The Protective Effects of Volatile Anesthetics Against the Bronchoconstriction Induced by an Allergic Reaction in Sensitized Rabbit Pups

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BACKGROUND: Volatile inhaled anesthetics exert a differential protective effect against bronchospasm development after cholinergic stimulation. However, their ability to inhibit the adverse respiratory consequences of an anaphylactic reaction after exposure to an allergen has not been characterized. We therefore compared the abilities of isoflurane, sevoflurane, and desflurane to prevent the lung constriction induced by an allergic reaction in a pediatric model of an anaphylactic reaction.

METHODS: Low-frequency respiratory input impedance (Zrs) was measured in 4 groups of ovalbumin (OVA)-sensitized 5-week-old rabbit pups anesthetized with midazolam (group IV) and with inhaled isoflurane (group ISO), sevoflurane (group SEVO), or desflurane (group DES) at 1 minimum alveolar concentration. Zrs was measured under baseline conditions and after an anaphylactic lung response provoked by IV allergen injection (OVA 1 mg), during which the changes in airway resistance (Raw), tissue damping (G), and elastance obtained from Zrs were followed for 15 minutes.

RESULTS: Allergen provocation generated immediate severe bronchoconstriction, with no statistically significant difference in Raw increase among the groups in the first 3 minutes. Conversely, the inhalation of volatile anesthetics accelerated the recovery from the allergen-induced bronchoconstriction, particularly in group SEVO where the Raw was significantly lower than that in group IV 4 minutes after the allergen challenge. These changes were paralleled by significant elevations in G in all groups, with a significantly more pronounced deterioration in the animals in group DES. The anesthetic regimen did not statistically significantly affect the sustained increases in elastance after OVA injections.

CONCLUSIONS: Our results reveal the lack of potential of the commonly used volatile anesthetics to inhibit the most severe acute phase of the constrictor response to allergen after anaphylaxis in both the central airway and peripheral lung compartments. Inhalation of volatile anesthetics, particularly sevoflurane, promotes an earlier easing of the bronchospasm; this beneficial profile may be advantageous in children with atopic lung diseases. (Anesth Analg 2013;XX:XX–XX)

The incidence of allergic reactions during anesthesia is currently increasing worldwide.[1–3] These allergic reactions may increase perioperative morbidity, which may result in life-threatening symptoms in the event of anaphylaxis.[1,4,5] Besides the severe cardiovascular collapse that is often encountered, bronchospasm may worsen the level of oxygenation and compromise the efficacy of resuscitation. Although bronchospasm is often encountered in anesthesia, its cause may be misinterpreted because this symptom may be the sole expression of an allergic reaction.[5] Moreover, we recently demonstrated that the intraoperative incidence of bronchospasm is increased in children with airway susceptibilities subsequent to allergic diseases such as asthma, eczema, and atopy.[6]

We have previously reported that volatile anesthetic drugs exert a protective effect against the stimuli induced by a nonspecific constrictor, methacholine (MCh), in naïve[7] and allergically sensitized animals.[8,9] Although MCh administration mimics bronchoconstriction subsequent to cholinergic stimulation (i.e., tracheal intubation and light anesthesia), provocation with MCh is not a suitable method with which to mimic an allergic reaction in the lungs, despite the fact that allergic reactions during anesthesia are increasingly encountered. The effects of allergic sensitization with ovalbumin (OVA) and subsequent provocation with the allergen resemble those of an anaphylactic reaction with mast cell degranulation and the subsequent release of endogenous mediators, such as histamine, bradykinin, and tachykinin, leading to bronchoconstriction.[8,10] Despite the availability of this allergic model, the efficacy of the various volatile anesthetics in inhibiting the adverse respiratory consequences of an allergic anaphylactoid reaction has not been studied.

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A major difference has been demonstrated between a nonspecific bronchoconstrictor challenge with MCh and an allergic reaction, the MCh-induced bronchospasm occurring primarily in the central conducting airways,[7,8,11] whereas an allergic reaction affects primarily the lung periphery.[12] Because volatile anesthetics may act differentially on the central and peripheral lung compartments,[13,14] we hypothesized that they may display differences in efficiency in protecting against the lung function impairment produced after exposure to an allergen. To test this hypothesis, we sought to compare the abilities of volatile inhaled anesthetics used commonly in clinical practice to prevent lung constriction development after an allergic reaction.

METHODS

Experimental Animals

After approval by the Experimental Ethics Committee of the University of Geneva (No. 09-44) and the Animal Welfare Committee of the Canton of Geneva, Switzerland (No. 1051-3543-2), the experiments were performed with 5-week-old white New Zealand rabbit pups (weights ranging from 392 to 995 g) of either sex. The treatment of all experimental animals adhered to the ethical guidelines throughout the entire study period, and the study was conducted in a manner that did not inflict any unnecessary pain or discomfort on the animals, as outlined by the United States Public Health Service Policy on Humane Care and Use of Laboratory Animals and the Guide for the Care and Use of Laboratory Animals (1996), prepared by the National Academy of Sciences' Institute for Laboratory Animal Research.

Ovalbumin Sensitization

All animals were sensitized over a 1-month period before the start of the experimental protocol, as detailed previously.[15] Briefly, intraperitoneal injections of a solution containing 0.1 mg OVA (chicken egg white; Sigma-Aldrich, Munich, Germany) and 10 mg aluminium hydroxide as adjuvant (Sigma-Aldrich) were administered at 1 and 3 weeks of age. At the age of 4 weeks, the animals were exposed to aerosolized OVA (10 mg/mL, for a 20-minute period) daily on 5 consecutive days before the experiments, using an ultrasonic nebulizer (Syst'am LS290; SYST'AM, Villeneuve sur Lot, France).

Animal Preparations

The animals were premedicated with an IM injection of xylazine (5 mg/kg). Anesthesia was then induced with an IV injection of xylazine (3–6 mg/kg) and midazolam (0.3 mg/kg) via an ear vein. The rabbits were next tracheotomized with a polyethylene cannula (2.5 mm internal diameter; Portex, Hythe, UK), and their lungs were mechanically ventilated (Maquet Servo-i Ventilator System V4.0, Maquet, Solna, Sweden) with a tidal volume of 7 to 9 mL/kg, at a frequency of 50/min and an inspired oxygen fraction of 0.3 in air; a positive end-expiratory pressure of 3 cmH_2O was maintained. A continuous IV infusion of midazolam (1 mg/kg/h) with fentanyl (40 μg/kg/h) and atracurium (1 mg/kg/h) was then administered via the ear vein for the maintenance of anesthesia throughout the study. The carotid artery was prepared surgically in a sterile manner and then cannulated (22-gauge catheter; Abbocath-T, Abbott, Sligo, Ireland) for blood sampling and continuous arterial blood pressure monitoring with a calibrated pressure transducer (model 156 PC 06-GW2; Honeywell, Zürich, Switzerland). The femoral vein was prepared for the IV OVA challenges. Airway pressure was measured continuously with a calibrated pressure transducer (model DP 45; Validyne, Northridge, CA). Rectal temperature was monitored with a temperature sensor (Homeothermic Monitor; Harvard Apparatus, Kent, UK) and was maintained at 38°C ± 0.5°C by a heating pad Homeothermic Blanket System (Harvard Apparatus). Airway and arterial blood pressures (including systolic, diastolic, and mean arterial pressures [MAPs]), heart rate, and rectal temperature were displayed and stored at a sampling rate of 50 Hz via an analog/digital interface converter (Biopac, Santa Barbara, CA) on a computer. Arterial blood samples were analyzed (i-STAT System; Abbott, Abbott Park, IL), and the variables of mechanical ventilation were adjusted to maintain normal gas exchange if necessary. The concentrations of O_2, CO_2, and the volatile anesthetic were monitored throughout the study (Ultima; Datex/Instrumentarium, Helsinki, Finland).

Measurement of Respiratory Mechanics

The animals were studied in the supine position. The input impedance of the respiratory system (Zrs) was measured at end-expiration with forced oscillations. The tracheal cannula was connected to a loudspeaker-in-box system at end-expiration that was pressurized to 3 cmH_2O to keep the mean transpulmonary pressure constant during measurements. The loudspeaker delivered a small-amplitude (<1 cmH_2O) pseudorandom signal (15 noninteger multiples between 0.5 and 21 Hz). Lateral pressures were measured at the loudspeaker end (P_1) and the distal end (P_2) of the wave tube with miniature sidearm transducers (ICS 33NA00D; ICSensors Inc., Milpitas, CA). These signals were low-pass filtered (<25 Hz) and digitized at a sampling frequency of 128 Hz. The pressure transfer function (P_1/P_2) was created by fast Fourier transformation from the 8-second recording. Zrs was computed from the pressure transfer function as the load impedance of the wave tube[16] by using the transmission line theory:[17]

$$Zrs = Z_0 \times sh(\gamma L) / [P_1 / P_2 - ch(\gamma L)]$$

where Z_0 is the characteristic impedance of the wave tube, and γ is the complex propagation wave number; these were determined from the geometrical parameters of the wave tube, the material constants of the tube, and the gas in it.

To separate the airway and tissue mechanics, a model containing a frequency-independent resistance (Raw) and inertance (Iaw) in series with a constant-phase tissue model[18] including tissue damping (G) and elastance (H) was fitted to the Zrs spectra by a computer algorithm that minimizes the differences between the measured and modeled impedance values:

$$Zrs = Raw + j\omega Iaw + (G - jH)/\omega^{\alpha}$$

where j is the imaginary unit, ω is the angular frequency ($2\pi f$) and $\alpha = 2/\pi \arctan(H/G)$. The data at frequencies coinciding with the heart rate and its harmonics were often corrupted, as evidenced by poor coherence and a high SD,

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and they were omitted from the model fitting. When this model is fitted to Zrs spectra, the parameter Raw is primarily related to the overall airway geometry, as the contribution of the chest wall to the frequency-independent Newtonian resistance is minor.[19] Similarly, the inertia of the gas in the airways predominates in the parameter Iaw.[19]

Analyses of the Bronchoalveolar Lavage Fluid

After the measurements of respiratory mechanics, bronchoalveolar lavage (BAL) fluid was collected. Nine milliliters of prewarmed (37ºC) sterilized Ca^{2+}, and Mg^{2+}-free Dulbecco's phosphate-buffered saline solution was injected through a small tube introduced into the endothracheal cannula until its tip gently "wedged" against a bronchial wall. The fluid was then slowly suctioned off immediately and stored in a sterile polystyrene tube. This procedure led to the withdrawal of approximately 50% of the injected fluid. The BAL fluid was centrifuged at 500*g* for 10 minutes at 4°C. After removal of the supernatant, the BAL cells in the pellet were suspended in 150 µL of normal saline and 150 µL of 4% formalin. One hundred microliters aliquots were centrifuged at 700 rpm for 7 minutes (Cytospin 4; Cytospin, Shandon, UK), air-dried, and stained with Congo red to facilitate the discrimination of the eosinophils.[20] Total cells and eosinophilic cells were counted in randomly selected areas of the cytospin preparations and were counted at a magnification of ×10 by using Nuclear Quant image analysis software (3DHistech, Budapest, Hungary).

Experimental Protocol

After stable hemodynamic and ventilatory conditions had been attained while the animal's lungs were ventilated at a positive end-expiratory pressure of 3 cmH_2O, 4 or 5 Zrs data epochs were collected at end-expiration while IV anesthesia was maintained. Continuous IV anesthesia was maintained in rabbits in group IV (n = 10), whereas in the other 4 groups anesthesia management was switched to the inhalation of either isoflurane (group ISO, n = 12), sevoflurane (group SEVO, n = 11) or desflurane (group DES, n = 11) at a concentration of 1 minimum alveolar concentration. After equilibration of the volatile drug and the establishment of steady-state anesthetic, hemodynamic, and respiratory conditions, a further set of Zrs data was collected to assess the effects of the volatile drugs on the basal respiratory mechanics. The allergen, OVA, was then injected IV at a dose of 1 mg, and Zrs data were collected at 1-minute interval for 15 minutes.

Statistical Analysis

The scatters in the parameters were expressed by the SEM values. The Lilliefors test was used to test data for normality. The percentage changes in the mechanical parameters were calculated in each protocol group relative to the baseline at characteristic time points of 2, 5, 10, and 15 minutes after the allergen challenges. The effects of the various anesthetic managements on the allergic lung responses were examined by 2-way mixed analysis of variance (ANOVA) models with time as repeated measures (within-subject) factor and group as between-subject factor. The choice of appropriate covariance structure was on the basis of Akaike information criterion measure. The assumption of normality of the residuals and equality of variances was checked. In case of non-normal distribution, a logarithmic transformation was used. In case of nonequal variances, models with different covariance matrices per groups were used. All examined parameters or their log transforms were normally distributed (all $P > 0.11$). Pairwise comparisons were performed on estimated marginal means by considering the presence or absence of interaction, P values were corrected by the Holm-Sidak method. All technically acceptable measurements were included in these analyses resulting in sample sizes of maximum 589 for Raw, Iaw, G, and H and 146 for their percentage changes at the characteristic time points selected. Another 2-way repeated measures mixed model ANOVA was used to test the differences in the MAPs with a sample size of 192 after keeping all technically acceptable readings. One-way ANOVA was used to evaluate the differences in BAL cell counts among the protocol groups. Statistical tests were performed with the significance level set at $P < 0.05$. SigmaPlot version 11 (SigmaPlot, Chicago, IL), and SAS version 9.2 (SAS, Cary, NC) were used in the analyses.

RESULTS

Four rabbits were excluded from the study as a consequence of the nonachievement of successful sensitization (2 each from the SEVO and DES groups). The eosinophilic cell count in these animals remained under 5% after the OVA sensitization, with a complete lack of response to OVA.

The protocol groups exhibited no statistically significant difference in terms of body weight (P = 0.25) or basal systemic hemodynamic (P = 0.14–0.51) or respiratory mechanical parameters (P = 0.51–0.88).

The changes in airway and respiratory tissue mechanical parameters in the 4 protocol groups after allergen administration are illustrated in Figure 1. The injection of the allergen induced marked and statistically significant increases in Raw ($P < 0.001$), G ($P < 0.001$), and H ($P < 0.001$), while the Iaw decreased ($P < 0.001$). The differences in Raw in the various protocol groups were not statistically significantly different in the first 3 minutes after OVA administration ($P > 0.11$ everywhere), and no statistically significant differences were obtained among the protocol groups in H during the entire protocol (P = 0.49). Conversely, the allergen-induced increases in G were statistically significantly higher during desflurane inhalation in the acute phase of the anaphylactic reaction (P = 0.027 at 2 minutes). The presence of the volatile anesthetics facilitated an earlier recovery from the bronchoconstriction induced by OVA than that observed in group IV, particularly for group SEVO where the Raw was statistically significantly lower than that in group IV 4 minutes after the allergen challenge ($P < 0.001$).

The lack of a statistically significant difference in the peak airway responses in the protocol groups (P = 0.72 at 2 minutes) and the earlier decrease in the Raw in the presence of volatile anesthetics, particularly sevoflurane (P = 0.035), were also observed by depicting the relative changes in the mechanical variables relative to the baseline at particular time points after allergen injections (Fig. 2). In group DES, OVA led to an approximately 2-fold larger increase in G at 2 minutes than that in the animals with IV anesthesia, whereas there was no statistically significant difference in G among

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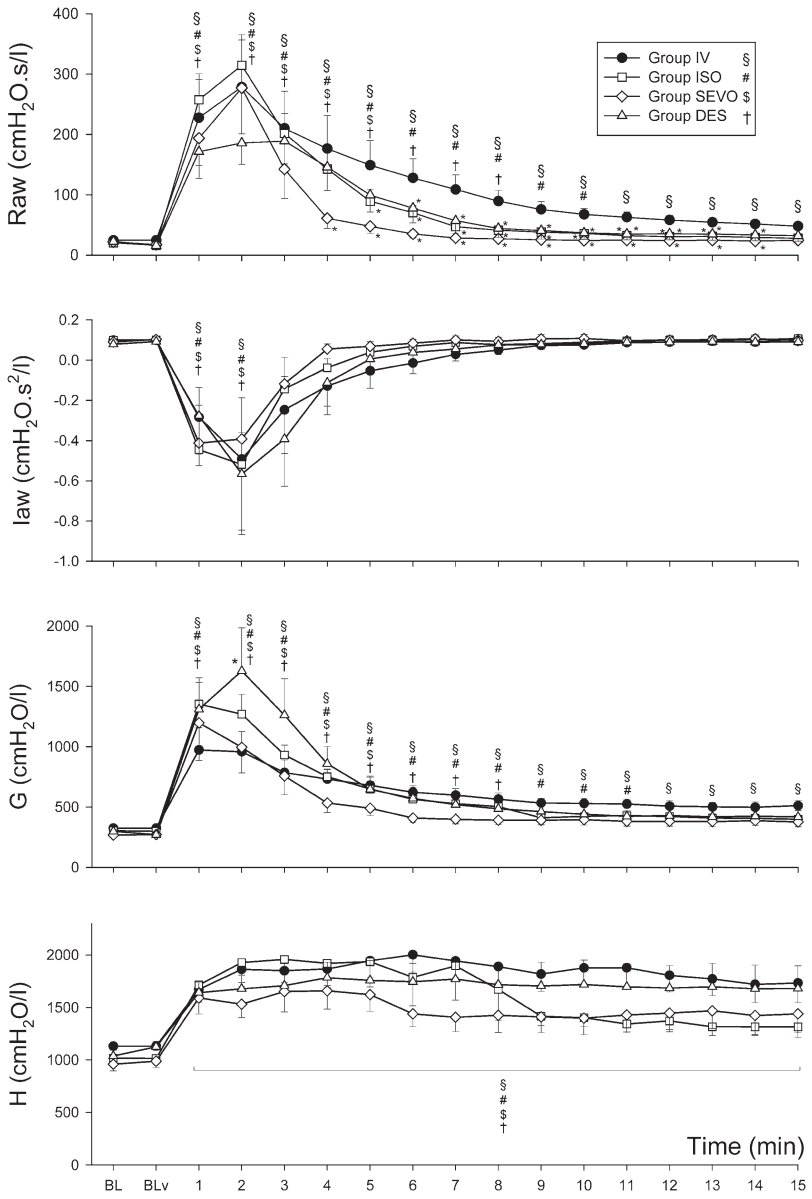

Figure 1. Airway and respiratory tissue mechanical variables after the IV induction of anesthesia (BL), after the introduction of the volatile agents (BLv), and 15 minutes after ovalbumin (OVA) administration to the rabbit pups, when the anesthesia was maintained IV (group IV) or with the inhalation of isoflurane (group ISO), sevoflurane (group SEVO), or desflurane (group DES). §, #, $, and † denote statistical significances relative to condition BLv within groups IV, ISO, SEVO, and DES, respectively. *$P < 0.043$ versus group IV at a particular time point for all P values (2-way repeated measures mixed model analysis of variance with Holm-Sidak post hoc analyses, first order autoregressive covariance structure, different covariance matrices per group). law = frequency-independent inertance; Raw = frequency-independent resistance; G = tissue damping; H = tissue elastance.

the protocol groups in the recovery phase. The increase in H after OVA provocation exhibited no statistically significant change during the study period.

The animals in the experimental groups did not exhibit any statistically significant difference in the total number of cells ($P = 0.39$), or in the total ($P = 0.08$) and relative eosinophil contents ($P = 0.16$) in the BAL fluid, demonstrating statistically no detectable difference in the degree of chronic inflammation in the rabbits enrolled into the protocol groups (Fig. 3). There was a tendency for desflurane to enhance the infiltration of eosinophils, but the difference did not reach the level of statistical significance ($P = 0.066$).

The changes in systolic MAP after OVA administration in the 4 protocol groups are presented in Figure 4. Under the baseline conditions, each of the volatile drugs administered decreased MAP significantly ($P < 0.001$ for all groups). MAP exhibited an initial increase after OVA injection, and inhibitory effect on this phenomenon was observed in group DES ($P = 0.012$). This initial increase was followed by a gradual second-phase decrease in MAP, which was further exaggerated by the inhaled anesthetics ($P < 0.001$ for all).

DISCUSSION

We investigated the ability of routinely used volatile anesthetics to protect against the respiratory consequences of anaphylactic reactions in the present study in a pediatric animal model of allergic sensitization. Separate assessment of the airway and the respiratory mechanics revealed the limited potential of isoflurane, sevoflurane, and desflurane to blunt the peak constrictor response to the allergen in both the central conducting and the peripheral airways. However, the recovery from the acute response to the allergic reaction was faster in the presence of all the volatile drugs studied and particularly when the anesthesia was maintained with sevoflurane. In contrast to the beneficial profile on the airway compartment, the inhaled anesthetic

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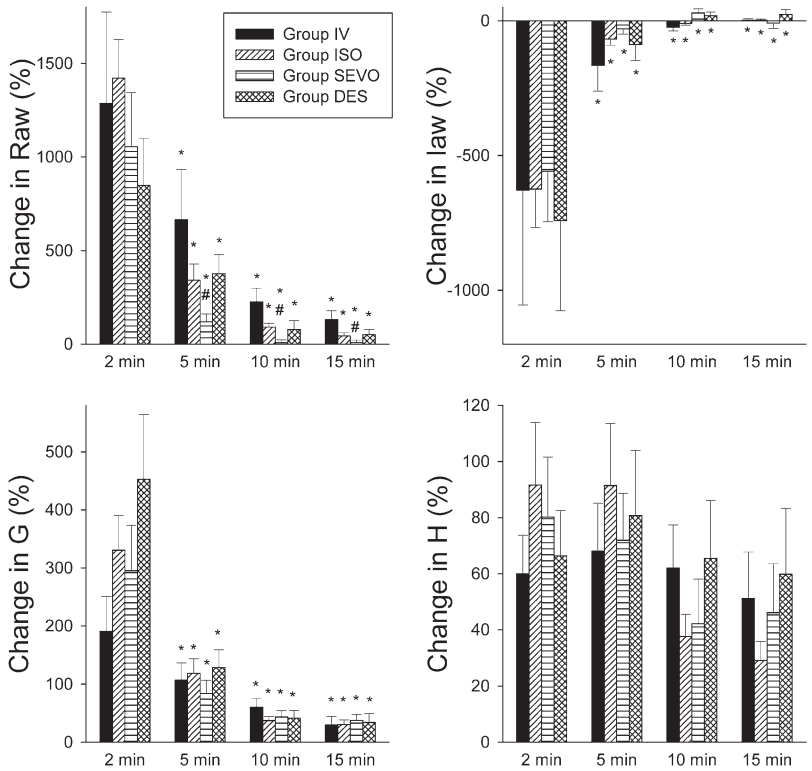

Figure 2. Percentage changes in airway and respiratory tissue mechanical variables relative to the baseline at 2, 5, 10, and 15 minutes after ovalbumin (OVA) administration to the rabbit pups, when the anesthesia was maintained IV (group IV) or with the inhalation of isoflurane (group ISO), sevoflurane (group SEVO), or desflurane (group DES). $*P < 0.05$ versus data obtained 2 minutes after OVA injection within a group; $^{\#}P < 0.05$ versus group IV at a particular time point (2-way repeated measures mixed model analysis of variance with Holm-Sidak post hoc analyses, unstructured covariance structure). law = frequency-independent inertance; Raw = frequency-independent resistance; G = tissue damping; H = tissue elastance.

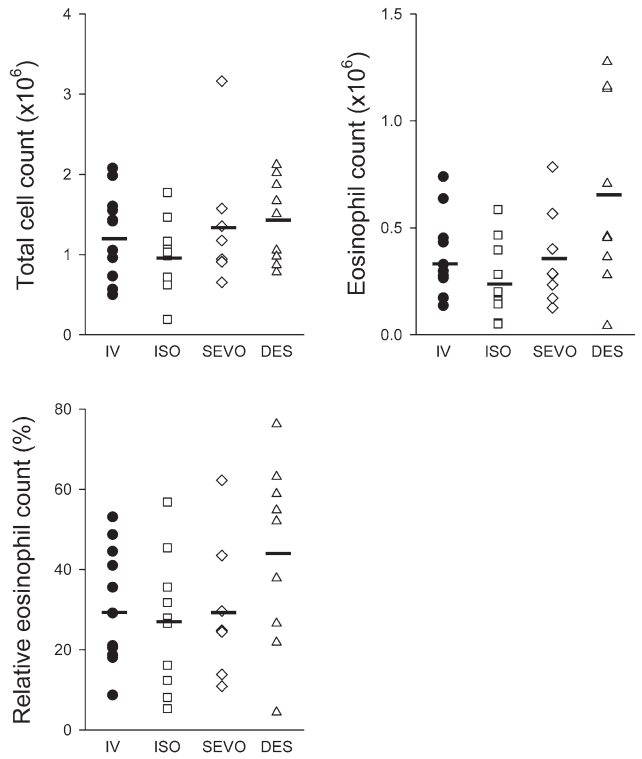

Figure 3. Total number of cells, and absolute and relative eosinophilic cell counts in the bronchoalveolar lavage fluid obtained from rabbit pups anesthetized with IV midazolam (group IV) or with the inhalation of isoflurane (group ISO), sevoflurane (group SEVO), or desflurane (group DES). The lack of statistical difference was tested by using 1-way analysis of variance.

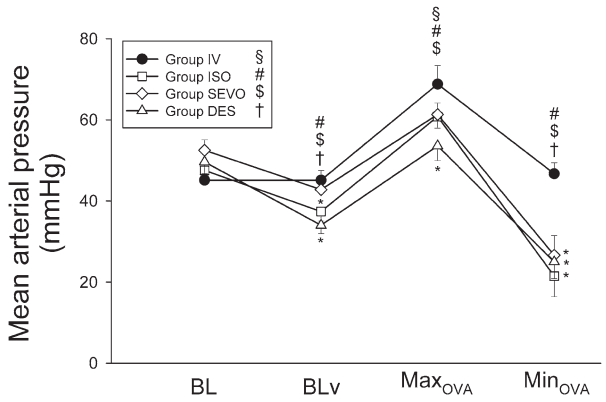

Figure 4. Mean systolic arterial blood pressure after ovalbumin (OVA) administration to the rabbit pups. BL = baseline after anesthesia induction with midazolam; BLv = baseline after maintenance of anesthesia with IV midazolam (group IV) or with the inhalation of isoflurane (group ISO), sevoflurane (group SEVO), or desflurane (group DES); Max_{OVA} and Min_{OVA} = maximum and minimum mean arterial pressures, respectively, after OVA challenges. §, #, $, and † denote statistical significances relative to condition BL within groups IV, ISO, SEVO, and DES, respectively. $*P < 0.045$ versus group IV (2-way repeated measures mixed model analysis of variance with Holm-Sidak post hoc analyses, unstructured covariance structure).

drugs investigated worsened the systemic blood pressure decrease that occurred after the anaphylactic response.

Allergic lung responses were studied by sensitizing the animals to a specific allergen, OVA. This extensively used model has been validated to mimic the hallmark features of allergic lung diseases with the consistent progression of eosinophilia,[21–24] the production of OVA-specific

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immunoglobulin E[24] and the development of bronchial hyperresponsiveness to nonspecific constrictor stimuli.[12,21–25] The accumulation of inflammatory cells with the particular evolution of eosinophilia was confirmed in the vast majority of the animals in the present study (Fig. 3). Four rabbits in which the eosinophilic cell count remained under 5%[21] with a subsequent lack of response to IV OVA were excluded; both findings confirmed that the sensitization in these animals was not successful. Because the rabbit pups in the experimental groups did not exhibit any difference in inflammatory cell count in the BAL fluid, the lack of significantly different inflammation profile was confirmed. The lung mechanical responses therefore can be compared among groups without the potential bias that may result from different inflammatory responses.

The IV administration of allergen was followed by immediate adverse changes in both the respiratory mechanical and the systemic hemodynamic variables, reflecting the key features of an anaphylactic reaction encountered in clinical practice. The pattern of the early phase of the allergen-induced bronchoconstriction observed in the present study, with the rapid development of bronchoconstriction and a slow subsequent recovery, is in agreement with the results of earlier studies in which the bronchospasm was induced by the IV administration of OVA in sensitized adult rodents.[12,26,27] Previous studies provided experimental evidence that this bronchospasm is due to mast cell degranulation, with the subsequent release of bronchoconstrictive mediators, such as histamine, serotonin, and various inflammatory cells.[28] As expected in a pediatric animal model characterized by smaller and more susceptible airways, a more severe bronchospasm was observed after the allergen challenge on rabbit pups than those obtained previously in adult mice,[27] rats,[26] and rabbits.[12] Furthermore, the persistence of a prolonged increase in respiratory H after OVA exposure fully agrees with previous findings and can be attributed to mucous obstruction of the peripheral airways leading to a sustained patchy lung volume loss.[12,27] The subsequent development of ventilation heterogeneities is responsible for the increases in G and the decreases in Iaw observed particularly in the first 5 minutes after OVA challenges.[29] In accordance with previous findings, ventilation heterogeneity overrides the potential increase of Iaw after an airway narrowing[12,30] and further increases the variables related to G.[12,29]

To the best of our knowledge, this is the first investigation of the preventive profiles of common volatile anesthetics against an allergic reaction with mast cell degranulation and subsequent transient severe bronchoconstriction. Our results demonstrate the lack of potential of the volatile drugs studied to inhibit the most severe acute phase (in the first 3 minutes) of the anaphylactic airway response (Fig. 1, top). It is important to note that volatile anesthetics exert their maximum beneficial effects of the airway at 1 minimum alveolar concentration[7] and thus, the lack of their protective potential in the present study is not related to the concentration administered. Partitioning of the lung response into components reflecting the central (Raw) and peripheral lung compartments (G and H) revealed that the volatile anesthetics are not able to attenuate the bronchospasm that occurs in the central conducting airways, and desflurane even has a potential to worsen the ventilation heterogeneities that develop in a sensitized lung after allergen exposure. This feature of desflurane is in accord with previous observations of the deleterious effects of this volatile anesthetic,[8,13] particularly in children with susceptible airways.[31] The results of previous investigations suggests that isoflurane and sevoflurane elicits airway relaxation properties in patients or experimental animals with normal and sensitized airways,[11,32–35] and desflurane seems to elicit the most severe detrimental effects in allergically sensitized animals[8] and in patients with bronchial hyperresponsiveness.[33,36] Comparing these previous results with the current findings indicate that the efficiency of the volatile anesthetics in preventing bronchospasm depends greatly on the mode of stimulus involved in the enhancement of airway tone.

The bronchoconstriction after an allergic reaction may be attributed to mast cell degranulation with the subsequent release of constrictor mediators (histamine, serotonin, tryptase, cytokines, etc.) and the activation of a cholinergic reflex via the parasympathetic vagal pathway.[37,38] The inhaled anesthetics used in the present study lacked the potential to inhibit the allergen-induced bronchoconstriction in the first 3 minutes, indicating their inability to counteract the deleterious effects of the mediators on the airway smooth muscle. Conversely, these volatile anesthetics did accelerate the recovery from the anaphylactic reaction to variable degrees. Although the details of the mechanism responsible for this effect are not clear, it seems likely that the inhaled anesthetics blunt the cholinergic reflex involved in the sustained bronchoconstriction after exposure to allergen. In this regard, the most beneficial profile, observed with sevoflurane, is in line with its highest potency to exert a relaxing effect of the airway smooth muscle via inhibition of the Ca^{2+} sensitivity during muscarinic receptor stimulation.[39]

In conclusion, we applied a validated allergic sensitization procedure to a pediatric experimental model to compare the protective profiles of common volatile anesthetic drugs against an anaphylactic airway response. IV administration of the allergen led to a severe anaphylactic reaction involving an immediate marked bronchoconstriction and deleterious changes in the lung periphery. In the acute severe phase of this response, none of the tested volatile inhaled drugs demonstrated the potential to counteract the allergen-induced bronchospasm, and desflurane even worsened the compromised peripheral ventilation heterogeneities. The recovery from this striking bronchospasm was accelerated by the presence of the inhaled drugs, with sevoflurane exhibiting the fastest improvement in bronchial smooth muscle tone. Since sevoflurane is the most frequent volatile anesthetic drug used in clinical practice, its beneficial profile after an anaphylactic lung response promotes its advantage in the anesthetic management of children with atopic diseases.

DISCLOSURES

Name: Eniko Lele, MD.
Contribution: This author performed the data collection and helped conducting the study.
Attestation: Eniko Lele approved the final manuscript. Eniko Lele attests to the integrity of the original data and the analysis reported in this manuscript. Eniko Lele is the archival author.

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Name: Ferenc Petak, PhD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Ferenc Petak approved the final manuscript. Ferenc Petak attests to the integrity of the original data and the analysis reported in this manuscript.
Name: Stephanie Carnesecchi, PhD.
Contribution: This author helped conduct the study and analyze the data.
Attestation: Stephanie Carnesecchi approved the final manuscript.
Name: Katalin Virag.
Contribution: This author helped in the statistical analyses and formulation of the corresponding parts of the manuscript.
Attestation: Katalin Virag approved the final manuscript.
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Contribution: This author helped analyze the data and write the manuscript.
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Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Habre Walid attests to the integrity of the original data and the analysis reported in this manuscript. Habre Walid is the archival author.
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