheal smooth muscle contraction at any given depolarization of the membrane produced by application of an outward current pulse, and raised the threshold membrane depolarization required to produce the contraction.[23] They demonstrated a reduction in the amplitude of contraction of 87, 77, 65, and 56% of control in the presence of 1, 2, 3, and 4% halothane, respectively. They concluded that halothane more effectively suppressed the tension development of the tracheal tissue when indirect (nerve-mediated) muscle stimulation was given.

Inhalational anesthetics are thought to block airway reflexes in a dose-related fashion.[6] Isoflurane has been shown to activate these reflexes to a greater extent than does halothane.[4] If inhalational anesthetics are equally effective at blocking reflexes, the differing effects of isoflurane and halothane in our study may reflect the greater activation of reflexes by isoflurane.

Our findings do not necessarily disagree with the findings of Alexander *et al.*, who measured changes in collateral resistance to a hypocapnic challenge. They found that isoflurane was more potent than halothane at attenuating this response. However, the location, amount of innervation, and type of airways measured differed from those in our study. We measured area changes in conducting airways as small as 1 mm in diameter, which have innervation. Alexander *et al.* measured changes in pressure related to air flow through collateral channels, which have little neural innervation. It is possible that low concentrations of halothane are better at blocking reflexes, whereas low concentrations of isoflurane are more effective at directly relaxing airway smooth muscle.

Vetterman *et al.* investigated the ability of enflurane and isoflurane to attenuate increases in R_L to vagal nerve stimulation in vagotomized dogs. They found no differences between the anesthetics. The component of R_L in constricted airways that accounts for conducting airways resistance may be small.[19] Therefore, the investigators may not have been able to detect even large changes in conducting airways, because such changes will be only a small component of R_L. At high concentrations of inhalational anesthetics, our results are consistent with those of virtually all other investigators. We found no difference between halothane and isoflu-

rane in their ability to dilate airways at a concentration of 1.7 MAC.

The differing effects of halothane and isoflurane were greatest in the smaller airways. One explanation for this differential bronchodilation is the statistical analysis. By transforming the data to percent changes, changes in smaller airways will be emphasized in the analysis. The same absolute change in a small airway will be recorded as a larger percent change than the same absolute change in a large airway. Therefore, the percent transformation can account for some of the differences in the magnitude of the change in the airway areas of small *versus* large airways. The transformation of the data cannot account for the differences observed between halothane and isoflurane in small, but not large, airways.

In summary, at low concentrations, halothane is a more potent bronchodilator than isoflurane at equivalent MAC multiples, and this effect appears to occur predominantly in the medium and small conducting airways. This finding may be relevant to the choice of an inhalational agent for patients with reactive airway disease who require general anesthesia. This study suggests that halothane is superior to isoflurane at low concentrations and may be a better choice for induction of anesthesia in patients with reactive airway disease.

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References

1. Vettermann J, Beck KC, Lindahl SHE, Brichant JF, Rehder K: Actions of enflurane, isoflurane, vecuronium, atracurium and pancuronium on pulmonary resistance in dogs. ANESTHESIOLOGY 69:688–695, 1988

2. Alexander CM, Chen L, Ray R, Marshall BE: The influence of halothane and isoflurane on pulmonary collateral ventilation. ANESTHESIOLOGY 62:135–140, 1985

3. Hirshman CA, Bergman NA: Factors influencing intrapulmonary airway calibre during anaesthesia. Br J Anaesth 65:30–42, 1990

4. Nishino T, Tanaka A, Ishikawa T, Hiraga K: Respiratory, laryngeal, and tracheal responses to nasal insufflation of volatile anesthetics in anesthetized humans. ANESTHESIOLOGY 75:441–444, 1991

5. Brown RH, Herold CJ, Hirshman CA, Zerhouni EA, Mitzner W: *In vivo* measurements of airway reactivity using high-resolution computed tomography. Am Rev Respir Dis 144:208–212, 1991

6. Brown RH, Mitzner W, Zerhouni E, Hirshman CA: Direct *in vivo* visualization of bronchodilation induced by inhalational anesthesia using high resolution computed tomography (HRCT). ANESTHESIOLOGY 78:295–300, 1993

7. Herold CJ, Brown RH, Mitzner W, Links JM, Hirshman CA, Zerhouni EA: Assessment of pulmonary airway reactivity with high-resolution CT. Radiology 181:369–374, 1991

8. Hickey RF, Graf PD, Nadel JA, Larson CP: The effects of halothane and cyclopropane on total pulmonary resistance in the dog. ANESTHESIOLOGY 31:334–343, 1969

9. Morr-Strathmann U, Morr H: Influence of inhalation anaesthetics on bronchomotor tone: Animal experiments on vago-vagal reflex bronchoconstriction. Acta Anaesthesiol Scand 41:39–42, 1979

10. Hirshman CA, Edelstein G, Peetz S, Wayne R, Downes H: Mechanism of action of inhalational anesthesia on airways. ANESTHESIOLOGY 56:107–111, 1982

11. Shah MV, Hirshman CA: Mode of action of halothane on histamine-induced airway constriction in dogs with reactive airways. ANESTHESIOLOGY 65:170–174, 1986

12. Tobias JD, Kubos KL, Hirshman CA: Aminophylline does not attenuate histamine-induced airway constriction during halothane anesthesia. ANESTHESIOLOGY 71:721–727, 1989

13. Webb WR, Gamsu G, Wall SD, Cann CE, Proctor E: CT of a bronchial phantom: Factors affecting appearance and size measurements. Invest Radiol 19:394–398, 1984

14. Regan MJ, Eger EI II: Effect of hypothermia in dogs on anesthetizing and apneic doses of inhalation agents: Determination of the anesthetic index (apnea/MAC). ANESTHESIOLOGY 28:689–700, 1967

15. Eger EI: Anesthetic Uptake and Action. Baltimore, Williams and Wilkins, 1974, pp 5

16. Dixon M, Jackson DM, Richards IM: The effects of histamine, acetylcholine and 5-hydroxytryptamine on lung mechanics and irritant receptors in the dog. J Physiol (Lond) 287:393–403, 1979

17. Richardson JB: Nerve supply to the lungs. Am Rev Respir Dis 119:785–802, 1979

18. Hirshman CA, Downes H: The basenji-greyhound dog model of asthma: Influence of atropine on antigen-induced bronchoconstriction. J Appl Physiol 50:761–765, 1981

19. Warner DO, Vettermann J, Brusasco V, Rehder K: Pulmonary resistance during halothane anesthesia is not determined only by airway calibre. ANESTHESIOLOGY 70:453–460, 1989

20. Joyner MJ, Warner DO, Rehder K: Halothane changes the relationship between lung resistances and lung volume. ANESTHESIOLOGY 76:229–235, 1992

21. Warner DO, Vettermann J, Brichant J-F, Rehder K: Direct and neurally mediated effects of halothane on pulmonary resistance *in vivo*. ANESTHESIOLOGY 72:1057–1063, 1990

22. Brichant J-F, Gunst SJ, Warner DO, Rehder K: Halothane, enflurane, and isoflurane depress the peripheral vagal motor pathway in isolated canine. ANESTHESIOLOGY 74:325–332, 1991

23. Korenaga S, Takeda K, Ito Y: Differential effects of halothane on airway nerves and muscles. ANESTHESIOLOGY 60:309–318, 1984