

Mechanism of Action of Inhalational Anesthesia on Airways

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To separate reflex from direct actions of anesthetics on airways, we studied the effects of halothane and isoflurane (1.5 MAC) on *Ascaris* antigen-induced (a mixed reflex and direct stimulus) and methacholine-induced (a direct acting stimulus) airway constriction in Basenji-Greyhound dogs. Prior to aerosol challenge, pulmonary resistance (R_L) and dynamic compliance (C_{dyn}) were not different during control (thiopental), halothane, and isoflurane anesthesia. R_L was 1.93 ± 0.15 (mean \pm SE), 1.81 ± 0.23 and 2.1 ± 0.12 cm $H_2O \cdot l^{-1} \cdot s$ during thiopental, halothane, and isoflurane, respectively. C_{dyn} was 116 ± 8 , 106 ± 16 and 110 ± 9 ml/cm H_2O during thiopental, halothane, and isoflurane anesthesia, respectively. In control studies (thiopental), *Ascaris* antigen increased R_L by 9.4 ± 2.44 fold and decreased C_{dyn} to $0.29 \pm .02$ times the prechallenge value. Both halothane and isoflurane anesthesia significantly attenuated the increase in R_L provoked by *Ascaris* antigen challenge and halothane significantly attenuated the decrease in C_{dyn} . During halothane and isoflurane anesthesia, *Ascaris* antigen increased R_L by 3.8 ± 0.96 and 3.5 ± 0.57 fold, respectively, and decreased C_{dyn} to 0.48 ± 0.09 and $0.38 \pm .07$ times the prechallenge value, respectively. In control studies (thiopental anesthesia), methacholine produced dose-related increases in R_L and decreases in C_{dyn} . Both halothane and isoflurane attenuated the increase in R_L and the decrease in C_{dyn} provoked by methacholine with halothane being more effective than isoflurane with regards to C_{dyn} . The mechanism of action of halothane and isoflurane on airways is similar and complex, involving depression of airway reflexes as well as direct effects on airway smooth muscle. (Key words: Airway: resistance. Anesthetics, volatile: halothane; isoflurane. Complications: asthma. Lung: Compliance.)

IN THE ANESTHETIC MANAGEMENT of patients with bronchospastic disease, the aim of the anesthesiologist is to prevent the development of airway constriction. Potent inhalation anesthetics may accomplish this indirectly by blocking airway reflexes or directly by relaxing the smooth muscle of the airway. The action of anesthetics on airway reflexes has been studied for decades and the ability of potent inhalation anesthetics to block a wide variety of airway reflexes has been well established.¹⁻³ On the other hand, very little is known about direct effects of anesthetics on airways *in vivo*. Clinically useful concentrations of halothane are relatively ineffective at relaxing tracheal smooth muscle *in vitro*⁴—im-

plying that in the intact animal or human, the major bronchodilator action of halothane is mediated by the depression of airway reflexes.

Airway constriction can be provoked in animal models by aerosol challenge with many agents that elicit airway constriction by specific mechanisms. Aerosol challenge with antigen provokes airway constriction indirectly by activating airway reflexes, as well as directly, by releasing mediators that constrict airway smooth muscle.^{5,6} Aerosol challenges with cholinergic agonists, such as methacholine, provoke airway constriction directly by stimulating cholinergic receptors located on the airway smooth muscle with no reflex (indirect) effects.⁷

To determine whether potent inhalation anesthetics have other than reflex (indirect) effects *in vivo*, we compared the ability of anesthetics to prevent the development of airway constriction provoked by *Ascaris* antigen and methacholine in the Basenji-Greyhound (BG) dog model of asthma. Moreover, we compared two inhalation anesthetics, halothane and isoflurane with thiopental, both prior to, and following aerosol challenge, to determine if these mechanisms are a common property of many potent inhalation anesthetics or are distinctive of halothane.

Methods

Seven Basenji-Greyhound dogs, ranging in age from 1 to 3 years, and weighing 16 to 22 kg, were subjects in these studies. The dogs were not premedicated and were anesthetized in the standing position, supported by a sling. After induction of anesthesia with intravenous thiopental (12 mg/kg), the dogs were paralyzed with succinylcholine, intubated with a cuffed endotracheal tube of 8.5 or 9 mm (internal diameter), and ventilated with 100 per cent oxygen. An esophageal balloon (Dynasciences, Blue Bell, Pennsylvania) was placed in the esophagus and positioned at the point where recorded end-expiratory pressure was lowest. The balloon contained 0.8 ml air. A separate catheter connected to suction was placed in the esophagus to keep it empty of air and liquid. The dogs were ventilated with a piston-type ventilator (Harvard Apparatus, Millis, Massachusetts) set to deliver a tidal volume of 400 ml at a frequency of 15/min.

Transpulmonary pressure (P_{ip}) was measured with a differential pressure transducer (Hewlett-Packard 270, Waltham, Massachusetts) connected to the esophageal balloon and to a needle inserted in the endotracheal tube.

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Airflow (\dot{V}) was measured with a pneumotachograph head (Hewlett-Packard 2100, Waltham, Massachusetts) and a differential flow transducer (Hewlett-Packard 4730A, Waltham, Massachusetts). Pressure and flow signals were recorded with a Hewlett-Packard 47601 recorder (Waltham, Massachusetts).

Dynamic pulmonary compliance (C_{dyn}) was calculated by dividing the tidal volume by the absolute difference in transpulmonary pressure at zero flow. Pulmonary resistance (R_L) was calculated using the method of Von Neergaard and Wirz.^{8,9} The elastic component of P_{ip} was subtracted from the total P_{ip} at mid-tidal volume. The remaining P_{ip} was divided by the mid-tidal inspiratory flow rate. Apparatus resistance, determined by ventilating a mechanical lung analog with known parameters, was subtracted from the resulting value to obtain R_L . All volumes were corrected to BTPS. R_L and C_{dyn} were reported as the mean of five consecutive breaths.

For control studies, additional increments of thiopental were administered as needed, which usually occurred at 15-min intervals. After measurement of R_L and C_{dyn} , halothane or isoflurane was administered until a steady state end-tidal anesthesia concentration of 1.5 MAC (MAC is defined as the minimal alveolar concentration required to prevent movement in 50 per cent of animals when painfully stimulated¹⁰) was established. MAC values of halothane and isoflurane in the dog were taken to be 0.87 per cent¹⁰ and 1.48 per cent,¹¹ respectively. End-tidal gases (halothane, isoflurane, oxygen, and CO_2) were sampled continuously using a Perkin-Elmer 1100 mass spectrometer (Pomona, California). The electrocardiogram was monitored throughout using a Tektronix 410[®] monitor (Beaverton, Oregon).

Five of a group of seven animals were used in each set of studies. Each animal served as its own control. At least one week elapsed between successive studies in any one animal. Studies were performed in a random order. Dogs were challenged with aerosols 40 min after the start of administration of inhalation anesthesia—the time needed to establish a reasonably steady state end-tidal anesthetic concentration of 1.5 MAC. Aerosol solutions were made up in distilled water and delivered by a Hudson 3000 nebulizer (Temecula, California) driven by compressed oxygen. The nebulizer delivered aerosol particles with a mass median diameter of 5.7 μM .

A purified extract of *Ascaris* antigen was prepared by Sephadex filtration according to the methods of Mackler *et al.*¹² A dose of 30 μg *Ascaris* protein in 10 ml water was administered over a 10-min period with the nebulizer inserted between the inspiratory limb of a circle anesthesia system and the endotracheal tube. To avoid residual contamination, the circle was changed after completion of the aerosol challenge. R_L and C_{dyn} were mea-

sured immediately at the end of challenge and at 5-min intervals thereafter for 30 min.

Methacholine was administered to the dogs as a series of challenges with increasing drug dose (methacholine bromide 0.075, 0.15, 0.30 mg/ml). Each dose was inhaled for five breaths with a 10-min interval between challenges. An Ayre's T tube was employed and the expiratory port was occluded until an inflation pressure of 15 cmH₂O had been obtained for each of the five breaths. R_L and C_{dyn} were measured immediately following challenge. R_L and C_{dyn} were expressed as absolute values and as the ratio of the postchallenge to the prechallenge values. R_L and C_{dyn} were compared during thiopental, halothane, and isoflurane anesthesia at 5-min intervals following antigen challenge, and at each of the three doses following methacholine challenge by a two-way analysis of variance¹³ and a Student-Newman Kuels test for multiple comparisons.¹⁴ The level of statistical significance used throughout was 0.05.

Results

Prior to *Ascaris* aerosol challenge, R_L and C_{dyn} were not significantly different during thiopental, halothane, and isoflurane anesthesia. R_L averaged 1.93 ± 0.15 (mean \pm SE), 1.81 ± 0.25 , and 2.10 ± 0.12 cmH₂O \cdot l⁻¹ \cdot s during thiopental, halothane, and isoflurane anesthesia, respectively. C_{dyn} averaged 116 ± 8 , 107 ± 0.16 , and 110 ± 9 ml/cm H₂O during thiopental, halothane, and isoflurane anesthesia, respectively. Increasing concentrations of anesthesia with halothane and isoflurane did not significantly increase or decrease R_L or C_{dyn} .

Ascaris antigen challenge produced changes in R_L and C_{dyn} , which were maximal 5-min after the end of antigen aerosol administration (fig. 1). During thiopental anesthesia (control studies), R_L increased by 9.4 ± 2.44 times the prechallenge value while C_{dyn} decreased to $0.29 \pm .02$ times the prechallenge value (fig. 1). Both 1.5 MAC halothane and 1.5 MAC isoflurane attenuated the increase in R_L provoked by antigen challenge ($P < 0.05$). There was no significant difference in R_L between isoflurane and halothane. During halothane anesthesia, R_L increased 3.8 ± 0.96 fold and during isoflurane anesthesia, R_L increased 3.5 ± 0.57 fold (fig. 1). Halothane significantly attenuated the decrease in C_{dyn} provoked by antigen challenge. The attenuation of C_{dyn} during isoflurane anesthesia experiments was not statistically significant. C_{dyn} decreased to $0.48 \pm .09$ and $0.38 \pm .07$ times the prechallenge C_{dyn} during halothane and isoflurane anesthesia, respectively (fig. 1).

During thiopental anesthesia (control studies), methacholine produced dose-related increases in R_L (fig. 2) and decreases in C_{dyn} (fig. 2). Both halothane and isoflurane

(1.5 MAC) significantly attenuated the increases in R_L provoked by methacholine. Although a statistically significant difference in R_L was not noted during isoflurane and halothane anesthesia, R_L was lower during halothane compared with isoflurane anesthesia in all five dogs at 0.075 and 0.3 mg/ml methacholine and in four of five dogs at 0.15 mg/ml methacholine. Both halothane and isoflurane attenuated the decrease in C_{dyn} provoked by methacholine (fig. 2). Halothane was significantly more effective ($P < 0.05$) than isoflurane (fig. 2). End-tidal CO_2 averaged 4.4 per cent during the studies. No ECG abnormalities were observed during the studies.

Discussion

The mechanism of action of potent inhalation anesthetics on airways is complex and involves depression of airway reflexes (indirect effects) as well as direct effects on airway smooth muscle.

A number of mechanisms interact to produce airway constriction after antigen challenge in animal models of acute asthma. Direct bronchoconstriction results from the effects of mediators released by sensitized cells directly on airway smooth muscle, whereas in reflex broncho-

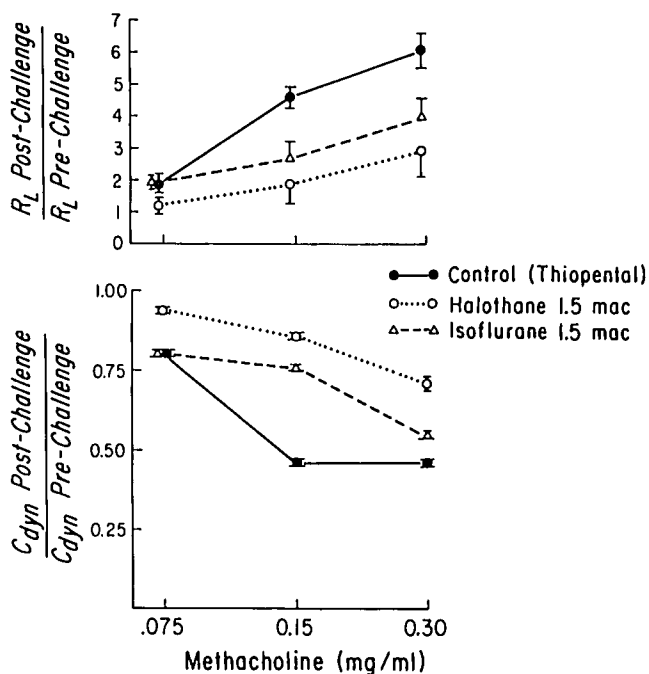


FIG. 2. Increase in R_L and decrease in C_{dyn} following incremental doses of methacholine during thiopental, halothane, and isoflurane anesthesia.

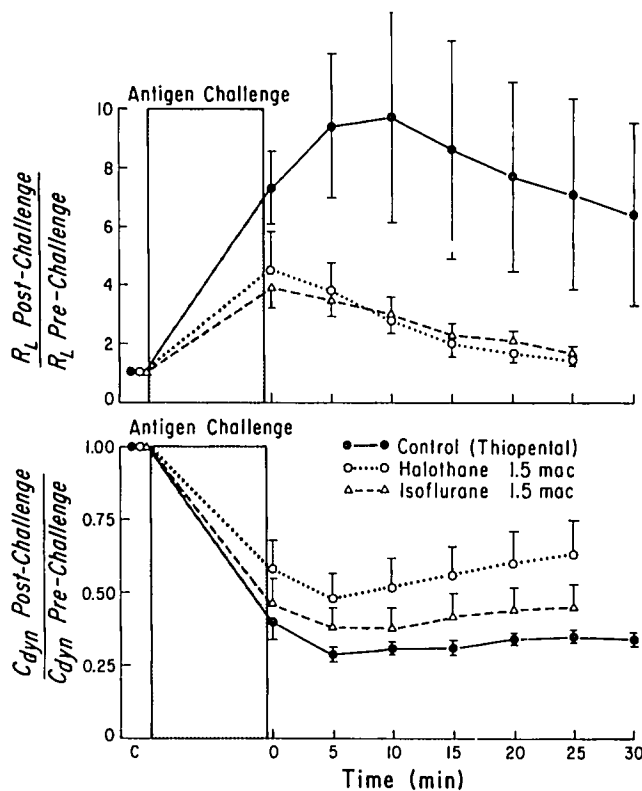


FIG. 1. Increase in R_L and decrease in C_{dyn} following *Ascaris* antigen challenge during thiopental, halothane, and isoflurane anesthesia. Abscissa shows elapsed time from end of antigen administration.

constriction, these chemical mediators first stimulate subepithelial irritant receptors with subsequent reflex bronchoconstriction.⁶ We have previously demonstrated that in our population of Basenji-Greyhound dogs, the prior administration of intravenous atropine⁵ or lidocaine¹⁵ reduced antigen-induced increases in R_L by approximately one third. Halothane and isoflurane produced a slightly greater effect (about a 50 per cent reduction in the antigen response) suggesting that these anesthetics have effects on airways in addition to blocking reflex pathways. Our studies involving methacholine challenge confirm this, as cholinergic agonists act directly on specific receptors on airway smooth⁷ muscle with little or no reflex effects.⁷ Although it is difficult to interpret changes in dose-response curves in studies involving intact animals, our data suggest that sensitivity of the cholinergic receptor is unaltered by both isoflurane and halothane, but that the subsequent muscle contraction is impaired. Thus, the threshold concentration of methacholine required to initiate contraction (0.075 mg/ml) is similar in control (thiopental) and in halothane- and isoflurane-anesthetized dogs; but the amplitude of contraction is depressed throughout the dose-response curve during halothane and isoflurane anesthesia. The methacholine responses were near maximal at 0.30 mg/ml and were not significantly increased at higher concentrations (0.75 mg/ml). It should be noted that although the pul-

monary response to methacholine was attenuated by 1.5 MAC anesthesia, it was not abolished. Thus, our studies indicate that potent inhalation anesthetics in clinically useful concentrations have a small direct action on airway smooth muscle.

Anesthetics may act on airways by a number of other mechanisms. Anesthetics may conceivably stabilize mast cell membranes and prevent mediator release, and may alter permeability of the bronchial epithelium allowing greater or lesser access to the subepithelial irritating receptors. Our experiments were not designed to look at these mechanisms. In 1967, Klide and Aviado¹⁶ concluded from a study in mongrel dogs that halothane causes bronchodilation by stimulation of beta adrenergic receptors in the airway. These investigators demonstrated a decrease in R_L and an increase in C_{dyn} with increasing concentrations of halothane in mongrel dogs with high baseline airway tone. After pretreatment with beta adrenergic blocking agents (MJ 1999 and nethalide), they could no longer demonstrate decreases in R_L or increases in C_{dyn} with increasing concentrations of drug. We question their interpretation of the results because R_L was lower and C_{dyn} higher in those particular dogs which were beta adrenergically blocked, than in dogs that were unblocked. Beta adrenergic antagonists may have central nervous system depressant effects similar to those produced by local anesthetics, which could have relaxed airway tone before administration of halothane. Therefore, halothane produced no further relaxation.

In our studies, the effects of halothane and isoflurane were compared with thiopental, both prior to aerosol challenge (unstimulated airway) and after challenge (stimulated airway). Thiopental, in doses used in our studies, has little effect on airway reflexes,⁵ or on other mechanisms since changes in R_L and C_{dyn} were similar after challenge in awake and thiopental-anesthetized dogs.¹⁷ Thiopental has been shown to constrict smooth muscle in some species.¹⁸ However, the concentrations needed to produce this effect are higher than achieved in blood during clinical anesthesia.

Neither halothane nor isoflurane altered R_L and C_{dyn} in the unstimulated airway; nor did R_L or C_{dyn} change as anesthetic depth increased. These findings agree with previous studies by Hickey and co-workers¹ and Colgan¹⁹ in intact halothane-anesthetized dogs. Klide and Aviado,¹⁶ on the other hand, found a reduction in R_L in spontaneously breathing dogs, as the inspired halothane concentration increased from 0.5 to 3 per cent; but the initial R_L measured in their studies was two to three times higher than in our studies and studies by others in dogs,^{1,19} suggesting that their animals had airway constriction initially. In contrast, our dogs and most other

dogs have dilated airways in the unstimulated state, and increasing concentrations of anesthesia have no further effect. Humans appear to be similar to the dog in this regard.^{20,21} Increasing concentrations of halothane²⁰ produced no significant change in airway tone. Rehder and co-workers²¹ found isoflurane to be similar to halothane in this regard, although they found a small but significant increase in R_L in the same subjects during isoflurane anesthesia compared to the awake state. However, their anesthetized subjects were intubated, and these investigators did not separate the reflex effects of the endotracheal tube and isoflurane on R_L . The constriction of airways distal to the endotracheal tube in intubated subjects recently described by Gal²² could well be responsible for the increase in R_L in their subjects.

Both halothane and enflurane have been shown to be effective at reversing antigen-induced bronchoconstriction in experimental asthma in Basenji-Greyhound dogs.²³ The ability of isoflurane to either prevent or reverse airway constriction *in vivo* has not, to our knowledge, been previously studied. Because isoflurane is less depressant to the cardiovascular system than halothane or enflurane,²⁴ one may speculate that it may be of particular advantage in asthmatic patients with limited cardiac reserve whose airways require a higher concentration of halothane or enflurane than their heart will tolerate. Moreover, isoflurane, like enflurane, has a higher arrhythmogenic threshold to catecholamines than halothane,²⁵ thereby decreasing the incidence of life-threatening arrhythmias.

There was no significant difference in the ability of halothane and isoflurane to prevent increases in R_L . There were, however, differences in C_{dyn} . Halothane (1.5 MAC) was more effective than isoflurane in preventing the decrease in C_{dyn} provoked by both antigen and methacholine-aerosol challenge. Because C_{dyn} is a function of a number of physiologic factors, including parenchymal distensibility, airway patency, and the uniformity of distribution of inspired air,⁶ the differences between halothane and isoflurane are difficult to interpret. Moreover, one can never be certain that 1.5 MAC of one anesthetic produces the same depressant effects as 1.5 MAC of another anesthetic or that the published MAC of anesthetics in mongrel dogs is similar in Basenji-Greyhound dogs.¹⁰

The Basenji-Greyhound dog model of asthma used in these studies appears to mimic symptomatic asthma in humans more closely than previously described animal models with respect to the changes in lung volumes following challenge,²⁶ the magnitude of airway constriction,²⁷ and the presence of nonspecific airway hyperreactivity.²⁷ These studies in the dog may not necessarily be applicable to humans but suggest that both halothane

and isoflurane may be effective in preventing airway constriction in humans and that their mechanism of action involves depression of reflex pathways, as well as direct effects on airway smooth muscle.

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