

Protective Effects of Volatile Agents against Methacholine-induced Bronchoconstriction in Rats

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Background: **The protective properties of common volatile agents against generalized lung constriction have previously been addressed only *via* estimations of parameters that combine airway and tissue mechanics. Their effectiveness in preventing airway constriction have not been compared systematically. Therefore, the authors investigated the abilities of halothane, isoflurane, sevoflurane, and desflurane to provide protection against airway constriction induced by methacholine.**

Methods: **Low-frequency pulmonary impedance data were collected in open-chest rats under baseline conditions and during three consecutive intravenous infusions of methacholine ($32\ \mu g \cdot kg^{-1} \cdot min^{-1}$) while the animals were anesthetized with intravenous pentobarbital (control group). Methacholine challenges were performed in four other groups of rats, first during intravenous anesthesia and then repeated during the inhalation of halothane, isoflurane, sevoflurane, or desflurane at concentrations of 1 and 2 minimum alveolar concentration (MAC). Airway resistance and inertance, parenchymal damping, and elastance were estimated from the impedance data by model fitting.**

Results: **The methacholine-induced increases in airway resistance during intravenous pentobarbital anesthesia (204 ± 53%) were markedly and significantly ($P < 0.005$) reduced by 1-MAC doses of halothane (80 ± 48%), isoflurane (112 ± 59%), sevoflurane (68 ± 34%), and desflurane (96 ± 34%), with no significant difference between the gases applied. Increasing the concentration to 2 MAC did not lead to any significant further protection against the increase in airway resistance.**

Conclusions: **These data demonstrate that isoflurane, sevoflurane, and desflurane are as effective as the widely accepted halothane in protecting against methacholine-induced airway constriction.**

ALTHOUGH anesthesia involves many procedures that have the potential to produce severe lung constriction,[1–5] a number of studies have documented significant improvements in lung function with administration of volatile agents.[6–17] Some investigations have focused on the protective effects of halothane,[6,9,11,13,16] isoflurane,[13,14] or sevoflurane,[13,14,16] whereas others were designed to examine the reversal of lung constriction with these volatile agents[12,17] or to investigate their effects on the spontaneous airway tone.[7,8,10,15] Nevertheless, there is still a lack of knowledge as to whether all of the routinely used volatile agents display comparable protective effects against airway constriction. Most of the studies have determined global parameters, such as the total lung resistance (RL),[6–9,13,14,17] to characterize the mechanical status of the lungs. Thus, the relative contributions of the airways and the tissues to the increases in RL remain unknown. The use of a technique with which airway and tissue properties may be determined separately provides anesthesiologists, who are primarily concerned with changes in airway mechanics, with a better description of the changes in the lungs.

Methacholine is commonly administered to mimic vagally induced changes in lung function, such as those caused by the stimulation of airway irritant receptors. In rats, the intravenous administration of methacholine has been demonstrated to alter predominantly airway mechanics.[18] Therefore, the use of a methacholine infusion in rats appears to be an appropriate model to investigate the effectiveness of volatile agents in reversing or preventing airway constriction.

The aim of the present study was to compare the protective effects of isoflurane, sevoflurane, and desflurane with that of halothane against airway constriction. Thus, we separated RL into its airway and parenchymal components to identify the airway responses.

Materials and Methods

Animal Preparation

After obtaining approval from the Animal Care Committee of the Canton of Geneva, 41 adult male Sprague–Dawley rats (293–434 g) were anesthetized (40 mg/kg pentobarbital intraperitoneally) and placed in the supine position. The rats were then tracheotomized with a polyethylene cannula (14-gauge; Braun, Melsungen, Germany) and mechanically ventilated (Model 683; Harvard Apparatus, South Natick, MA) with a tidal volume of 10 ml/kg at a frequency of 75 breaths/min and an inspired oxygen fraction of 0.3 in air. The femoral artery was prepared surgically in a sterile manner and then cannulated (28-gauge catheter; Portex, Hythe, UK) 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 in the same way as the femoral artery and cannulated for drug delivery. Muscle paralysis was achieved by the intravenous administration

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of pancuronium bromide (1 mg/kg initial dose, supplemented with 0.3 mg/kg every 40 min). The thorax was opened by means of a midline thoracotomy, and the ribs were widely retracted. After the chest opening, a positive end-expiratory pressure of 2.5 cm H_2O was maintained.

Airway pressure was measured continuously using a calibrated pressure transducer (Validyne DP 45, Northridge, CA). Rectal temperature was monitored with a temperature sensor (Thermalert, model TH-8; Physitemp, Clifton, NJ) and was maintained at 37 ± 0.5°C with a heating pad (Miostar, Zürich, Switzerland). Airway and arterial pressures, 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 microcomputer.

Impedance Measurements

We applied the wave-tube technique to measure lung input impedance (ZL), as described in detail previously.[18] This technique was specially designed to measure the forced oscillatory input impedance of small animals without the need to estimate the oscillatory flow.[5,18–20] Briefly, a three-way tap was used to switch the tracheal cannula from the respirator to a loudspeaker-in-box system at end expiration. The pressure in the box chambers was set to 2.5 cm H_2O to keep the mean transpulmonary pressure constant during measurements. The loudspeaker delivered a computer-generated small-amplitude (< 1 cm H_2O) pseudorandom signal (15 noninteger multiples between 0.5 and 21 Hz) through a 100-cm-long, 2-mm ID polyethylene tube. Two identical pressure transducers (model 33NA002D; ICSensors, Malpitas, CA) were used to measure the lateral pressures at the loudspeaker end (P_1) and at the tracheal end (P_2) of the wave tube. The signals P_1 and P_2 were low-pass filtered (fifth-order Butterworth, 25-Hz corner frequency) and sampled with an analog–digital board of another microcomputer at a rate of 256 Hz. Fast Fourier transformation with 4-s time windows and 95% overlapping was used to calculate the pressure transfer functions (P_1/P_2) from the 6-s recordings. ZL was calculated as the load impedance of the wave tube[21]:

$$ZL = Z_o \sinh(\gamma L)/[(P_1/P_2) - \cosh(\gamma L)]$$

where L is the length, Z_o is the characteristic impedance, and is the complex propagation wave number of the wave tube. The latter two parameters are determined by the geometric data and the material constants of the tube wall and the air.[22]

Separation of Airway and Parenchymal Parameters

The distinctly different frequency dependencies of the airways and the parenchyma at low oscillation frequencies were used to separate the mechanical properties of the two compartments.[5,18–20,23–25] Numerous studies have demonstrated that the airways can be described by a frequency-independent airway resistance (R_{aw}) and inertance (I_{aw}).[5,18–20,23–25] In contrast, both the parenchymal resistance and reactance have been shown to decrease roughly inversely with increasing frequency. On the basis of these characteristics, the airway and parenchymal properties were separated by fitting a model incorporating an airway compartment containing R_{aw} and I_{aw}, in series with a constant-phase tissue model[23] including damping (G) and elastance (H), to the ZL spectra by minimizing the differences between the measured and modeled impedance values:

$$ZL = R_{aw} + j\omega I_{aw} + (G - jH)/\omega^{\alpha}$$

where j is the imaginary unit, ω is the angular frequency ($2\pi f$), and $\alpha = 2/\pi \arctan(H/G)$. Impedance data at frequencies coinciding with the heart rate and its harmonics often showed poor reproducibility in subsequent measurements under identical experimental conditions and were therefore omitted from the model fitting. The reported R_{aw} and I_{aw} values were corrected for the resistance and inertance, respectively, of the measurement set-up, including the tracheal cannula.

For each parameter and experimental condition, the percentage change from the preinfusion baseline was calculated. Because the composition of the intrapulmonary gas was the same within each group of animals under all conditions, potential problems associated with the different physical properties of the intrapulmonary gas and the consequent effects on the airway parameters were avoided by the normalization.

Study Protocol

Before administration of the constrictor agent, the lungs were hyperinflated by superimposing two inspiratory cycles to standardize the volume history. After 4–6 successive baseline ZL recordings, the intravenous infusion of methacholine was started at 32 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with a constant-flow infusion pump (ID2S, model ID 2 ET, Asnieres, France). ZL was then recorded at 1-min intervals, and 4–6 ZL measurements were performed after the establishment of a stable level of constriction.

After completion of the first methacholine challenge, the rats were randomly assigned to the five protocol groups. In the control group (n = 8), the same dose of methacholine was infused twice to test the reproducibility of the responses while pentobarbital was injected intravenously (10 mg/kg every 40 min) to maintain anesthesia. The anesthesia was maintained in the other groups with halothane (n = 9), isoflurane (n = 8), sevoflurane (n = 8), or desflurane (n = 8). When the end-tidal concentration of the volatile agent reached 1 minimum alveolar concentration (MAC) (1, 1.4, 2.4, and

6.9% for halothane,[26] isoflurane,[26] sevoflurane,[27] and desflurane,[28] respectively) and stable hemodynamic conditions had been established, ZL measurements were performed to obtain new baseline data, and the methacholine challenge was repeated, as detailed previously. Finally, the volatile agent concentration was increased to 2 MAC, and data were collected again before and during methacholine infusion.

Arterial blood samples were analyzed radiometrically (model 505; Acid Base Laboratory, Copenhagen, Denmark) before each methacholine challenge. The concentrations of oxygen, carbon dioxide, and the volatile agent were monitored throughout the study (Ultima; Datex/Instrumentarium, Helsinki, Finland).

Statistical Analysis

Scatters in the parameters were expressed in SD values. The Kolmogorov-Smirnov test was used to test data for normality. Within the protocol groups, repeated measures of one-way analysis of variance was used to assess the effects of the volatile agents on the methacholine responses. One-way analysis of variance was applied to compare the mechanical parameters between the independent protocol groups. The Student-Newman-Keuls multiple-comparison procedure based on the means was applied to compare the different conditions (for repeated measures) or protocol groups (for independent groups). Statistical tests were performed with a significance level of P less than 0.05.

Results

Figure 1 illustrates the real (RL) and imaginary parts (XL) of ZL as functions of the oscillation frequency and the corresponding model fits obtained in a representative rat under control conditions and during steady state constriction induced by constant-flow methacholine infusion when anesthesia was achieved with intravenous pentobarbital and when 1 MAC desflurane was inhaled. In consequence of the decreasing contribution of the tissue resistance ($R_{ti} = G/\omega^{\alpha}$), the RL values decrease with increasing frequency and approach plateaus corresponding to the flow resistances of the airways. The elastic behavior of the parenchyma is reflected mainly in the quasi-hyperbolic increases in XL ($XL = EL/j\omega$, where EL is the lung elastance), whereas the linearly increasing inertive components in the XL data become appreciable at high frequencies. The low variabilities during methacholine infusions indicate very stable plateau responses. Methacholine-induced increases in RL can be observed at all frequencies. The parallel increases in RL indicate marked elevations in R_{aw}, whereas the smaller changes in the frequency dependence of RL suggest an elevated R_{ti}. Administration of methacholine during desflurane caused a markedly smaller response in RL: a decrease in the high-frequency range indicates a significantly smaller constrictor response in R_{aw}, whereas the smaller change in the low-frequency gradient of RL suggests a reduction in the response in R_{ti}. In general, the changes in RL were associated with relatively smaller changes in XL, indicating no obvious protective effect of desflurane on the methacholine-induced response in elastance.

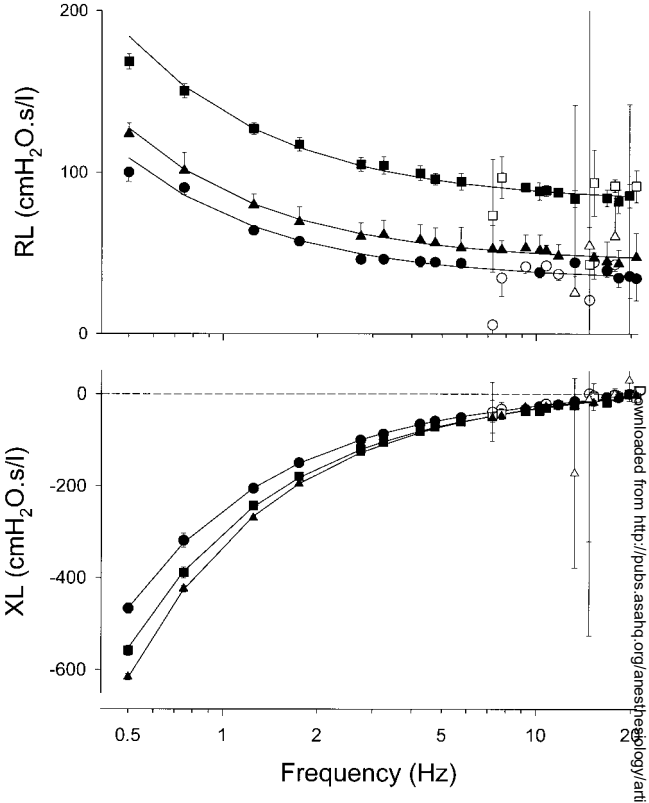

Fig. 1. Real (RL) and imaginary parts (XL) of pulmonary input impedance in a representative rat during baseline conditions (circles) and intravenous methacholine infusions at a rate of 32 $\mu g \cdot kg^{-1} \cdot min^{-1}$, while anesthesia is maintained with intravenous pentobarbital (squares) or with 1 MAC of desflurane (triangles). Symbols with bars represent mean ± SD values from four to six consecutive measurements. Lines indicate the corresponding model fits. Hollow symbols indicate data points that were excluded from model fits because of corruption by cardiac artifacts.

Figure 2 depicts the changes in the airway and tissue parameters during methacholine challenges in the five groups of rats. In agreement with our previous findings,[18,20] intravenous methacholine induced marked increases in R_{aw} and G, essentially no change in I_{aw}, and slight increases in H. While the rats were anesthetized with pentobarbital, the first methacholine challenge induced the same magnitude of change in the lung parameters in all protocol groups. The baseline values of R_{aw}, G, and H before each methacholine challenge were very similar in all groups. However, in consequence of the significantly higher density of the volatile agents compared with that of the carrier gas, I_{aw} showed a significant increase with increase of the volatile agent concentration. This effect was most marked with desflurane,

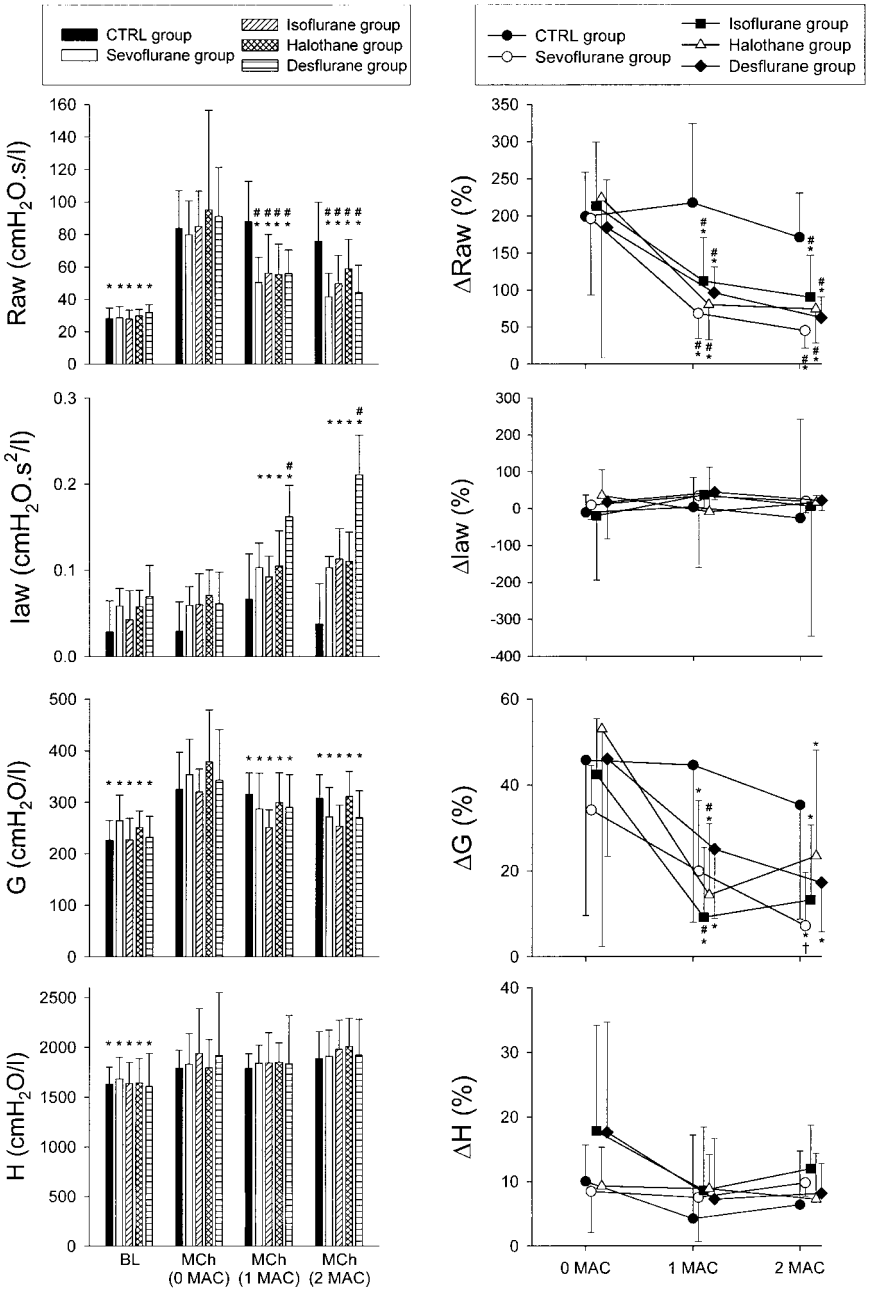

Fig. 2. Values of airway resistance (R_{aw}), airway inertance (I_{aw}), tissue damping (G) and elastance (H) (*left*) and their relative percentage changes from the baseline values (*right*) in response to three consecutive methacholine challenges (MCh) in the control (CTRL) group and in rats in which intravenous pentobarbital anesthesia (0 MAC) was followed by inhalations of volatile agents at 1 or 2 MAC. BL = baseline condition. **P* less than 0.05 compared with control (methacholine 0 MAC) methacholine challenge; †*P* less than 0.05 compared with parameter values at 1 MAC; #*P* less than 0.05 between the control group and the groups given volatile agent anesthesia.

which requires the highest relative concentration to achieve 1 MAC. The methacholine-induced increases in R_{aw} were reproducible in the control group, with no statistically significant difference in response after the three successive challenges. However, methacholine generated a markedly lower ($P < 0.005$) airway constriction when the anesthesia was maintained with the volatile agents. The increase of the concentration of the volatile agents to 2 MAC tended to enhance their protective effects, although this dose dependence was not statistically significant. The comparisons of the groups revealed no statistically significant difference between the volatile agents with regard to the ability to protect against the methacholine-induced airway constriction. Although I_{aw} increased with increasing volatile agent concentration, as a consequence of the increased density of the gas mixture in the lungs (data not shown), methacholine had no effect on this parameter.

The increases in the parenchymal parameters during methacholine infusion were always far lower than those in R_{aw}. No statistically significant difference in the elevation of G was found between the methacholine challenges in the control group, whereas all the volatile agents decreased the elevations in G significantly ($P < 0.05$). There was no difference between the volatile agents in moderating the increases in G. The elevation of the concentration of sevoflurane and desflurane from 1 to 2 MAC tended to intensify their protective effects,

whereas such dose-dependent effects were not obvious with halothane and isoflurane. The slight, although statistically significant, increases in H were not affected by administration of the volatile agents.

Discussion

Many previous studies have focused on the potent bronchodilation effect of halothane[6–13,15,16] and have demonstrated its relaxation properties on the parenchymal contractile elements.[10,15] This is the first study in which the protective effects of all current volatile anesthetic agents against bronchoconstriction have been investigated. The study has revealed that isoflurane, sevoflurane, and desflurane are as effective as halothane in protecting against methacholine-induced airway constriction.

The mechanical properties of the airways are of primary interest to anesthesiologists because many of the procedures routinely used in anesthetic practice may involve the stimulation of irritant receptors resulting in cholinergic-mediated bronchospasm. We therefore applied a measurement technique that permits separation of the airway resistance from the parenchymal components. To partition RL into R_{aw} and R_{ti}, we collected low-frequency ZL data by adopting the wave-tube technique of ZL measurement. This technique avoids the technical difficulties associated with flow measurements in a small animal and provides reliable ZL data in rats.[5,18–20] The ZL data obtained in the present study are comparable to those reported from previous studies in this species.[5,18,20] Likewise, in agreement with previous findings,[5,18–20,23–25] the model involving an airway and a constant-phase tissue compartment was consistent with the frequency dependence of ZL.

Interpretation of Methacholine Responses

We applied intravenous methacholine infusion to induce lung constriction. In accord with previous results, intravenous methacholine induced marked increases in R_{aw} and moderate elevations in G, with far smaller changes in H.[18,20] Previous studies validating the reliability of the separation of airway and parenchymal parameters *via* model-based evaluation of the low-frequency ZL spectra revealed that R_{aw} accurately characterizes the overall airway resistance.[5,18–20,23–25] Nevertheless, it has also been demonstrated that the parenchymal parameters of a single-compartment constant-phase model may be affected by severe peripheral airway heterogeneities, which may develop during severe constriction.[18,25] Such a phenomenon was shown to be manifested in a marked elevation in R_{aw}, associated with a parallel increase in G and no change in H. Because we obtained the same pattern of change in the mechanical parameters, we can conclude that intravenous methacholine induced a marked and highly heterogeneous airway constriction, whereas the increases in G were primarily caused by enhanced ventilation inhomogeneities.

Protective Effects of Volatile Agents

Because the previous investigations used global measures to characterize the mechanical status of the lungs, the protective effects of volatile gases against airway and parenchymal responses were not estimated separately. Katoh and Ikeda[13] reported that sevoflurane is less potent than halothane or enflurane in attenuating the histamine-induced changes in total RL and compliance. Ishikawa *et al.*[17] observed no difference between the dilator properties of isoflurane and sevoflurane when the constriction was induced by an intravenous infusion of methacholine. Similar results were obtained by Mitsuhata *et al.*[14] when these volatile agents were used to protect against the increases induced in RL by anaphylaxis. However, in these studies, the R_{aw} was not estimated, and the changes in total RL were used as an index of bronchoconstriction. Because RL incorporates R_{aw} and a component related to ventilation heterogeneities,[5,18–20,23–25] the true airway responses were not assessed in these previous studies. In the current protocol, the overall airway properties were determined without the disturbing influence of the parenchymal viscoelasticity or ventilation heterogeneities. Brown *et al.*[12] used high-resolution computed tomography and found that halothane was significantly more effective than isoflurane in reversing histamine-induced airway narrowing at low doses, whereas there was no difference between these agents at the dose of 1.7 MAC.

In the present study, all volatile agents administered at 1 MAC exerted comparable protective effects against methacholine-induced airway constriction. Additionally, they counteracted the development of ventilation inhomogeneities during methacholine challenge, as evidenced by the lower increases in G. This may suggest that all volatile agents involved in the present study act preferentially on the small peripheral airways where the heterogeneities originate, and there is no significant difference between the volatile agents in this regard. Ishikawa *et al.*[17] used alveolar capsules to estimate the reversal of ventilation inhomogeneities and demonstrated that sevoflurane was less effective than isoflurane in this respect. However, the three alveolar regions sampled in this way were unlikely to represent the global behavior of the lungs,[24] and, with the additional factor of the difference in species, this may explain the discrepancy between the two studies.

Effects of Volatile Agent Concentration

Previous studies of the protective effects of halothane,[6,9,11,13,16] isoflurane,[13,17] and sevoflurane[17] indicated no dose dependence when concentrations greater than 1 MAC were used. In agreement with those previ-

ous observations, we found that increasing the concentration to 2 MAC did not result in any significant additional protective effect for any of the anesthetic gases. Accordingly, our data suggest that a concentration of 1 MAC already exerts virtually the maximal protective effect against bronchospasm.

Many studies have focused on the mechanism of bronchodilation caused by halothane and have demonstrated both a direct effect on the smooth muscles and the depression of vagally mediated airway reflexes.[6,8,9,11] The uniformity of the effects of the volatile agents used in the present study on the pulmonary mechanical parameters suggests that all of these agents may exert their protective effects against bronchoconstriction *via* the same mechanism, although our results do not allow the description of the potential mechanisms involved.

In summary, the results of this study demonstrate that all of the currently used volatile agents exert a marked protective effect against bronchoconstriction. In addition, sevoflurane and desflurane are as effective as the gold standard, halothane, in preventing bronchospasm. By virtue of their beneficial pharmacologic properties,[29–32] sevoflurane and desflurane are gaining increasing popularity in clinical practice. Our results appear to indicate their additional beneficial effects in situations in which there is a high risk of stimulation of the bronchial irritant receptors.

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