

Sevoflurane and Isoflurane Protect against Bronchospasm in Dogs

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Background: Halothane and isoflurane have been shown to be effective in reversing bronchoconstriction; however, the effects of sevoflurane have not been well defined. We studied whether sevoflurane, compared with isoflurane, attenuates bronchospasm in dogs.

Methods: Twenty-four dogs sensitized to *Ascaris suum* were assigned to three groups: control (n = 8), sevoflurane (n = 8), or isoflurane (n = 8). In all dogs, anesthesia was induced with pentobarbital. In the sevoflurane and isoflurane groups, the volatile anesthetics were administered at an end-tidal anesthetic concentration of 1 MAC throughout the study. After measurement of pulmonary resistance (R_L) and dynamic pulmonary compliance (C_{dyn}) at baseline, *A. suum* antigen was administered intravenously into the systemic circulation to induce anaphylaxis, and R_L and C_{dyn} were recorded continuously for 120 min after antigen challenge.

Results: Effects on R_L and C_{dyn} were maximal 5 min after the start of systemic administration of antigen in all groups. Both 1 MAC sevoflurane and 1 MAC isoflurane significantly attenuated the increase in R_L provoked by antigen challenge, but the attenuation from 10 to 15 min after challenge in the sevoflurane group was not significantly different from that in the control group. There was no significant difference in R_L between sevoflurane and isoflurane. For both sevoflurane and isoflurane, attenuation of the decrease in C_{dyn} was not statistically significant. There was no significant difference in C_{dyn} between sevoflurane and isoflurane.

Conclusions: Sevoflurane is as effective as isoflurane in attenuating bronchoconstriction associated with anaphylaxis in dogs. Sevoflurane may be a useful alternative to halothane, enflurane, or isoflurane in the treatment of bronchospasm in asthma or anaphylaxis. (Key words: Airway; bronchocon-

striction; pulmonary resistance. Anaphylaxis. Anesthetics, volatile: isoflurane; sevoflurane.)

VOLATILE anesthetics have been shown to be effective in preventing and reversing bronchoconstriction¹ and appear to be effective in the treatment of asthma refractory to conventional therapy, including β -adrenergic agonists, methylxanthines, and corticosteroids.² Halothane and isoflurane have been used for the treatment of bronchospasm and the maintenance of anesthesia in asthmatic patients.²⁻⁶

Halothane, enflurane, and isoflurane attenuate antigen-induced bronchoconstriction in sensitized canine airways.^{7,8} However, the effects of sevoflurane, a new volatile anesthetic, on bronchoconstriction have not been clearly defined. The current study was designed to investigate whether sevoflurane attenuates bronchospasm in a canine model of anaphylaxis compared with the results of experiments with isoflurane.

Materials and Methods

The study protocol was approved by the Animal Care Committee of our institution. The study involved 24 randomly selected mongrel dogs (body weight 10–15 kg). None of these animals was immunized with a specific antigen, but all had positive skin-test reactivity (>10 mm induration at 15 min) to the intradermal injection of 0.1 ml 1:100 dilution of an aqueous extract of *Ascaris suum* antigen with an N_2 concentration of 2.5 mg · ml⁻¹ (Greer Laboratories, Columbia, SC). The dogs were anesthetized with intravenous pentobarbital (30 mg · kg⁻¹), and their tracheas were intubated with a cuffed endotracheal tube with an internal diameter of 8.5 mm. The dogs were paralyzed with pancuronium (0.1 mg · kg⁻¹). Ventilation was maintained with a piston ventilator (Harvard, Natick, MA) with 100% O₂, and the tidal volume was adjusted to maintain an end-tidal CO₂ level of 35–40 mmHg and a respiratory rate of 8–15 breaths · min⁻¹.

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An esophageal balloon (Nihon Kodan, Tokyo, Japan) was placed in the esophagus and positioned at the point where the recorded end-expiratory pressure was at a minimum. The balloon contained 0.2 ml air. Transpulmonary pressure (P_{tp}) was measured with a differential pressure transducer (TP-603T, Nihon Kodan) with one side connected to the esophageal catheter and the other side attached to an orifice in the side of the proximal end of the endotracheal tube. Air flow was measured with a pneumotachograph head (Fleisch type, TV-112T, Nihon Kodan) and a differential flow transducer (TP-602T, Nihon Kodan). Tidal volume was obtained by continuous electrical integration of the flow signal. Pressure, flow, and volume signals were recorded with a thermal tip recorder (Omnirecorder 8M15, NEC San-ei, Tokyo, Japan). Dynamic pulmonary compliance (C_{dyn}) was calculated by dividing the tidal volume by the absolute difference in P_{tp} at zero flow. Pulmonary resistance (R_L), which is the sum of airway resistance and lung tissue resistance, was calculated by the method of Amdur and Mead.⁹ The elastic and flow-resistive components of P_{tp} can be separated by relating the P_{tp} to specific points in the volume and flow rate cycles. At points of equal lung volume, differences in P_{tp} reflect the resistance to air flow in lung tissues and airways. R_L was calculated by dividing the difference in P_{tp} by the difference in flow between points of equal volume in the respiratory cycle. C_{dyn} and R_L are reported as the mean values for three consecutive breaths.

Experimental Protocol

Each of 24 dogs was assigned to one of three groups: 8 dogs served as a control group; 8 dogs received sevoflurane; and 8 dogs received isoflurane. Dogs in the control group received 10 mg·kg⁻¹ of pentobarbital after initiation of controlled ventilation and then by 5 mg·kg⁻¹ pentobarbital every 45–60 min to maintain adequate anesthesia. Dogs in the sevoflurane and isoflurane groups did not receive additional pentobarbital during the study. Pancuronium was administered every 60 min. The volatile anesthetic was started immediately after intubation and administered until a steady-state end-tidal anesthetic concentration of 1 MAC had been established. MAC values of sevoflurane and isoflurane in dogs were taken to be 2.4% and 1.4%, respectively.^{10,11} End-tidal anesthetic concentration was monitored continuously with a respiratory gas monitor (5250 RGM, Ohmeda, Madison, WI). Systolic, diastolic, and mean arterial pressures were monitored with a microanometer-tipped catheter (7-French, 45326,

Toyoda, Tokyo, Japan) placed in the abdominal aorta *via* the right femoral artery, and two flow-directed thermodilution pulmonary artery catheters (one in a peripheral pulmonary artery and one in the right atrium) were inserted *via* the external jugular vein. Right atrial and pulmonary pressures and the surface electrocardiogram were monitored. All signals were monitored continuously using a multichannel polygraph (360, NEC San-ei). Lactated Ringer's solution was infused into the right femoral vein to maintain a right atrial pressure equal to the prechallenge value throughout the experiment. Temperature was monitored with an esophageal thermometer and maintained at 35–37°C with an external heating pad. After baseline values were measured, 0.5 ml (0.125 mg) aqueous extract of *A. suum* was administered over a 30-s period into the systemic circulation to induce anaphylaxis. R_L and C_{dyn} were recorded continuously for the subsequent 120 min. R_L and C_{dyn} were expressed as the ratio of postchallenge to prechallenge values.

An experimental design using three groups of animals, rather than a protocol in which each animal served as its own control, was selected because studies have shown that after repeated challenge with antigen, the anaphylactic reaction may vary or may not occur at all because of desensitization.^{12,13}

All data are expressed as means ± SEM for eight dogs. R_L , C_{dyn} , and hemodynamic parameters during anesthesia with each anesthetic were compared for 120 min after challenge with *A. suum* antigen by a two-factor analysis of variance and a single-factor analysis of variance for multiple comparisons, followed by the Fisher's protected least significant difference test. A value of $P < 0.05$ was considered statistically significant.

Results

Baseline R_L and C_{dyn} values did not differ significantly between groups before *A. suum* challenge. Baseline R_L values were 4.00 ± 0.23 , 3.85 ± 0.23 , and 3.84 ± 0.15 cmH₂O·l⁻¹·s in groups C, S, and I, respectively. Baseline C_{dyn} values were 47.68 ± 2.70 ml·cmH₂O⁻¹ in all dogs. Antigen challenge resulted in changes in R_L and C_{dyn} that were maximal 5 min after the start of administration in all three groups (figs. 1 and 2). In the control group, R_L significantly increased to 9.4 ± 1.97 times the prechallenge value, whereas C_{dyn} significantly decreased to 0.45 ± 0.06 times the prechallenge value (figs. 1 and 2). R_L values during 1 MAC

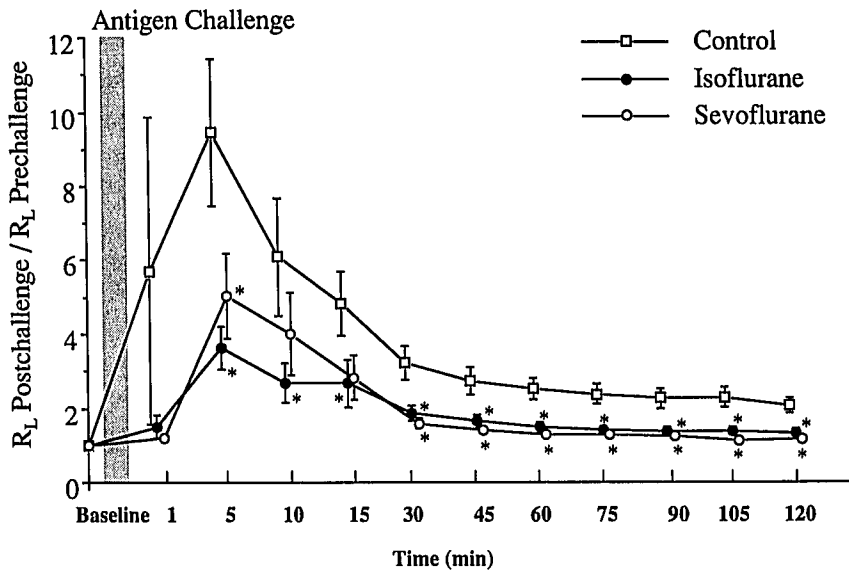


Fig. 1. Changes in pulmonary resistance (R_L) after systemic *Ascaris suum* antigen challenge during pentobarbital anesthesia (control group), sevoflurane anesthesia at 1 MAC, or isoflurane anesthesia at 1 MAC. Shaded area = period of antigen challenge. * $P < 0.05$ versus control group.

sevoflurane anesthesia differed significantly from those observed during pentobarbital anesthesia (control group) from 5 min after the start of administration of antigen, except for the period from 10 to 15 min after challenge, and R_L values during 1 MAC isoflurane anesthesia differed significantly from those in the control group at all measured times from 5 min after the start of administration (fig. 1). There were no significant differences in R_L between sevoflurane and isoflurane. During sevoflurane anesthesia, R_L increased to 5.02 ± 1.15 times the prechallenge value, and during isoflu-

rane anesthesia, R_L increased to 3.64 ± 0.57 times the prechallenge value (fig. 1). For both sevoflurane and isoflurane, the attenuation of the decrease in C_{dyn} was not statistically significant. C_{dyn} decreased to 0.58 ± 0.07 and 0.60 ± 0.05 times the prechallenge value during sevoflurane and isoflurane anesthesia, respectively (fig. 2). No significant differences were observed between sevoflurane and isoflurane with regard to changes in C_{dyn} .

The heart rate and pulmonary arterial pressure in the three groups were comparable to prechallenge values.

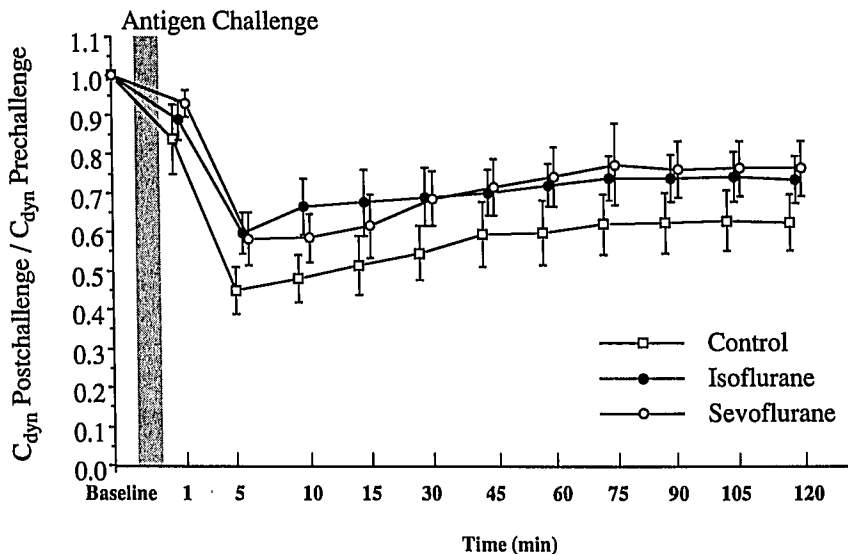


Fig. 2. Changes in dynamic pulmonary compliance (C_{dyn}) after systemic *Ascaris suum* antigen challenge during pentobarbital anesthesia (control group), sevoflurane anesthesia at 1 MAC, or isoflurane anesthesia at 1 MAC. Shaded area = period of antigen challenge.

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Antigen challenge resulted in changes in arterial pressure, with a maximal decrease 5 min after the start of administration in all three groups, and changes in mean arterial pressure in the pentobarbital group (control) were significantly higher than those in the sevoflurane or isoflurane groups at all measured times from 60 min after the start of administration of antigen. There were no significant differences in heart rate, right atrial pressure, mean pulmonary arterial pressure, or mean arterial pressure between the sevoflurane and isoflurane groups.

Discussion

The results of this study show that sevoflurane significantly attenuated the increase in R_L produced by systemic challenge with *A. suum* antigen. There were no significant differences in the ability of sevoflurane and isoflurane to prevent increases in R_L during maximal bronchoconstriction. Neither isoflurane nor sevoflurane significantly attenuated the decrease in C_{dyn} during anaphylaxis. The changes observed in R_L and C_{dyn} during isoflurane anesthesia were in agreement with the findings of Hirshman *et al.*⁸ The differences between the changes in R_L and C_{dyn} provoked by anesthetics are difficult to interpret. When simultaneous measurement of R_L and C_{dyn} are made, changes in R_L primarily reflect changes in the central airways, whereas changes in C_{dyn} reflect changes in the peripheral airways.^{14,15} Because peripheral bronchoconstriction may be influenced more easily than central bronchoconstriction by several other physiologic factors, including hemodynamic changes and parenchymal distensibility, it is possible that changes in C_{dyn} may not be apparent compared with those in R_L . Sevoflurane at a concentration of 1 MAC did not completely attenuate the increase in R_L . Halothane, enflurane, and isoflurane attenuate the increase in R_L in a dose-dependent manner,^{15,16} and a recent study by Brown *et al.* of high-resolution computed tomography also showed that halothane and isoflurane dilate histamine-constricted airways in a dose-dependent manner, and that at low concentrations (0.6 and 1.1 MAC) halothane is a more effective bronchodilator than is isoflurane at equivalent MAC.¹⁷ Isoflurane and halothane have similar mechanisms of inhibiting collateral airway constriction, despite their different chemical structures.¹⁶ In this regard, sevoflurane, the chemical structure of which differs from that of isoflurane or halothane, at a

concentration greater than 1 MAC is likely to attenuate the increase in R_L .

In the current study the effects of sevoflurane and isoflurane on bronchospasm were compared with those of pentobarbital (control group). Because pentobarbital at concentrations similar to those found in plasma during anesthesia inhibits bronchoconstriction in dogs,^{18,19} the pentobarbital used in the control group may have attenuated bronchoconstriction associated with anaphylaxis. However, because the other two anesthetics significantly attenuated bronchospasm compared with pentobarbital (control), pentobarbital, even though it may act as a bronchodilator, had little effect on the results of this study. Because the cardiovascular responses to antigen challenge were similar in all three groups, although isoflurane and sevoflurane caused greater depression of the cardiovascular system than did pentobarbital, hemodynamic changes may have had little effect on changes in R_L in response to the antigen.

To investigate the effects of anesthetics on antigen-induced bronchoconstriction, Hirshman *et al.*^{7,8} and Hermens *et al.*²⁰ studied antigen-induced bronchoconstriction in experimental asthmatic models in Basenji-Greyhound dogs. In the current study, we investigated the effects of anesthetics on bronchoconstriction in an anaphylaxis model because in dogs with positive cutaneous reactivity to *A. suum* antigen, spontaneous hypersensitivity reactions similar to those in human anaphylaxis develop, and a circulating antibody seen in dogs appears to belong to a class of immunoglobulins analogous to human immunoglobulin E.²¹ Intravenous administration of *A. suum* antigen to the dog is a suitable model for studying the biochemical and physiologic mechanisms of anaphylaxis,²² and thus several investigators have used this model to study the cardiopulmonary, immunologic, and pharmacologic mechanisms of acute systemic immunoglobulin E-mediated hypersensitivity reactions.²²⁻²⁶ The responses that occur in canine anaphylaxis are characterized by significant changes in R_L and C_{dyn} when systemic anaphylaxis is induced.^{24,25}

The mechanisms by which inhalational anesthetics increase airway caliber and prevent or reverse bronchospasm are complex but primarily involve inhibition of neural pathways.^{15,16} Halothane, enflurane, and isoflurane inhibit the increase in R_L provoked by vagal nerve stimulation when administered at equivalent multiples of the MAC and appear to have similar mechanisms of action despite their different chemical structures.^{1,15} Hirshman *et al.* concluded from a study using

a Basenji-Greyhound dog model of asthma that the mechanism of action of isoflurane and halothane on the airway involves depression of reflex pathways as well as a direct effect on airway smooth muscle.⁸ The current study was not designed to investigate the mechanism of sevoflurane on bronchoconstriction. Lazarus *et al.* concluded from a study with the same anaphylaxis model as in the current study that narrowing of the airways is the result of acute smooth muscle contraction rather than the accumulation of edema or mucus during the 5-min period after antigen challenge, because increased R_L and decreased C_{dyn} in anaphylaxis were reversed by β -adrenergic agonists.²² Sevoflurane produced a reduction of about 50% in R_L 5 min after antigen challenge, when the most severe reaction occurred, suggesting that the effect of sevoflurane on the airways is due at least partially to a direct effect on airway smooth muscle.

We conclude that sevoflurane is as effective as isoflurane in attenuating bronchoconstriction associated with anaphylaxis. Sevoflurane may be a useful alternative to halothane, enflurane, or isoflurane in the treatment of bronchospasm in asthma or anaphylaxis.

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