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Effect of the Physical Properties of Isoflurane, Sevoflurane, and Desflurane on Pulmonary Resistance in a Laboratory Lung Model

Vasilia G. Nyktari, M.D., Alexandra A. Papaioannou, M.D., Ph.D., D.E.A.A.,† George Prinianakis, M.D., Ph.D.,‡ Eytichis G. Mamidakis, M.D.,§ Dimitris Georgopoulos, M.D., Ph.D.,‖ Helen Askitopoulou, M.D., Ph.D.#*

Background: **Airway resistance depends not only on an airway's geometry but also on flow rate, and gas density and viscosity. A recent study showed that at clinically relevant concentrations, the mixtures of volatile agents with air and oxygen and oxygen–nitrogen affected the density of the mixture. The goal of the current study was to investigate the effect of different minimum alveolar concentrations (MACs) of three commonly used volatile agents, isoflurane, sevoflurane, and desflurane, on the measurements of airway resistance.**

Methods: **A two-chamber fixed-resistance test lung was connected to an anesthesia machine using the volume control mode of ventilation. Pulmonary resistance was calculated at baseline (25% oxygen in air); at 1.0, 1.5, and 2.0 MAC; and also at the same concentrations, 1.2% and 4%, of isoflurane, sevoflurane, and desflurane mixtures with 25% oxygen in air. The analysis of variance test for repeated measures and probabilities for *post hoc* Tukey and least significant difference tests were used.**

Results: **Isoflurane affected pulmonary resistance only at 2 MAC. Sevoflurane caused a significant increase of pulmonary resistance at 1.5 and 2 MAC, whereas desflurane caused the greatest increase in pulmonary resistance at all MAC values used. At 1.2% concentration, no difference from the baseline resistance was observed, whereas at 4%, the three agents produced similar increases of pulmonary resistance.**

Conclusion: **High concentrations of volatile agents in 25% oxygen in air increased the density of the gas mixture and the calculated resistance of a test lung model with fixed resistance.**

AIRWAY resistance depends on airway geometry, flow rate, and gas density and viscosity.[1–3] When the flow is laminar, viscosity is the only physical property of the inspired gas that may influence resistance. However, if the gas flow is turbulent, resistance depends mainly on the density of the gas. In a recent study, Habre *et al.*[4] showed that clinical concentrations of volatile agents in mixtures with air, oxygen, and oxygen–nitrogen did not markedly affect the viscosity of the mixture, whereas they affected the density of the mixture at routinely used clinical concentrations, with maximal increase in the density of desflurane in air by 47.7% at 2 minimal alveolar concentration (MAC).[4] The aim of the current study was to compare the effect of different concentrations of isoflurane, sevoflurane, and desflurane on the measured pulmonary resistance under experimental conditions in a laboratory lung model with fixed resistance. The working hypothesis was that the volatile agents with high density would increase the density of their mixture with 25% oxygen in air and would lead to an increased pulmonary resistance. This effect should have been greater at higher volatile concentrations.

Materials and Methods

The setup of the experiment is presented in figure 1. A two-chamber test lung with fixed resistance (5600i Dual Adult System; Michigan Instruments, Grand Rapids, MI) was connected to an anesthesia machine (Julian; Draëger Medical, Lübeck, Germany) using the volume control mode of ventilation. The test lung served as a quantitative, calibrated "test load" simulating human pulmonary physiology. The elastance and resistance of the experimental chambers were set at 20 cm $H_2O \cdot l^{-1}$ and 15 cm $H_2O \cdot l^{-1} \cdot s^{-1}$, respectively.[5]

A screen pneumotachograph, which used a differential pressure–based flow sensor and was used for the measurement of flow rate (RSS100-HR; Hans Rudolph, Kansas City, MO), and a pressure transducer were inserted between the endotracheal tube and the Y piece of the respiratory circuit for the continuous recordings of measured flow, tidal volume, and inspiratory pressures (P_{peak} and $P_{plateau}$). This particular pneumotachograph provides correction for gas density, viscosity, temperature, and barometric pressure. Moreover, to confirm accuracy, the flows measured at baseline and after the addition of anesthetic gases were compared. Because the lung model was ventilated with volume control mode, it was mandatory that flow remain constant, and only minor breath-to-breath variations should have been recorded. The pulmonary resistance (R_{plm}) was calculated by the inspiratory pressure method,[6] where the driving pressure for airflow is the difference between end-inspiratory peak airway pressure and plateau pressure ($P_{peak} - P_{plateau}$) during occlusion of the expiratory port. The P_{peak} and $P_{plateau}$ pressures were measured from the waveform of the inspiratory pressure. Flow was measured from the waveform of the pneumotachograph (fig. 2). The overall pulmonary resistance (R_{plm}) was calculated from the equation: pulmonary resistance $R_{plm} = (P_{peak} - P_{plateau})/(\text{flow})$ at baseline, when a mixture of 25% oxygen in air was used (without volatile agent) and also at mixtures of 1.0, 1.5, and 2.0 MAC of isoflurane,

* Resident in Anesthesiology, † Consultant, § M.D. Resident in Anesthesiology, # Professor and Chair, Department of Anesthesiology, ‡ Consultant, Intensive Care Unit, ‖ Professor and Chair, Intensive Care Medicine.

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Address correspondence to Dr. Papaioannou: Livadias 11A, 71409, Heraklion, Crete, Greece. fraidako@med.uoc.gr.

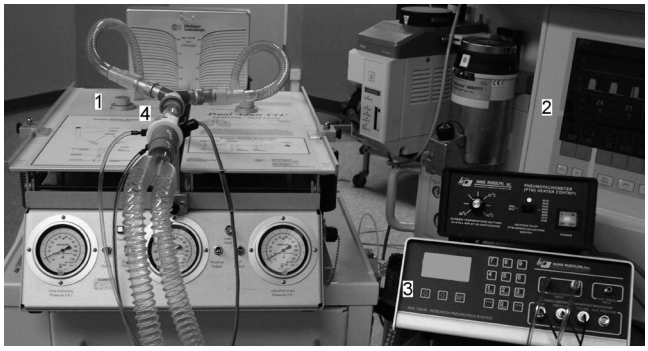

Fig. 1. Setup of the experiment. The two-chamber test lung (*1*) was connected to the anesthesia machine (*2*). The pneumotachograph (*3*) and the pressure transducer were inserted between the endotracheal tube and the Y piece (*4*) of the respiratory circuit for the continuous recordings of measured flow, tidal volume, and inspiratory pressures.

sevoflurane, and desflurane with 25% oxygen in air. Finally, to discriminate between the effects of the concentration of the anesthetics or the effects of their physical properties, we also measured the resistance at the same low (1.2%) and high (4%) concentrations of isoflurane sevoflurane, and desflurane with 25% oxygen in air. These particular concentrations were chosen because 1.2% was 1 MAC of isoflurane, and 4% is the highest concentration that could be delivered from the isoflurane vaporizer. For each concentration of the volatile agent, five measurements were recorded.

The parameters of the volume control mode of ventilation were the same for all measurements: tidal volume = 600 ml, respiratory rate = 8 breaths/min, positive end-expiratory pressure = 0 cm H_2O, T_I:T_E = 1:1.5, T_I:$T_{plateau}$ = 50%, and fresh gas flow = 8 l/min. The MAC values of each anesthetic agent were calculated by the Agent Analyser (IRIA; Draëger Medical, Lübeck, Germany) of the anesthetic apparatus using the volatile agent end-expiratory concentrations and corrected for age (at a set age of 40 yr), altitude, and gas mixture. IRIA measures the concentration of the anesthetics based on

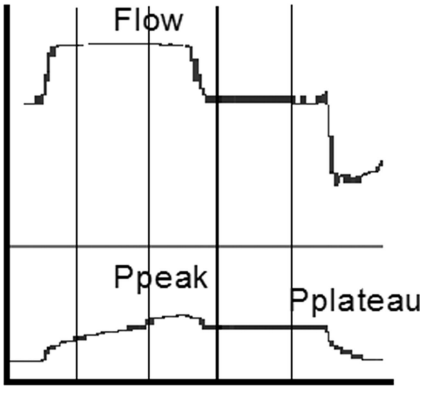

Fig. 2. Recorded waveforms of flow and pressure. Total pulmonary resistance was calculated according to the equation: pulmonary resistance (R_{plm}) = (P_{peak} − $P_{plateau}$)/flow. The use of the laboratory model resulted in no time constant inequalities, and P_1 pressure is not observed.

Table 1. End-expiratory Concentrations (%) for Isoflurane, Sevoflurane, and Desflurane

	1 MAC	1.5 MAC	2 MAC
Isoflurane	1.2	1.8	2.4
Sevoflurane	1.8	2.8	3.6
Desflurane	6.6	9.7	13.3

End-expiratory concentrations (%) for isoflurane, sevoflurane, and desflurane at the relevant minimum alveolar concentration (MAC) settings measured by the anesthetic apparatus.

infrared light absorption. The absorption of infrared light at 3 μm is used for the measurement of carbon dioxide–nitrous oxide and at 8 μm for the measurement of end-expiratory volatile anesthetics. Age-corrected MAC values were then calculated according to the Mapleson formula for patients older than 1 yr: $MAC_{age} = MAC_{40} \times 10\ [-0.00269 \times (age - 40)]$.[7]

Statistical Analysis

All values represent the means from a total of five consecutive respiratory cycles. The increase of pulmonary resistance caused by the volatile agents was also expressed as a percentage of the baseline value. Data were analyzed by analysis of variance for repeated measurements, and *post hoc* Tukey and least significant difference tests *were* used. All values are expressed as mean ± SD.

Results

The measured end-expiratory concentrations for isoflurane, sevoflurane, and desflurane at the three studied MAC values are shown in table 1. Desflurane was used at greater end-expiratory concentrations at all MAC values (6.6, 9.7, and 13.3% representing 1, 1.5, and 2 MAC, respectively), because it is the least potent of the three volatile agents.

The flow measurements for all gas compositions are shown in table 2. None of the differences recorded were significant. This finding confirmed that the pneumotachograph measures were valid because, with the use of volume control ventilation mode, inspiratory flow was mandatory to remain constant, and only minor breath-to-breath variations were acceptable. Otherwise, the pneumotachograph gave false values because of the altered physical properties of the gas mixtures.

The baseline value of pulmonary resistance of the lung model at 25% oxygen in air was 15.64 ± 0.15 cm $H_2O \cdot l^{-1} \cdot s^{-1}$. The effects of the different concentrations of isoflurane, sevoflurane, and desflurane in 25% oxygen in air on pulmonary resistance are shown in table 3 and figure 3.

Comparison at Equivalent MAC Values

Compared with the baseline value, isoflurane significantly increased pulmonary resistance only at 2 MAC

Table 2. Flow Measurements (l/min) at the Different Concentrations of Volatile Agents

	Mean	SD	*P* Value
Baseline	30.8	0.60	—
Isoflurane, 1 MAC	30.8	0.60	NS
Isoflurane, 1.5 MAC	30.72	0.60	NS
Isoflurane, 2 MAC	30.78	0.24	NS
Isoflurane, 4%	30.76	0.60	NS
Sevoflurane, 1 MAC	30.8	0.00	NS
Sevoflurane, 1.5 MAC	30.8	0.48	NS
Sevoflurane, 2 MAC	30.78	0.24	NS
Sevoflurane, 1.2%	30.8	0.00	NS
Sevoflurane, 4%	30.8	0.00	NS
Desflurane, 1 MAC	30.81	0.24	NS
Desflurane, 1.5 MAC	30.78	0.24	NS
Desflurane, 2 MAC	30.77	0.06	NS
Desflurane, 1.2%	30.8	0.00	NS
Desflurane, 4%	30.78	0.24	NS

Flow measurements (l/min) at the different concentrations of volatile agents, expressed as mean and SD. None of the differences observed were significant.

MAC = minimum alveolar concentration; NS = not significant.

($P = 0.005$). Sevoflurane increased pulmonary resistance at 1.5 and at 2 MAC by 17.8% and 23.3%, respectively ($P < 0.001$ for both comparisons). Desflurane increased the calculated resistance of the test lung model at all concentrations used ($P < 0.001$ for all concentrations). At 1 MAC, where the end-expiratory concentration of desflurane was 6.6%, the increase of pulmonary resistance from the baseline value was 44.5%. At 1.5 MAC desflurane, an end-expiratory concentration of 9.7% was used, and the increase of pulmonary resistance was 63.7% from the baseline value. The greatest increase of pulmonary resistance, by 87%, was observed at 2 MAC when an end-expiratory concentration of 13.3% was used.

Table 3. Pulmonary Resistance (cm $H_2O \cdot l^{-1} \cdot s^{-1}$) at the Different Concentrations Studied

	Mean	SD	% Increase from Baseline	*P* Value
Baseline	15.64	0.1565	—	—
Isoflurane, 1 MAC	16.21	0.2396	3.6	NS
Isoflurane, 1.5 MAC	17.06	0.2219	9	NS
Isoflurane, 2 MAC	17.37	0.1299	11	0.005
Isoflurane, 4%	20.14	0.29	28	< 0.001
Sevoflurane, 1 MAC	16.53	0.4461	5.7	NS
Sevoflurane, 1.5 MAC	18.43	0.3256	17.8	< 0.001
Sevoflurane, 2 MAC	19.30	0.3146	23.3	< 0.001
Sevoflurane, 1.2%	15.87	0.0541	1.5	NS
Sevoflurane, 4%	20.16	0.3250	28.9	< 0.001
Desflurane, 1 MAC	22.60	0.2499	44.5	< 0.001
Desflurane, 1.5 MAC	25.30	0.1870	63.7	< 0.001
Desflurane, 2 MAC	29.24	0.2507	87	< 0.001
Desflurane, 1.2%	16,186	0.0581	3.45	NS
Desflurane, 4%	19.67	0.0212	25.8	< 0.001

Values of pulmonary resistance (cm $H_2O \cdot l^{-1} \cdot s^{-1}$) at the different concentrations studied for each volatile agent, expressed as mean and SD and the respective percentage increases from the baseline value. The *P* values refer to comparisons with the baseline value.

MAC = minimum alveolar concentration; NS = not significant.

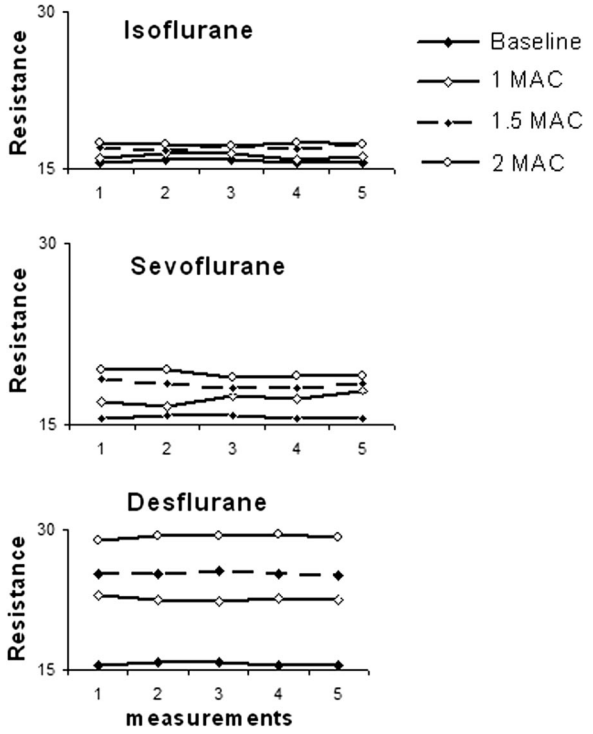

Fig. 3. Comparison of the effects of isoflurane, sevoflurane, and desflurane at 1.0, 1.5, and 2 minimum alveolar concentration (MAC) on total pulmonary resistance. Isoflurane caused a statistically significant ($P = 0.005$) increase of the resistance at 2 MAC compared with baseline. Sevoflurane caused significant increase of the resistance at 1.5 and 2 MAC compared with baseline ($P < 0.001$ for both comparisons). Desflurane caused significant increase of the resistance from baseline at the three concentrations studied ($P < 0.001$ for all comparisons).

When comparing the effect of the three volatile agents on the pulmonary resistance at equivalent concentrations, it was shown that at 1 MAC isoflurane and sevoflurane had similar effects on pulmonary resistance, whereas desflurane caused a significant increase compared with the two other agents ($P < 0.001$; fig. 4). At 1.5 MAC, sevoflurane caused a significant increase of pulmonary resistance compared with isoflurane ($P < 0.001$), and desflurane caused the greatest increase compared with the two other agents ($P < 0.001$ for all comparisons). Sevoflurane and desflurane did increase overall pulmonary resistance by 17.8% and 63.7%, respectively. At 2 MAC, a statistically significant increase of pulmonary resistance was observed with all of the three volatile agents. Sevoflurane had a significantly greater effect compared with isoflurane ($P < 0.001$), and desflurane caused the greatest increase compared with the two other agents ($P < 0.001$ for both comparisons; table 3 and fig. 4).

Comparison at the Same Concentrations

There was no significant increase of pulmonary resistance from the baseline when the three anesthetics were

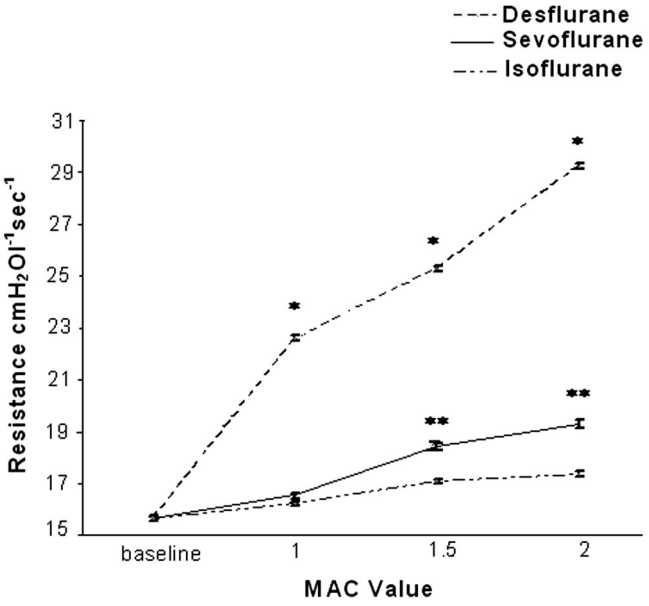

Fig. 4. Comparison of the effect of different volatile anesthetics at equivalent concentrations on total pulmonary resistance. At 1 minimum alveolar concentration (MAC), only desflurane significantly increased pulmonary resistance compared with isoflurane and sevoflurane ($P < 0.001$ for both comparisons). The difference between isoflurane and sevoflurane was not statistically significant ($P = 0.15$). At 1.5 MAC, sevoflurane significantly increased ($P = 0.015$) total pulmonary resistance compared with isoflurane, whereas desflurane caused a more pronounced increase compared with isoflurane and sevoflurane ($P < 0.001$ for all comparisons). The same findings apply at 2 MAC. Sevoflurane significantly increased pulmonary resistance compared with isoflurane ($P < 0.001$) and desflurane caused a significant increase compared with the other two volatile agents ($P < 0.001$ for both comparisons). * Increased pulmonary resistance compared with seroflurane and isoflurane; ** increased pulmonary resistance compared with isoflurane.

delivered at the same low concentration of 1.2%, whereas at 4%, all three produced a significant increase that ranged from 25.8% for desflurane to 28% for isoflurane and 28.9% for sevoflurane ($P < 0.001$ for the three agents; table 3). The differences between the three anesthetics at the aforementioned concentrations were not significant.

Discussion

Pulmonary resistance is defined as the opposition to the flow of gases caused by frictional forces within the respiratory system, and it is calculated according to the equation: Resistance = driving pressure/flow rate.[1] These frictional pressure losses (ΔP) produced by flow in tubes are a function of flow rate, tube geometry, and fluid physical properties.[2]

The inspiratory pressure method[6] was used to calculate the overall pulmonary resistance according to the equation $R = (P_{peak} - P_{plateau})/flow$. During passive ventilation, rapid airway occlusion at the end of inspiration produces an immediate decrease in transpulmonary pressure from its peak (P_{peak}) to a lower value (P_1), followed by a gradual decrease in pressure to an apparent plateau ($P_{plateau}$), which represents the static end-expiratory elastic recoil of the lung. This permits pulmonary flow resistance to be partitioned between the true intrinsic resistance of the airways ($R_{min} = (P_{peak} - P_1)/flow$) and an additional effective resistance due to time-constant inequalities and tissue stress adaptation ($R_L = (P_1 - P_{plateau})/flow$).[8]

This method provides comparable values of resistance with other techniques but does not permit discrimination between patients with airway obstruction and those with infiltrative lung disease. However, the limitations of this method are not considered to affect the measurements during the experiment of the current study.[9]

In the current study, the use of a laboratory lung model that simulates the respiratory tract eliminated the effects of lung volume and bronchial tone on airway resistance that largely affect airway resistance *in vivo*. Therefore, any change to the calculated resistance resulted from changes in the gas mixture physical properties, and changes in the flow pattern that influences the pressure decrease determined by the difference between peak pressure and plateau pressure ($\Delta P = P_{peak} - P_{plateau}$). The test lung served as a quantitative, calibrated "test load" simulating human pulmonary physiology for use in testing respiratory equipment and pulmonary research. It is designed to realistically simulate the mechanics of the adult respiratory system from the upper airway. The lung model is not a detailed model of actual human anatomy, and its use helped in determining whether the physical properties of a gas mixture alter the measurements of a fixed resistance. The adult airway is constructed by using a hose assembly, and the airway resistance exhibits parabolic characteristics in regard to pressure change as a function of flow. This nonlinear parabolic characteristic is similar to that seen in standard endotracheal tubes. Similar models have been previously used for studies examining lung mechanics during different modes of ventilation.[5,10] Compliance can be independently set for each lung using a precision-calibrated spring, and plug-in resistors are provided to simulate pulmonary resistance. The baseline resistance selected ($15\ cm\ H_2O \cdot l^{-1} \cdot s^{-1}$) has previously been reported to occur during general anesthesia.[11] The lung model mostly represents the central airways and more specifically the trachea and the main bronchi, whereas it cannot simulate alveoli. Therefore, time constant inequalities did not occur, P_1 pressure was not observed, and only P_{peak} and $P_{plateau}$ pressures were recorded (fig. 2).

The lung model was ventilated with constant flow inflations, and the inspiratory flow was recorded with screen pneumotachograph that provided correction for gas density, viscosity, temperature, and barometric pressure. This type of pneumotachograph contains a fine-mesh screen that provides a small fixed resistance to

airflow. As gas flows through the pneumotachograph, a microprocessor-based system converts the measured differential pressure to volumetric flow rate. The screen is actively heated to prevent condensation, which leads to alterations of the resistance and inaccurate results. Furthermore, it was easy to confirm its accuracy by comparing the flow measured at baseline and after the addition of anesthetic gases. Because the lung model was ventilated with volume control mode, it was mandatory that flow remain constant, and only minor breath-to-breath variations should have been recorded.

The fact that flow measurements remained constant for all gas mixtures delivered confirmed the accuracy of the pneumotachograph.

Volatile anesthetic agents produce dose-dependent decreases in airway resistance after antigen-induced bronchoconstriction in animal models.[12] Halothane is considered to have the most potent bronchodilatory properties due to decreased vagal tone,[13] but all volatile anesthetics possess bronchodilatory properties.[14,15] However, there are no studies regarding the effects of the physical properties of volatile anesthetics on airway resistance. Habre *et al.*[4] estimated the viscosity and density values of the pure component of volatile anesthetics. (isoflurane: viscosity 0.892 Pa s $\times$ 10^{-5}, density 5.19 kg/m^3; sevoflurane: viscosity 1.276 Pa s $\times$ 10^{-5}, density 6.12 kg/m^3; desflurane: viscosity 1.452 Pa s $\times$ 10^{-5}, density 5.44 kg/m^3). They also calculated the viscosity and density of their mixtures with air, 100% oxygen, and 50% oxygen. They concluded that volatile agents in the clinically applied concentrations produced a relatively small decrease of the viscosity values of gas mixtures with maximal decrease in viscosity of 3.3–3.5% at 2 MAC desflurane, whereas they significantly increased the density of the gas mixture with maximal increase of density to 47.7% at 2 MAC desflurane in air.[4] It should be mentioned that either increased density or decreased viscosity increase pulmonary resistance. The current study clearly demonstrated that isoflurane, sevoflurane, and desflurane at high concentrations increased the calculated overall pulmonary resistance in a test lung model, and the greatest increase was observed at high desflurane concentrations (2 MAC). The significant increase of pulmonary resistance observed with desflurane was considered to be the result of the high concentrations required to achieve 1, 1.5, and 2 MAC values (6.6, 9.7, and 13.3%, respectively; table 1) and not from unusually deviant values of viscosity and density of the pure component of the anesthetic.[4] This observation was supported by the finding that the three anesthetics produced similar effects on airway resistance when delivered at the same low or high concentration, suggesting that the increase of the resistance is due to the concentration delivered rather than differences of the physical properties of the agents used. Similar effects of increased resistance measurements are reported in previous studies regarding the effects of xenon on respiratory mechanics,[16,17] which showed that the high density of xenon increased airway pressure and resistance in animal models.

The findings of the current study may explain the discrepancies between *in vivo* and *in vitro* studies regarding the bronchodilatory properties of desflurane. Mercier *et al.*[18] found that desflurane relaxed proximal isolated human bronchi in a dose-dependent manner. On the contrary, Goff *et al.*[19] found that desflurane exerted no bronchodilation in patients undergoing elective surgery during general anesthesia. In the former study, the relaxation of the bronchi was measured directly, whereas in the latter, the isovolume method was used to assess total airway resistance, which is a product of bronchial tone, lung volume, flow rate, and the physical properties of the inspired gas. The current study may also explain the results of Dikmen *et al.*,[11] who found that desflurane produced bronchodilation at 1 MAC but increased airway resistance at 2 MAC. At 2 MAC, the increased density of the gas mixture may have offset the bronchodilatory effect of the anesthetic, and the overall resistance measured was increased. Theoretically, the increased pulmonary resistance caused by the physical properties of anesthetics might have deleterious effects on patients with chronic obstructive pulmonary disease or asthma. However, desflurane, which had the most pronounced effects of pulmonary resistance, has been widely used without adverse effects even in patients breathing spontaneously,[20] and there are no studies in humans to support that it should be used with caution in patients with airway hyperreactivity.

In conclusion, the high density of volatile anesthetics significantly increases airway resistance. This phenomenon is more pronounced with less potent agents that are delivered in high concentrations. Studies of the effects of these agents on airway resistance should take into account that a percent of these effects may result from the altered density of the inspired gas mixture.

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