Original Article

Bronchial mucus transport velocity in patients receiving desflurane and fentanyl vs. sevoflurane and fentanyl

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Summary

Background and objective: Sevoflurane has been shown to distinctly reduce bronchial mucus transport velocity, an essential determinant of mucociliary clearance and pulmonary complications. However, sevoflurane is regarded as one of the least irritant volatile anaesthetics, especially when compared with desflurane. Hence, the aim of this double-blind, randomized, controlled trial was to assess differences in bronchial mucus transport velocity between sevoflurane and desflurane. **Methods:** Twenty patients listed for general surgery were randomized to receive either maintenance of anaesthesia with desflurane and fentanyl, or sevoflurane and fentanyl. Thirty minutes after tracheal intubation, bronchial mucus transport velocity was assessed by fiberoptic observation of the movement of methylene blue dye applied to the dorsal surface of the right main bronchus. **Results:** Both agents distinctly reduced bronchial mucus transport velocity when compared with previous studies, but the degree of impairment did not significantly differ between the investigated groups (median [25%/75% percentile]): desflurane 1.5 [0.5/4.2] vs. sevoflurane 1.3 [0.3/2.9] mm min⁻¹, $P = 0.343$). **Conclusions:** Desflurane is commonly regarded as more irritant to the airway, but as far as bronchial mucus transport velocity is concerned, the choice between sevoflurane and desflurane does not seem to matter.

Keywords: ANAESTHESIA INHALATIONAL; DESFLURANE; SEVOFLURANE; MUCUS; BRONCHIAL, transport velocity.

Introduction

Intact mucociliary clearance is paramount for removal of inhaled particles and micro-organisms from the upper and lower respiratory tract. Impairment of cilia beat frequency, a key mechanism of mucociliary clearance and thus bronchial mucus transport velocity (BTV) is associated with a significantly higher risk for pulmonary complications, at least in ventilated ICU patients [1]. Volatile anaesthetics are known to reduce cilia beat frequency *in vitro* [2,3]. *In vivo*, isoflurane- and sevoflurane-based anaesthesia resulted in a sig-

nificantly lower cilia beat frequency when compared with the use of propofol [4,5]. These findings suggest that patients who are anaesthetized with a volatile agent might exhibit impaired bronchial mucus transport. Desflurane is commonly regarded to cause more adverse responses to the airway than sevoflurane [6]. Hence we hypothesized that a volatile-based anaesthetic with desflurane would affect BTV to a greater extent than with sevoflurane. Therefore, the aim of this study was to compare BTV among patients having maintenance of anaesthesia with either desflurane and fentanyl or sevoflurane and fentanyl.

Methods

After approval by the regional Ethics Committee and having given written informed consent,

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Accepted for publication 26 March 2008 EJA 4931
First published online 9 May 2008

20 patients (ASA physical status I-II) undergoing elective general surgery were randomized by sealed envelope allocation to receive either maintenance of anaesthesia with desflurane and fentanyl (Group DES) or with sevoflurane and fentanyl (Group SEVO). Patients with a history of respiratory tract pathology, expected difficult airway, atopy, smoking or those using drugs known to influence the BTV (β -adrenoceptor antagonists, cortisone, atropine, theophylline and catecholamines) were excluded from the study. Patients did not receive sedative or anticholinergic premedication.

Induction of anaesthesia was standardized. After insertion of a peripheral intravenous (i.v.) cannula, fentanyl $1 \mu\text{g kg}^{-1}$ was given. Two minutes later, a bolus of propofol 2 mg kg^{-1} was administered and cisatracurium 0.15 mg kg^{-1} was given for neuromuscular block. Patients' tracheas were then intubated using a tracheal tube size 7.5 mm (ID) for female and 8.0 mm (ID) for male patients. The cuff was inflated with air until no leak of air was heard. The lungs of the patients were ventilated using a pressure-controlled mode with a maximum pressure of $25 \text{ cm H}_2\text{O}$ and a positive end-expiratory pressure (PEEP) of $5 \text{ cm H}_2\text{O}$. A circle anaesthetic breathing system (Aestiva 5TM; Datex Ohmeda Inc., Madison, WI, USA) with an antimicrobial filter for air humidification (Thermovent HEPATM; Portex Inc., Keene, NH, USA) was used. Fresh gas flow was 2 L min^{-1} with an inspired oxygen fraction ($F_{\text{I}}\text{O}_2$) of 0.5 in an oxygen-air mix. Ventilation rate and maximum airway pressure were adjusted to maintain a normal end-tidal CO_2 (ETCO_2) ($33\text{--}43 \text{ mmHg}$). In the DES group, anaesthesia was maintained with desflurane targeting an end-tidal minimum alveolar concentration (MAC) of $0.8\text{--}1.5$ and fentanyl boluses $0.5\text{--}1 \mu\text{g kg}^{-1}$ as required. In the SEVO group, patients received sevoflurane $0.8\text{--}1.5$ MAC end-tidal and fentanyl boluses $0.5\text{--}1 \mu\text{g kg}^{-1}$ as required. In both groups, the dose of the drugs was adjusted to clinical need, within the aforementioned limits. Preferably, the repetitive doses of fentanyl were adjusted as the first step to keep the dose of desflurane and sevoflurane as stable as possible and achieve a steady-state concentration of these drugs.

Thirty minutes after tracheal intubation, and with the patient in supine position, a swivel connector (Bodai PEEP SafeTM; Sontek Medical Inc., Hingham, MA, USA) was inserted between the tracheal tube and the circle system. BTV was assessed using a modification of the method described by Keller and Brimacombe [7] and Sackner and colleagues [8] (Fig. 1). A fibrescope (Videoscope type PI60TM; Olympus Optical Co. GmbH, Hamburg, Germany) was passed through

Figure 1.

Method of bronchial mucus transport velocity (BTV) assessment. (a) After placement of a drop of 1% methylene blue dye on the dorsal surface of the right main bronchus, the bronchoscope is marked at the entry point of the swivel connector () and removed thereafter. (b) 2, 4 and 6 min later, the bronchoscope is pushed back in and its tip levelled with the position of the methylene blue. The bronchoscope is marked again at the entry point of the swivel connector, and the distance to the first mark is assessed.*

the swivel connector and the right main bronchus was visualized. A 16-G epidural catheter (Portex Inc.) with the tip cut off to achieve one single, end-standing hole, was inserted into the working channel of the scope. The catheter was inserted until it was seen through the lens of the scope and was almost touching the mucus membrane of the right main bronchus. A drop of 1% methylene blue dye (approximately 0.02 mL) was introduced into the epidural catheter and flushed through with an air-filled 1-mL syringe, to place it onto the posterior surface of the bronchial mucosa, approximately 2.5 cm below the carina. The time required to apply the dye was approximately 1 min . After placement of the dye, the lens of the bronchoscope was positioned neutrally and moved up to the proximal margin of the drop. The scope was marked where it entered the swivel connector and removed from the tube. The distance between the connector and the mark was considered the baseline value. At 2, 4 and 6 min after the application of the dye, the position of the proximal margin of the dye was determined again by the method described (Fig. 1). The mean of the three assessments was calculated and divided by two to give the BTV in mm min^{-1} . In our experience, the method of BTV assessment has a certain probability of error due to either overestimating or underestimating the position of the dye. Hence, three assessments every 2 min were preferred to only one assessment after 6 min, to minimize the source of error. Nasal core body temperature, doses of desflurane, sevoflurane, fentanyl, ETCO_2 , $F_{\text{I}}\text{O}_2$, maximum airway pressure and PEEP, ventilation rate and tidal volumes were all recorded at the times

of BTV assessment. Two investigators (TL, AM), blinded to the volatile agent used (by means of covering the vapours and volatile-associated parameters on the monitor), performed all assessments. In addition, the investigators were blinded to the previous marks on the scope by utilizing the scope's video screen, rather than looking at the scope lens itself.

For sample size estimation we used the data (mean, SD) published by Ledowski and colleagues [5] and calculated that a minimum number of eight patients per group was required to detect a difference of at least 3.5 mm min^{-1} (a value demonstrated by Konrad and colleagues [1] to be clinically significant) with a power of 80%. To account the possible loss of patients as experienced in a previous study using the same method [5], we included 10 patients per group. Statistical analysis was performed using two-factor analysis of variance (ANOVA), Spearman's correlation coefficient and the χ^2 -test (comparison of type of operation between groups). The Kolmogorov–Smirnov test was used for testing the data for normal distribution and the homogeneity of variance test (Levene statistic) was used to test for the equality of group variances. Alpha-error was 0.05 and β -error 0.2. Unless otherwise stated, normally distributed data are presented as mean $\pm$ SD. Non-parametric data (BTV) are presented as median [25%/75% percentile], using the *U*-test for statistical comparison.

Results

Data of all 20 patients (age 18–75 yr) were included in the subsequent analysis. The groups showed no significant differences regarding type of surgery, age, height, body weight, body temperature, F_1O_2 , ETCO_2 , peak airway pressures and fentanyl dosage (Table 1). None of these parameters showed a significant correlation with BTV. The mean end-tidal volatile anaesthetic concentration at the time of BTV assessment was $5.8 \pm 2.1 \text{ vol\%}$ in the DES group and $2.3 \pm 0.48 \text{ vol\%}$ in the SEVO group.

BTV values did not differ significantly between the groups (median [25%/75% percentile]): DES group ($1.5 [0.5/4.2] \text{ mm min}^{-1}$) and SEVO group ($1.3 [0.3/2.9] \text{ mm min}^{-1}$; $P = 0.383$) (Fig. 2).

Discussion

Mucociliary clearance is an integral part of lung defence mechanisms, enabling efficient clearance of inhaled particles, including micro-organisms, from the respiratory tract [9,10]. Impairment of the mucociliary clearance may lead to deleterious pulmonary complications such as retention of

Table 1. Patient characteristics in the desflurane and sevoflurane groups.

	Desflurane (<i>n</i> = 10)	Sevoflurane (<i>n</i> = 10)
Age (yr)	50 $\pm$ 22	46 $\pm$ 15
Height (cm)	162 $\pm$ 5	169 $\pm$ 8
Body weight (kg)	78 $\pm$ 16	83 $\pm$ 19
Body temperature ($^{\circ}\text{C}$)	36 $\pm$ 0.3	36 $\pm$ 0.5
Fentanyl (μg)	215 $\pm$ 103	212 $\pm$ 119
End-tidal CO_2	35.3 $\pm$ 3.3	36.7 $\pm$ 4.9
F_1O_2	0.56 $\pm$ 0.13	0.5 $\pm$ 0.23
Peak airway pressure (cm H_2O)	19 $\pm$ 5	19 $\pm$ 5
Positive airway pressure (cm H_2O)	5 $\pm$ 2	3 $\pm$ 3
Ventilation rate ($\times \text{min}^{-1}$)	12 $\pm$ 1	11 $\pm$ 2
Tidal volume (mL)	574 $\pm$ 154	504 $\pm$ 70

Data are given as mean $\pm$ SD. No significant differences were seen between the groups (ANOVA). F_1O_2 : fraction of inspired oxygen.

Figure 2. Bronchial mucus transport velocity (BTV) (median, 25%/75% percentile) in patients anaesthetized with either sevoflurane and fentanyl (SEVO) or desflurane and fentanyl (DES). No significant differences in BTV were found between the two groups. $P = 0.343$ (*U*-test).

secretions, atelectasis and lower respiratory tract infections. Konrad and colleagues demonstrated a reduction in BTV to be associated with an increased rate of pulmonary complications in critically ill patients [1]. The same authors compared BTV in postoperative ventilated chronic smokers vs. non-smokers after major abdominal or thoracic surgery. Smokers presented a significant reduced BTV (median BTV 2.5 vs. 8.2 mm min^{-1}), which was correlated with a higher rate of pulmonary complications [11]. Several studies have confirmed that anaesthetic agents affect ciliary function [3,4]. Raphael and colleagues demonstrated that the volatile anaesthetics halothane, isoflurane and enflurane depress ciliary function *in vitro* [2,3]. More recently, Raphael and colleagues' experimental data were confirmed *in vivo*: anaesthesia maintenance

with sevoflurane resulted in a significantly reduced BTV when compared with total i.v. anaesthesia [5].

Desflurane is widely regarded to be more pungent than sevoflurane. An increased incidence for adverse airway responses, attributed to an increased airway irritability, has been reported with the use of desflurane, compared to sevoflurane and isoflurane [6,12,13].

These clinical observations are backed by an animal study of Cervin and Lindberg who compared changes of mucociliary activity with the use of halothane, isoflurane and desflurane in the rabbit maxillary sinus [14]. The authors concluded that the inflammatory, NK1 mediated response to the exposure to halogenated agents likely accounted for their airway-irritating properties. This response was found most pronounced for desflurane. Surprisingly, our study did not detect differences in BTV between desflurane and sevoflurane.

However, both volatile anaesthetics reduced BTV substantially when compared with previously published own results comparing sevoflurane and total i.v. anaesthesia [5].

A potential limitation of our study is that patients were not exposed to different standardized concentrations of desflurane and sevoflurane. Instead, we opted to allow for administration of the volatile agents within a certain range as this reflects clinical practise. However, the effect of volatile agents on BTV do not appear to be dose dependant: Raphael and colleagues [2,3] demonstrated a similar depression of cilia function after 1 or 3 MAC of halothane, enflurane or isoflurane.

We did not assess clinical outcome, hence we are unable to comment on this issue from our own data. When compared with published data for BTV during total i.v. anaesthesia [15], BTV in the current trial appears to be reduced during both sevoflurane- and desflurane-based anaesthesia. However, a direct comparison between the results of both studies is difficult, as Ledowski and colleagues [15] used a laryngeal mask airway, whereas the current trial investigated intubated patients.

Since Konrad and colleagues [1] described a reduction in BTV of as little as 3.5 mm min^{-1} to be associated with an increase in pulmonary complications, the difference seen between our aforementioned studies may indicate clinical significance. However, Konrad and colleagues performed their studies in patients who were ventilated for at least 4 days. Therefore, it remains unclear, whether or not short-term exposure to volatile agents contributes to an increase in pulmonary risk. Raphael and colleagues [3] demonstrated a recovery of ciliary beat frequency within 60 min after enflurane or isoflurane withdrawal *in vitro*. The assessment of BTV in our study was limited to one time point only.

Hence, we are unable to comment on the duration of volatile-induced changes in BTV.

In conclusion, though having been described to be more irritant to the airway, anaesthesia with desflurane did not show significant differences in BTV when compared with sevoflurane in intubated subjects. Therefore, as far as BTV is concerned the choice of volatile does not seem to matter.

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