RESPIRATION AND THE AIRWAY

Respiratory resistance during anaesthesia with isoflurane, sevoflurane, and desflurane: a randomized clinical trial

V. Nyktari1*, A. Papaioannou1, N. Volakakis2, A. Lappa3, P. Margaritsanaki1 and H. Askitopoulou1

1 Department of Anaesthesiology, University Hospital of Heraklion, Heraklion, Greece
2 Medical School, University of Crete, Greece
3 Anaesthesiology, District General Hospital of Sitia, Greece

* Corresponding author. E-mail: vnyktari@yahoo.com

Editor’s key points
• Neither sevoflurane nor isoflurane produced bronchodilation at 1 and 1.5 MAC.
• Desflurane did not affect respiratory resistance at 1 MAC, but at 1.5 MAC caused significant increase in both total and airway resistance with return to near baseline values after discontinuation of the agent.

Background. To investigate whether the effects of desflurane on inspiratory resistance are similar to those of isoflurane and sevoflurane during 30 min administration at 1 and 1.5 MAC in patients with healthy lungs.

Methods. Seventy-one patients undergoing elective surgery were randomly assigned to receive isoflurane, sevoflurane, or desflurane. Baseline inspiratory resistance was obtained after intubation and establishment of volume control ventilation. Anaesthesia was maintained with desflurane, isoflurane, or sevoflurane at 1 MAC for 30 min followed by 1.5 MAC for another 30 min. Tidal volume, flow, and inspiratory pressures were continuously recorded with a pneumotachograph. Total inspiratory resistance (Rrs), minimal resistance (Rmin), and effective resistance (DRrs) were calculated every 5 min using the end-inspiratory occlusion technique.

Results. No significant differences of the evaluated parameters (Rrs, Rmin and DRrs) were observed during administration of the three agents at 1 MAC for 30 min. At 1.5 MAC, desflurane caused a maximum increase in Rrs by 26% and in Rmin by 30% above baseline, in contrast to isoflurane and sevoflurane which did not display a significant effect on Rrs (+3.7% by isoflurane and +7.6% by sevoflurane) and Rmin (+4.7% by isoflurane and +9.6% by sevoflurane). All parameters returned to baseline after discontinuation of the volatile agent.

Conclusions. In healthy adults, neither sevoflurane nor isoflurane produced bronchodilation at 1 and 1.5 MAC. Desflurane did not affect respiratory resistance at 1 MAC, but at 1.5 MAC caused significant increase in both total and airway resistance with return to near baseline values after discontinuation of the agent.

Keywords: anaesthetics; inhalation; respiratory mechanics

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Previous studies have shown that volatile anaesthetics may decrease lung resistance and elastance by several mechanisms.1−3 The bronchodilatory actions of halothane, isoflurane, and sevoflurane have been well documented in previous studies.4−18 Current literature displays conflicting evidence regarding the effects of desflurane on respiratory resistance. Although in vitro animal studies support a strong direct relaxation effect on preconstricted airway smooth muscle,4,5 in vivo studies demonstrate the opposite effect with desflurane, causing an increase in lung resistance.19 Clinical studies reveal a significant variability on desflurane’s action on respiratory resistance with a tendency to aggravate bronchoconstriction.16,20 In addition, it has been shown in a laboratory lung model that high concentrations of desflurane induced an increase in pulmonary resistance due to an increase in inspired gas mixture’s density.21

The aim of the present study was two-fold: (i) to investigate the effects of 1 and 1.5 MAC desflurane on total inspiratory resistance (Rrs) and its components during 30 min administration in patients with healthy lungs undergoing general anaesthesia and (ii) to compare the effects of desflurane, isoflurane, and sevoflurane on respiratory resistance in patients with healthy lungs.

Our primary hypothesis was that desflurane at high concentrations would cause an increase in respiratory resistance partially due to increased density of the inspired gas mixture.

Methods

The study was approved by the Institutional Ethics Committee and the study protocol was registered at http://www.controlled-trials.com/ISRCTN33947005/ (ISRCTN33947005). Between November 2004 and January 2010, all patients...
aged 18–75 yr old, undergoing elective non-abdominal, non-thoracic surgery under general anaesthesia were considered eligible to enter the study. Written informed consent was obtained from all patients who entered the study.

Exclusion criteria included history of asthma, chronic obstructive pulmonary disease, or malignant hyperthermia, and also previous treatment with bronchoactive drugs (β-agonists or antagonists, theophylline, anticholinergics, and corticosteroids). Patients who consented to enter the study were randomized to receive isoflurane, sevoflurane, or desflurane for anaesthesia maintenance, using the method of random numbers.

**Study protocol**

Patients were premedicated with midazolam 0.05 mg kg⁻¹ i.m. 1 h before operation. In the operating theatre, they were connected to standard basic monitoring to follow-up electrocardiography, non-invasive arterial pressure, and pulse oximetry.

Intraoperative monitoring included \( F_{\text{IO}_2} \), capnography, inspiratory and expiratory concentrations of inhaled agents, MAC, airway pressures, and tidal (\( V_T \)) and minute volumes (\( V_m \)). The end-tidal concentrations of each anaesthetic agent were measured by an infrared light absorption agent analyser (IRIA; Draeger Medical, Lübeck, Germany) and adjusted to the target MAC values using Mapleson’s formula \( \text{MAC}_{\text{age}} = \text{MAC}_{40} \times 10(0.00269 \times \text{age} - 40) \). \( \text{MAC}_{40} \) corresponded to an end-tidal concentration of 1.9% for sevoflurane, of 1.2% for isoflurane, and of 6.5% for desflurane. For anaesthesia induction, remifentanil 0.1 μg kg⁻¹, propofol 2 mg kg⁻¹, and cisatracurium 0.2 mg kg⁻¹ were administered. Tracheal intubation was performed under direct laryngoscopy with a 7.5 mm cuffed tracheal tube (TT) in all patients. An arterial line was inserted for continuous monitoring of arterial pressure and sampling of arterial blood gases. Volume control ventilation (Primus, Draeger Medical) was set as described below.

Tidal volume 7 ml kg⁻¹ of ideal body weight, ventilatory frequency 10 bpm, PEEP 5 cm H₂O, inspiratory plateau time (time of inspiratory hold) equal with 50% of total inspiratory time, and fresh gas flow (FGF) 5 litre min⁻¹. A screen pneumotachograph with a differential pressure-based flow sensor (RSS100-HR; Hans Rudolph, Kansas City, MO, USA) was inserted between the TT and the Y piece of the respiratory circuit, for the measurement of flow and tidal volume. The readings were corrected automatically for gas density, viscosity, temperature, and barometric pressure by selecting the corresponding anaesthetic agent from the menu of the pneumotachograph’s software. The accuracy of the readings was easily confirmed by the fact that during volume control ventilation, flow remained constant. A pressure transducer was also inserted between the tracheal tube and the Y piece of the respiratory circuit for continuous recordings of inspiratory pressures. At the beginning of the study, a first baseline measurement was obtained after tracheal intubation and initiation of mechanical ventilation, before the administration of the volatile agents. Thereafter, anaesthesia was maintained with 1 MAC end-tidal concentration of sevoflurane, isoflurane, or desflurane. Measurements of flow and pressures were recorded for five consecutive breaths every 5 min for 30 min at 1 MAC steady state. Subsequently, the inhaled agent was turned off and two further measurements of flow and airway pressures were recorded, when end-tidal concentrations reached 0.5 and 0 MAC. A second baseline measurement was obtained after the first series of recordings at 1 MAC were conducted, the volatile agent was turned off, and the end-tidal concentration of the volatile was zeroed. After the second baseline measurement, the volatile agent was turned on to achieve 1.5 MAC. All baseline measurements of both \( R_{\text{rs}} \) and \( R_{\text{min}} \) are included in Table 1.

**Table 1** Patients’ characteristics. No differences were noted among the three volatile groups. Values are expressed as mean (SD) unless otherwise stated. \( R_{\text{rs, baseline}} \), baseline total resistance; \( R_{\text{min, baseline}} \), baseline minimal resistance. *Significant difference between sevoflurane and isoflurane.

<table>
<thead>
<tr>
<th></th>
<th>Group D (n = 22)</th>
<th>Group S (n = 19)</th>
<th>Group I (n = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [yr, median (so)]</td>
<td>58.04 (19.55)</td>
<td>66.27 (15.8)</td>
<td>65.19 (14.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>8/15</td>
<td>5/15</td>
<td>3/13</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>28.4 (5.5)</td>
<td>28.7 (8.4)</td>
<td>31 (5.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (Yes/No)</td>
<td>3/20</td>
<td>3/17</td>
<td>2/14</td>
<td>NS</td>
</tr>
<tr>
<td>ETCO₂ (mm Hg)</td>
<td>33.06 (0.9)</td>
<td>32.5 (1.1)</td>
<td>32.7 (0.53)</td>
<td>NS</td>
</tr>
<tr>
<td>PAO₂ (mm Hg)</td>
<td>38.8 (4.2)</td>
<td>39 (4.5)</td>
<td>39.4 (4.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Time from 2nd baseline measurement until achievement of 1 MAC (min)</td>
<td>6.8 (1.8)</td>
<td>5.9 (3.1)*</td>
<td>8.6 (3)*</td>
<td>0.019</td>
</tr>
<tr>
<td>RSs (cm H₂O litre⁻¹ s⁻¹) [mean (SD)]</td>
<td>8.7 (0.8)</td>
<td>7.2 (4.6)</td>
<td>7.9 (4.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Before administration of 1 MAC</td>
<td>9.35 (1.6)</td>
<td>7.06 (2.8)</td>
<td>7.7 (4.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Before administration of 1.5 MAC</td>
<td>6.8 (0.7)</td>
<td>5.5 (2.7)</td>
<td>6.6 (3.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Before administration of 1.5 MAC</td>
<td>6.9 (1.3)</td>
<td>5.1 (2.5)</td>
<td>6.2 (3.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Measurements

Total inspiratory resistance ($R_{rs}$) was calculated using the inspiratory hold manoeuvre. During the end-inspiration flow pause, the static airway pressure waveform has a characteristic trend, with the highest peak at end-inspiration [$P_{max}$], followed by a rapid decrease after the zeroing of flow [$P_1$], and a slow decay until a plateau is reached [$P_{plat}$] (Fig. 2). The accuracy of the results requires passive conditions; therefore, all patients were paralysed under deep anaesthesia.

Total inspiratory resistance ($R_{rs}$) and its components, minimal resistance ($R_{min}$) and effective resistance ($D_{rs}$), were calculated according to the equations: $R_{rs} = [P_{max} - P_{plat}]/V'$, $R_{min} = [P_{max} - P_1]/V'$, $D_{rs} = (P_1 - P_{plat})/V'$, where $V'$ denotes flow.

$R_{min}$ reflects mainly airway and tracheal tube resistance and denotes the flow-dependent component of $R_{rs}$.23 24 $D_{rs}$ represents two phenomena, time-constant inhomogeneities within the lung and the viscoelastic behaviour of the pulmonary tissues and chest wall.23–25 Respiratory values are expressed as the mean of five consecutive breaths.

Statistical analysis

In order to detect a difference of 1 SD between respiratory resistance measurements in the desflurane group and the study to have a power of 80% and type of a error of 0.05, it was estimated that a minimum of 16 patients per group were required.

To enable comparison of the changes of the respiratory resistance between groups, all evaluated parameters are expressed as percentages of baseline values and each patient served as their own control. Statistical analysis of respiratory resistance was performed with two-way ANOVA for repeated measurements and Bonferroni’s post hoc test. Data are expressed as mean values (SD). A P-value of <0.05 was considered significant.

Results

Seventy-one patients were randomized into three groups to receive desflurane (n=25), sevoflurane (n=24), and...
Isoflurane (n=22). In the final analysis, a total of 12 patients were excluded (three in the desflurane group, five in the sevoflurane group, and four in the isoflurane group), as shown in Figure 3.

Patient characteristic data (age, height, weight, ASA physical status, and smoking history) did not differ among groups (Table 1). Baseline values of $R_{rs}$ and $R_{min}$ were within previously established values for healthy intubated subjects [8.5 (1.5) cm H$_2$O litre$^{-1}$ s$^{-1}$],22 23 and did not differ among groups.

We studied the effects of 1 MAC of all three volatile agents on $R_{rs}$, $R_{min}$, and $D_{rs}$. The administration of 1 MAC concentrations of the volatile agents did not have a significant effect on all evaluated parameters.

We also studied the effects of 1.5 MAC of all three volatile agents on $R_{rs}$, $R_{min}$, and $D_{rs}$. Of the three volatile agents administered at 1.5 MAC, only desflurane had a significant effect characterized by an increase in all evaluated parameters ($R_{rs}$, $R_{min}$, and $D_{rs}$, Fig. 4).

$R_{rs}$ and $R_{min}$ increased during the 30 min of desflurane administration ($P<0.001$ for all comparisons, Fig. 4) and decreased to near baseline values after discontinuation of the agent, but surprisingly the trends were not parallel.

The maximum increase from baseline for $R_{rs}$ was observed at 0 min [+25.7 (5.23%) above baseline, $P<0.001$], but thereafter declined slowly and at 30 min of administration, $R_{rs}$ was significantly lower compared with the maximum value observed at 0 min [$R_{rs}$ at 30 min vs $R_{rs}$ at 0 min $-12.7$ (2.4%), $P<0.01$]. The same was observed for the comparisons between 0 min and 0.5 and 0 MAC $-21.1$ (0.9%), $P<0.001$ for both comparisons, Fig. 4).

The maximum increase in $R_{min}$ was observed at 10 min [+31.78 (10.31%) above baseline, $P<0.001$] and thereafter declined slowly. After 30 min of administration, $R_{min}$ decreased significantly compared with the maximum increase at 10 min [$R_{min}$ at 30 min vs $R_{min}$ at 10 min $-13.3$ (4.4%), $P<0.05$]. The same was true for the comparisons between 10 min and 0.5 and 0 MAC $-29.3$ (3.6%) and $16.6$ (4.8%), $P<0.001$ for both comparisons, Fig. 4).

The initial significant increase in $D_{rs}$ at 0 min [+45.5 (12.6%), $P<0.001$] was not sustained (Fig. 4).

In the sevoflurane group, a trend towards higher $R_{rs}$ and $R_{min}$ was observed, but changes were not statistically significant. On the other hand, the isoflurane group showed a trend towards decreased values of $R_{rs}$ and $R_{min}$. The highest decreases compared with baseline values were observed after discontinuation of the agent [$R_{rs}$ at 0.5 MAC $-9$ (3.5%) and at 0 MAC $-7.7$ (3.0%), $R_{min}$ at 0.5 and at 0 MAC $-9.9$ (3.2%) and $-9.8$ (4%), respectively] but did not reach statistical significance.

**Comparison of agents**

The desflurane group was associated with higher $R_{rs}$ and $R_{min}$ when compared with the sevoflurane group. $R_{rs}$ was significantly higher at 0 min ($P<0.01$), 5 and 20 min of administration ($P<0.05$) (Fig. 5). $R_{min}$ was significantly higher at 5, 10, and 20 min ($P<0.05$).

The differences between desflurane and isoflurane were more pronounced. $R_{rs}$ was higher in the desflurane group during the whole period of administration ($P<0.001$ at 0, 5, and 25 min, $P<0.01$ at 15 and 20 min, and $P<0.05$ at 30 min). The same applied for $R_{min}$ ($P<0.01$ during the first 20 min of volatile administration, $P<0.001$ at 25 min, and $P<0.05$ at 30 min). Regarding $D_{rs}$, no difference was noted between desflurane and sevoflurane, whereas comparison of desflurane with isoflurane revealed a significant difference only at 0 min ($P<0.01$) (Fig. 5). No differences of $R_{rs}$, $R_{min}$, and $D_{rs}$ were noted between isoflurane and sevoflurane.
Discussion

The present study investigated the effects of desflurane, sevoflurane, and isoflurane on the inspiratory resistance in healthy adults. The results showed that at 1 MAC, none of the three agents significantly affected inspiratory resistance.

At 1.5 MAC, only desflurane had a significant effect on all evaluated parameters ($R_{rs}$, $R_{min}$, and $D_{Rrs}$). A comparison among the three agents revealed that desflurane at 1.5 MAC significantly increased $R_{rs}$, $R_{min}$, and $D_{Rrs}$ compared
with sevoflurane and isoflurane. It was also found that $R_{rs}$ and $R_{min}$ returned to near baseline values as soon as the inhaled agent was discontinued. To our knowledge, it is the first study to separate $R_{rs}$ into its components ($R_{min}$ and $D_{rs}$) and to examine the effects of the abovementioned agents over a longer period of 30 min at 1 and 1.5 MAC concentrations.

Only two studies have investigated the effects of desflurane on respiratory resistance in humans with healthy lungs and their results are in agreement with the present study. Goff and colleagues showed no bronchodilatory properties of desflurane at 1 MAC on healthy intubated subjects, but significant increases of total respiratory resistance in smokers. Dikmen and colleagues found that 2 MAC of desflurane caused a significant increase in total respiratory resistance. However, the differences in methodology and the duration of the measurements between these studies make a comparison of the results difficult.

The observed sustained increase in airway resistance caused by 1.5 MAC of desflurane could be explained by two mechanisms: an increase in the inspired gas mixture density due to the high concentrations of desflurane used.

**Fig 5** $R_{rs}$, $R_{min}$, and $D_{rs}$ during the 30 min administration of 1.5 MAC of the three volatile agents. $R_{rs}$, total respiratory; $R_{min}$, minimal resistance; $D_{rs}$, effective resistance. The effect of the volatile agents is expressed as the mean % difference from baseline respiratory resistance (SEM). *Comparison of desflurane with isoflurane. No difference between sevoflurane and isoflurane is observed.
airway resistance would remain constant or even increase in the 
result of bronchial constriction, it would be expected that 
airway resistance would remain constant or even increase 
during the whole period of administration. Most probably, 
the initial increase in $R_{\text{min}}$ was the result of the density of 
the inspired mixture which was slowly attenuated by the 
capacity of desflurane to dilate bronchial musculature.

The effect of volatile anaesthetics on the density of an 
inspired mixture was first described by Habre and colleagues. A previous study conducted in our institution showed that high concentrations of desflurane increased the calculated pulmonary resistance of a laboratory lung model due to an increase in the gas mixture's density. The density effect could explain the trend for higher $R_{\text{min}}$ (increase up to 9.5 (3.4%)) during 1.5 MAC administration of sevoflurane. This unfavourable effect on airway resistance is counterbalanced by a concurrent decrease in $D_{\text{pers}}$, representing improvement of either the time-constant inhomogeneities within the lung or the viscoelastic behaviour of the pulmonary tissues.

The inspiratory occlusion method used in our study has been extensively used in sedated, paralysed subjects and is now considered as the method of reference. This method allowed us to separate the mechanical properties of the airways and the tissues. This is the first clinical study to suggest that $R_{\text{min}}$ reflecting airway resistance is affected not only by alterations of bronchial tone (bronchospasm or bronchodilation) but also by increased density of the inspired gas mixture. The absence of bronchodilation with isoflurane and sevoflurane is not in contradiction with previous scientific evidence. Even though our results showed that isoflurane was associated with a trend to decrease respiratory resistance, the study was underpowered for these differences to reach a statistical significance. Furthermore, previous studies documented a decrease in respiratory resistance after volatile administration in conditions of high baseline airway tone. No effect of halothane and isoflurane on respiratory resistance and compliance was shown on the unstimulated airway.

In conclusion, from the commonly used volatile anaesthetics, no agent can surpass the others regarding their effect on respiratory resistance, when administered at concentrations of 1 MAC for a period of 30 min. The higher concentrations of desflurane used to achieve 1.5 MAC caused an increase in total respiratory resistance. This effect should be taken into account in patients with hyperventilatory airways or in cases where the anaesthetist attempts to overcome intraoperative bronchospasm by increasing anaesthetic depth using high inspired concentrations of desflurane. On the other hand, 1.5 MAC concentrations of desflurane could be associated with improvement of time-constant inhomogeneities within the lung. Further studies are needed to confirm whether more prolonged administration of high concentrations of desflurane could have a favourable effect on the component of resistance attributed to tissue viscoelastic properties and alveolar time-constant inequality.

**Conflict of interest**
None declared.

**References**