# Attenuation of Histamine-Induced Airway Constriction by Albuterol during Halothane Anesthesia

Joseph D. Tobias, M.D.,* Carol A. Hirshman, M.D.†

The effect of albuterol (a $\beta_2$ specific adrenergic agonist) on airway reactivity to histamine aerosol challenge was evaluated during halothane anesthesia and thiopental-fentanyl anesthesia in five Basenji Greyhound dogs. Responses to histamine aerosol challenges (0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/ml) were measured during thiopental-fentanyl anesthesia and during halothane anesthesia in the presence and absence of iv albuterol (2.5 µg/kg). Prior to aerosol challenges, baseline pulmonary resistance ($R_L$) and dynamic compliance ($C_{dyn}$) did not differ in the four conditions. Albuterol significantly attenuated the pulmonary response to histamine during thiopental-fentanyl anesthesia. Although halothane itself significantly attenuated the pulmonary response to histamine, this response was further attenuated by the addition of albuterol. This study suggests that albuterol is effective in attenuating bronchoconstriction during both thiopental-fentanyl and halothane anesthesia. As the effects of albuterol and halothane on the airways are additive, $\beta$-adrenergic agonists such as albuterol are the agents of choice to treat bronchospasm in patients anesthetized with inhalational anesthetics. (Key words: Allergy, asthma: airway reactivity; bronchoconstriction. Anesthetics, intravenous: fentanyl; thiopental. Anesthetics, volatile: halothane. Histamine. Lungs: pulmonary resistance. Sympathetic nervous system, beta receptor agonist: albuterol.)

INHALATIONAL ANESTHETICS are the agents of choice in patients with reactive airway disease as they attenuate the pulmonary bronchoconstrictor response to numerous agents primarily by blocking vagal reflexes.[1–3] Despite this, intraoperative bronchospasm occurs during general anesthesia and often requires further therapy.

Methylxanthines, $\beta$-adrenergic agonists, and anticholinergics are the major bronchodilators currently available but neither methylxanthines[4] nor anticholinergics[1] attenuate bronchoconstriction during inhalational anesthesia. $\beta$-adrenergic agonists act through $\beta_2$ receptors on airway smooth muscle to dilate airways and are the agents of choice for treating bronchospasm in unanesthetized individuals.

In addition to its effects on vagally mediated reflexes and smooth muscle, it has been suggested that halothane may affect pulmonary responses through augmentation of $\beta$-adrenergic tone.[5] Therefore, $\beta$-adrenergic agonists such as albuterol may not offer additional protection during inhalational anesthesia since $\beta$-adrenergic bronchodilatation may already be maximal. We compared the effects of albuterol (a $\beta$-adrenergic agonist) on pulmonary reactivity to histamine aerosol challenges during thiopental-fentanyl anesthesia and during halothane anesthesia in our dog model of chronic airway hyperreactivity.[6]

## Methods

### GENERAL CONDITIONS

These studies were approved by the animal research committee of both the School of Medicine and the School of Hygiene and Public Health of the Johns Hopkins University. The animals employed in the study were five Basenji Greyhounds (BG) ranging in age from 1–2 yr and in weight from 17–23 kg. Each dog was studied under four conditions performed in random order and each study was separated by at least 1 week. These four conditions included: 1) thiopental-fentanyl anesthesia; 2) thiopental-fentanyl anesthesia with iv albuterol (2.5 µg/kg); 3) halothane anesthesia (1.5 MAC); and 4) halothane anesthesia with iv albuterol (2.5 µg/kg). The dogs were fasted overnight, received no premedication, and were anesthetized while standing and supported in a sling. Anesthesia was induced in all conditions with iv thiopental (15 mg/kg) and tracheal intubation was facilitated with succinylcholine (0.5 mg/kg). The dogs' tracheas were intubated with an 8.5-mm cuffed endotracheal and the lungs were mechanically ventilated (Harvard Apparatus, Millis, MA) with 100% oxygen at a tidal volume of 15 ml/kg and a rate of 15 breaths per min. End-tidal $CO_2$ varied from 38–42 mmHg. Heart rate was continuously monitored with a needle electrode electrocardiogram (Tektronics 412, Beaverton, OR) and blood pressure was measured with an automated blood pressure cuff (Datascope Accutor 1A, Paramus, NJ).

In studies involving thiopental-fentanyl anesthesia, anesthesia was maintained with a continuous infusion of thiopental (0.2 mg·kg⁻¹·min⁻¹)[7] and fentanyl (1 µg/kg) every 20 min until completion of the study (fig. 1). No additional muscle relaxants were used. In studies involving inhalational anesthesia, halothane was started 5 min after induction and was administered until a steady-state, end-tidal concentration of 1.5 MAC was achieved (fig. 1). The MAC value of halothane in the dog was taken to be 0.87.[8] End-tidal halothane and $CO_2$ were sampled con-

tinuously using a Perkin Elmer 1100 mass spectrometer (Pomona, CA).

Albuterol was reconstituted from powder with sterile saline to a concentration of 10 $\mu$g/ml and administered intravenously in a dose of 2.5 $\mu$g/kg over 15 min starting 5 min after induction of anesthesia (fig. 1).

## MEASUREMENT OF AIRWAY MECHANICS

Airflow ($\dot{V}$) was measured by a pneumotachograph (Fleisch type No. 1, OEM Medical Inc., Richmond, VA) and a differential pressure transducer (Validyne DP 45-16, Northridge, CA) that was connected to one channel of a pen recorder (Gould 2500S, Cleveland, OH). A balloon (Spectramed, Dayton, OH) was placed in the esoph-

agus, filled with 0.8–1.2 ml of air and withdrawn to the point where end-expiratory pressure was most negative. A second catheter was placed alongside the balloon and connected to suction to keep the esophagus free of air and secretions. Transpulmonary pressure was recorded by connecting one side of a differential pressure transducer (Validyne MP 45-18, Northridge, CA) to the esophageal balloon and the other side to a needle in the airway. The output of the pressure transducer was recorded on the second channel of the pen recorder. Both records were electronically integrated by a dedicated pulmonary mechanics microprocessor (Buxco Model 6, Sharon, CT) to give values for lung resistance ($R_L$) and dynamic compliance ($C_{dyn}$), which was averaged over the six preceding breaths by a computer (Texas Instruments,
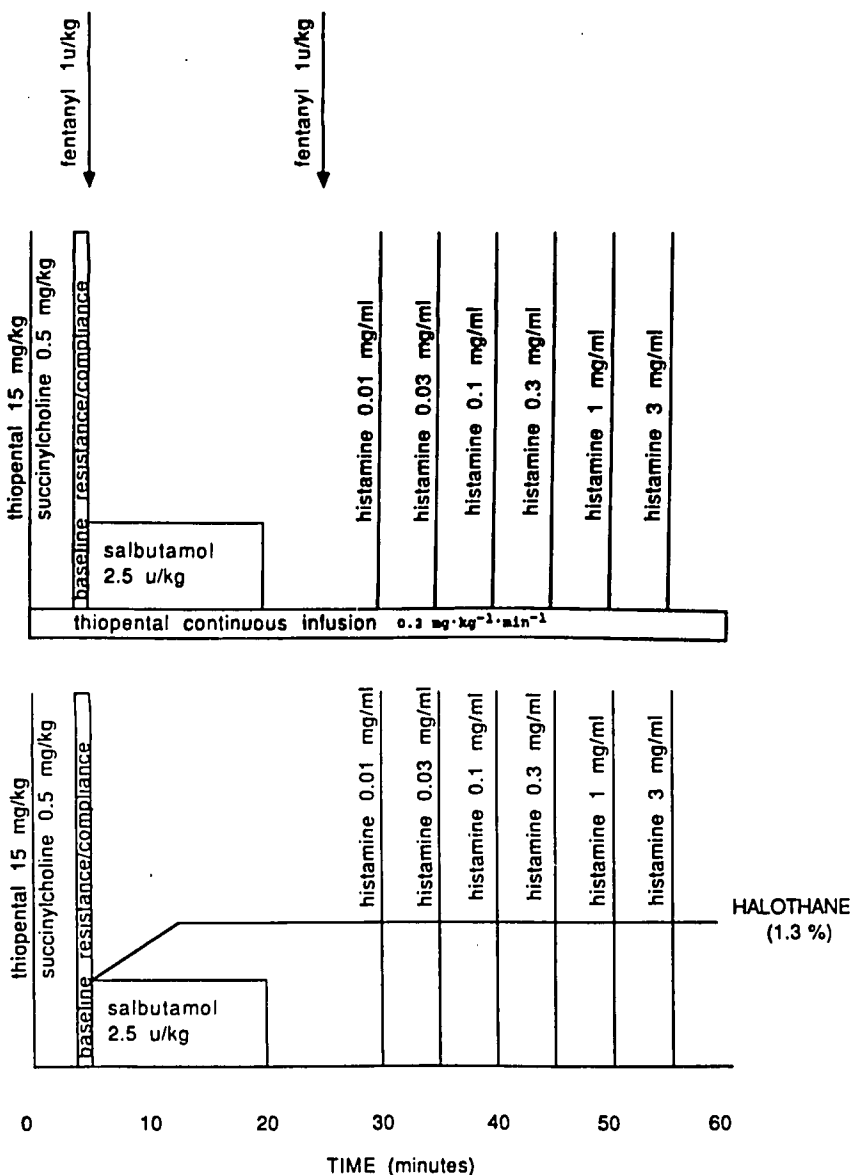


FIG. 1. Experimental protocol of thiopental-fentanyl anesthesia (*above*) and halothane anesthesia (*below*) showing the timing of albuterol infusion and histamine challenges.

Model 703, Temple, TX) and printed out. Apparatus resistance (2 $cmH_2O \cdot l^{-1} \cdot s^{-1}$), determined by ventilating a mechanical lung analog with known parameters, was subtracted from the results to give $R_L$.

## AEROSOL CHALLENGES

Thirty minutes after the induction of anesthesia, inhalational challenges with incremental doses of histamine (0.01, 0.03, 0.1, 0.3, 1.0, 3.0 mg/ml) were administered during the four different conditions (fig. 1). Aerosols were delivered by a Hudson 3000 nebulizer (Hudson, Temecula, CA) driven by compressed oxygen that delivered aerosol particles with a mass median of 5.7 $\mu$m. All solutions were dissolved in distilled water. Histamine was administered for five standardized breaths using an Ayre's t-tube inserted between the nebulizer and the endotracheal tube.[9] The expiratory port was occluded until an inflation pressure of 15 $cmH_2O$ had been obtained. Aerosol histamine challenges were administered at 5-min intervals even when resistance did not fall to baseline values and the maximal changes in $R_L$ and $C_{dyn}$ were recorded.

## STATISTICAL ANALYSIS

Baseline $R_L$ (obtained prior to histamine challenge) was subtracted from the maximal $R_L$ following each challenge to give change in $R_L$. The lowest $C_{dyn}$ postchallenge was divided by $C_{dyn}$ prechallenge to give the fractional decrease in compliance from baseline. All data were expressed as a mean ± SEM of five dogs and analyzed using a two-way analysis of variance with a $P < 0.05$ considered significant. The significant difference between paired groups was then tested by the least significant difference method.

## Results

Prior to histamine challenge, there were no significant differences in baseline $R_L$ and $C_{dyn}$ between the four conditions (table 1). The administration of halothane and/or albuterol did not significantly alter $R_L$ or $C_{dyn}$ from the baseline values.

Histamine produced dose-related increases in $R_L$ and decreases in $C_{dyn}$ in all four conditions. The increase in $R_L$ and the decrease in $C_{dyn}$ was significantly attenuated by albuterol pretreatment during both thiopental-fentanyl anesthesia and halothane anesthesia (figs. 2 and 3). During thiopental-fentanyl anesthesia (condition 1 vs. 2), the increase in pulmonary resistance and the decrease in dynamic compliance were attenuated at all concentrations of histamine. This attenuation of the increase in resistance was statistically significant at histamine concentrations of 0.1 mg/ml ($P < 0.05$), 0.3 mg/ml ($P < 0.05$), and 1.0

TABLE 1. Baseline Values of Pulmonary Resistance ($R_L$) and Dynamic Compliance ($C_{DYN}$)*

| | $R_L$ $cmH_2O \cdot l^{-1} \cdot s^{-1}$ | $C_{DYN}$ cc/$cmH_2O$ |
|---|---|---|
| Thiopental/Fentanyl | 2.64 ± .09 | 60 ± 2.7 |
| Thiopental/Fentanyl/Albuterol | 2.50 ± .20 | 68 ± 6.1 |
| Halothane | 2.94 ± .12 | 63 ± 2.2 |
| Halothane/Albuterol | 3.06 ± .37 | 62 ± 4.6 |

* Measurements made prior to the start of aerosol histamine challenges after achieving end-tidal halothane = 1.3% and/or iv administration of albuterol (2.5 $\mu$g/kg). Each value is the mean ± SEM of five dogs.

mg/ml ($P < 0.01$) (fig. 2). During halothane anesthesia (condition 3 vs. 4), histamine-induced bronchoconstriction (increase in $R_L$) was significantly attenuated by albuterol ($P < 0.05$) at histamine concentrations of 0.3, 1.0, and 3.0 mg/ml (fig. 3). Likewise, albuteral attenuated the decrease in dynamic compliance in response to histamine challenges. This attenuation was statistically significant ($P < 0.05$) at histamine concentrations of 0.3 and 1.0 mg/ml during thiopental-fentanyl anesthesia and at histamine concentrations of 1.0 and 3.0 mg/ml during halothane anesthesia.

Regardless of the anesthetic technique, cardiovascular changes (heart rate and blood pressure) were noted during the albuterol infusion. During thiopental-fentanyl anesthesia, baseline heart rates varied from 150–160 beats per min and systolic blood pressure from 130–150 mmHg. During halothane anesthesia, the heart rate averaged 90–100 beats per min and systolic blood pressure 90–100 mmHg. During albuterol infusion (during both thiopental-fentanyl and halothane anesthesia), heart rates increased to 190–200 beats per min with no significant change in systolic blood pressure during halothane anesthesia, and a decrease to 90–100 mmHg during thiopental-fentanyl anesthesia.

## Discussion

Inhalational anesthetics prevent or reverse bronchospasm provoked by a wide variety of substances. The mechanisms involved include blocking airway reflexes, directly relaxing airway smooth muscle, inhibiting mediator release, or augmenting β-adrenergic tone.[1–3,5] To treat bronchospasm occurring during inhalational anesthesia, one must demonstrate that the effects of the bronchodilator are additive to the effects of the inhalational anesthetic.

We have previously evaluated the effects of aminophylline during halothane anesthesia[4] and found that during thiopental-fentanyl anesthesia, aminophylline increased endogenous catecholamine levels and attenuated histamine-induced bronchospasm, while during halothane anesthesia, which blocks the release of endogenous cate-
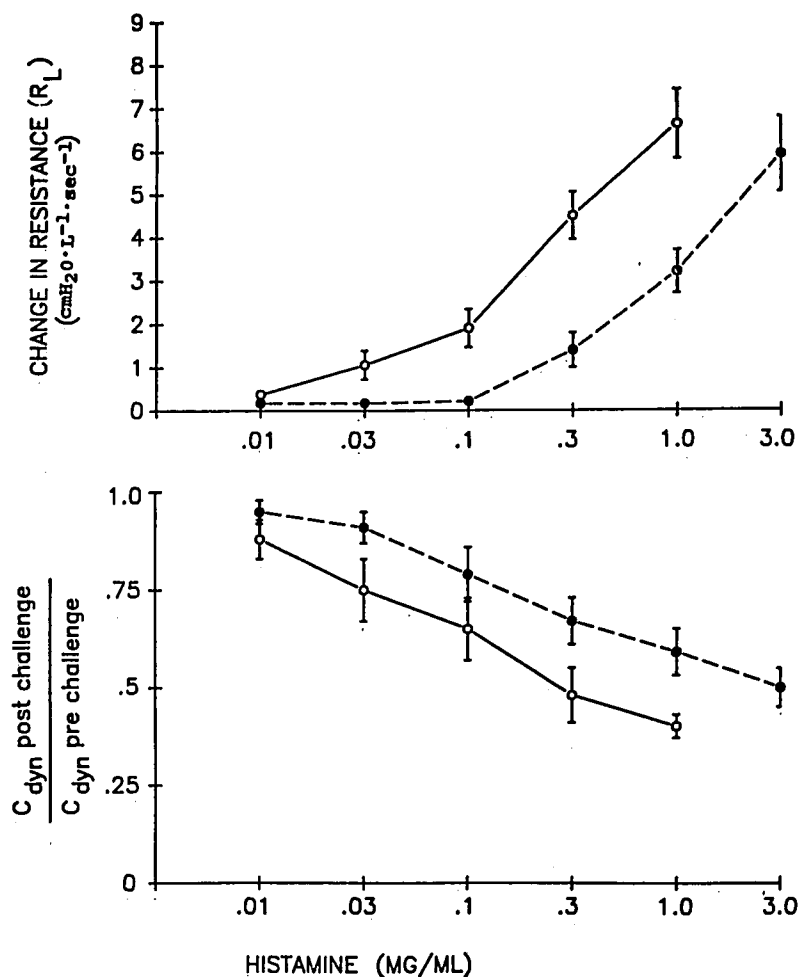
FIG. 2. Dose-response curves during thiopental-fentanyl anesthesia with (*dashed line*) and without (*solid line*) albuterol. Pulmonary resistance ($R_L$) above and dynamic compliance ($C_{dyn}$) below. Each point is the mean ± SEM of five dogs.

cholamines,[10] no increase in endogenous catecholamines occurred and no attenuation in histamine-induced bronchoconstriction was achieved.

We have also previously evaluated the use of anticholinergics to attenuate pulmonary responses during inhalational anesthesia and found that aerosolized atropine was ineffective in attenuating histamine-induced bronchoconstriction during halothane anesthesia.[1] Atropine's effect on pulmonary responses lies in its ability to block vagally mediated reflexes. A similar effect (blockade of vagally mediated reflexes) has been shown to be one of the mechanisms through which inhalational anesthetics alter pulmonary mechanics and responses.[1,11]

Therefore, the only major therapeutic modality remaining to treat bronchospasm during inhalational anesthesia, aside from deepening the level of anesthesia, is the administration of $\beta$-adrenergic agonists. The use of adrenergic agonists in the treatment of bronchospasm began in the early 1900s with the use of substances obtained from desiccated adrenal glands.[12] Although human airway smooth muscle lacks sympathetic innervation,[13] it contains adrenergic receptors that respond to endogenous and exogenous adrenergic agonists. These receptors are pre-dominantly $\beta_2$ and their activation leads to increased conversion of ATP to 3'5' cyclic AMP. This conversion is mediated by regulatory proteins such as the GTP binding protein $G_S$. Increases in intracellular cyclic AMP lead to relaxation of airway smooth muscle. In addition to its effects on airway smooth muscle, stimulation of $\beta_2$-adrenergic receptors also stabilizes mast cells and alters vascular/epithelial permeability.[14]

In contrast to aminophylline and atropine, albuterol was effective in attenuating histamine-induced bronchoconstriction during both thiopental-fentanyl and halothane anesthesia. Although halothane by itself attenuated histamine-induced bronchoconstriction when compared to thiopental-fentanyl anesthesia (condition 1 vs. 3), the administration of albuterol further attenuated the response even in the presence of halothane (condition 3 vs. 4). Therefore, if halothane does augment $\beta$-adrenergic tone,[5] this effect is not maximal and further bronchodilatation is possible with $\beta$-adrenergic agonists even in the presence of inhalational agents.

We chose albuterol in our study because it is more $\beta_2$ selective than other agents such as isoproterenol and isoetharine. It can be administered orally, by aerosol, and
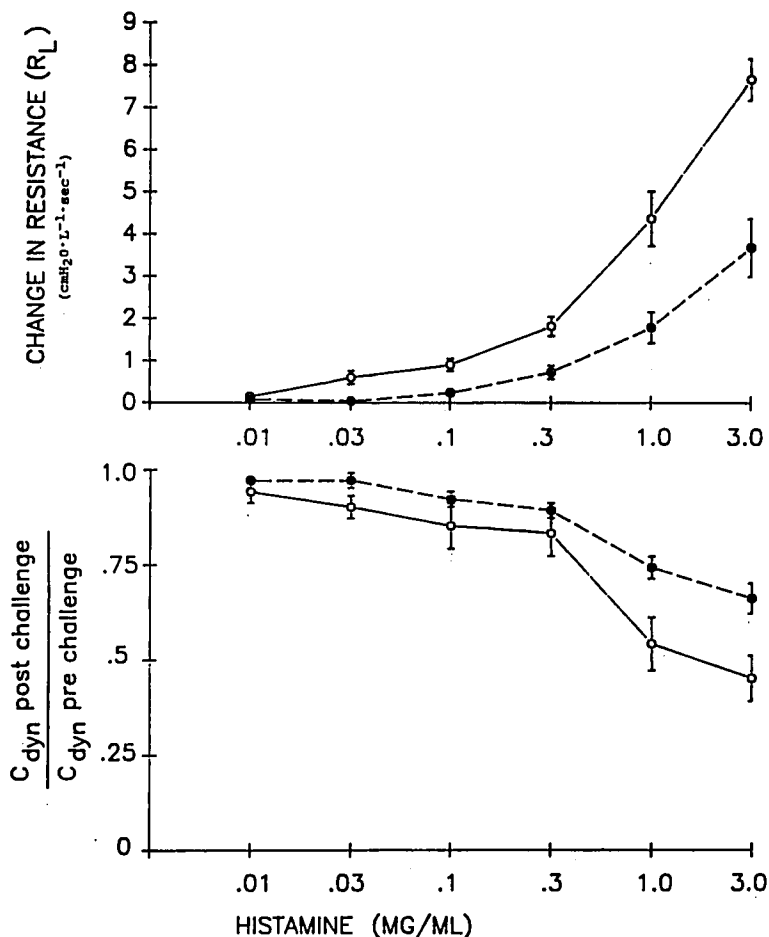
FIG. 3. Dose response curves during halothane anesthesia with (dashed line) and without (solid line) albuterol. Pulmonary resistance ($R_L$) above and dynamic compliance ($C_{dyn}$) below. Each point is the mean ± SEM of five dogs.

intravenously (although not available for iv use in this country).[15] When administered intravenously, its half-life is such that for short experimental protocols it can be administered as a single bolus without the need for continuous infusions. In this evaluation of the efficacy of albuterol, we chose the iv route to avoid the uncertainties of dosage and delivery that can occur with aerosolized medications, especially through an endotracheal tube. Although we found albuterol effective in attenuating histamine-induced bronchoconstriction, we noted $\beta_1$ effects manifested by tachycardia when albuterol was used by the iv route. These $\beta_1$ effects are less common and the bronchodilator effects are comparable when albuterol is used by the aerosol route.[16]

As in previous studies with this model, we have measured pulmonary resistance and taken this to reflect airway caliber. Although recent work has shown that pulmonary resistance is comprised of both airway resistance and tissue resistance (viscance) and that both of these components respond to aerosol challenges,[17] Ludwig et al. have shown that the percentage of pulmonary resistance due to airway resistance is constant throughout the histamine dose response curve (20%) and therefore a linear relationship

exists between our measure of pulmonary resistance and airway resistance (caliber).[18]

In conclusion, we found that albuterol is effective in attenuating pulmonary responses to histamine during both thiopental-fentanyl anesthesia and during inhalational anesthesia with halothane. This synergy can be attributed to the different mechanisms of action of albuterol and halothane on airway tone and reactivity. Although one should be cautious in extrapolating results from laboratory animals to patients, these data suggest that $\beta$-adrenergic agonists are the bronchodilators of choice to treat bronchospasm occurring during inhalational anesthesia.

## References

1. Shah MV, Hirshman CA: Mode of action of halothane on histamine-induced airway constriction in dogs with reactive airways. ANESTHESIOLOGY 65:170–174, 1986
2. Hirshman CA, Edelstein G, Peetz S, Wayne R, Downes H: Mechanism of action of inhalational anesthesia on airways. ANESTHESIOLOGY 56:107–111, 1982

3. Hirshman CA, Bergman NA: Halothane and enflurane protect against bronchospasm in an asthma dog model. Anesth Analg 57:629–633, 1978

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

5. Klide AM, Aviado DM: Mechanism for the reduction in pulmonary resistance induced by halothane. J Pharmacol Exp Ther 158:28–35, 1967

6. Hirshman CA: The Basenji-Greyhound dog model of asthma. Chest 87:172S–178S, 1985

7. Baggot JO, Toutan PL, Brandon RA: Effect of premedication with acetylpromazine on the distribution kinetics of thiopental. J Vet Pharmacol Ther 7:197–202, 1984

8. Quasha AL, Eger EI, Tinker JH: Determination and application of MAC. ANESTHESIOLOGY 53:315–334, 1980

9. Hirshman CA, Downes H, Veith L: Airway responses in offspring of dogs with and without airway hyperreactivity. J Appl Physiol 56:1272–1277, 1984

10. Gothert M, Dorn W, Loewenstein I: Inhibition of catecholamine release from the adrenal medulla by halothane. Naunyn-Schmiedeberg's Arch Pharmacol 294:239–249, 1976

11. Vetterman J, Beck KC, Lindahl SGE, Brichant JF, Rehder K: Action of enflurane, isoflurane, vecuronium, atracurium, and pancuronium on pulmonary resistance in dogs. ANESTHESIOLOGY 69:688–695, 1988

12. Solis-Cohen S: The use of adrenal substance in the treatment of asthma. JAMA 34:1164–1167, 1900.

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

14. Hirshman CA: Airway reactivity in humans: Anesthetic implications. ANESTHESIOLOGY 58:170–177, 1983

15. Bohn D, Kalloghlian A, Jenkins J, Edmonds J, Barker G: Intravenous salbutamol in the treatment of status asthmaticus in children. Crit Care Med 12:892–896, 1984

16. Smith SR, Ryder C, Kendall MJ, Holder R: Cardiovascular and biochemical responses to nebulised salbutamol in normal subjects. Br J Clin Pharmacol 18:641–644, 1984

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

18. Ludwig MS, Romero DV, Bates JHT: A comparison of dose-response behavior of canine airway and parenchyma. Am Rev Respir Dis 139:A133, 1989