Airway irritation produced by volatile anaesthetics during brief inhalation: comparison of halothane, enflurane, isoflurane and sevoflurane

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Eleven male volunteers were studied to compare the airway irritation produced by the four anaesthetic agents: halothane, enflurane, isoflurane and sevoflurane at two concentrations, equivalent to one and two MAC. Tidal volume, respiratory frequency and functional residual capacity changes induced by 15 sec inhalation of the anaesthetics were measured using respiratory inductive plethysmograph. Appearance of the cough reflex was also observed. The order of subjective airway irritation was evaluated by the volunteers. Inhalation of the anaesthetic agents induced a decrease in tidal volume, increase in respiratory frequency and decrease in functional residual capacity. Significant changes were considered to have occurred if tidal volume and respiratory frequency changed by more than 30% from the resting values for at least ten seconds, or if functional residual capacity changed by more than 30% of the value at resting tidal volume, for at least ten seconds. Each change was induced most frequently by isoflurane followed by enflurane, halothane and, least frequently, by sevoflurane. The orders of appearance of the cough reflex and of subjective airway irritation were similar. Sevoflurane did not elicit a cough reflex. It is concluded that sevoflurane was the least irritant anaesthetic and is considered to be the most suitable for inhalational induction of anaesthesia.

Sept volontaires du sexe masculin font partie d'une étude visant à comparer les effets irritants de quatre agents anesthésiques sur les voies respiratoires: l'halothane, l'enflurane, l'isoflurane et le sévoflurane, à deux concentration qui équivalent soit à MAC 1, soit à MAC 2. On mesure les changements de volume courant, de fréquence respiratoire et de capacité résiduelle fonctionnelle à l'aide d'un pléthysmographie à induction. On note l'apparition du réflexe de toux. De plus, on évalue le degré subjectif d'irritation éprouvé par les sujets. L'inhalation d'agents anesthésiques cause une baisse du volume courant, une augmentation de la fréquence respiratoire et une diminution de la capacité résiduelle fonctionnelle. On considère significatifs les changements de volume courant et de fréquence respiratoire de plus de 30% des valeurs de repos pour au moins dix secondes, les changements de capacité résiduelle fonctionnelle de plus de 30% de sa valeur au volume courant de repos pour au moins dix secondes. Les changements sont initiés principalement par l'isoflurane, suivi par l'enflurane, l'halothane et moins fréquemment par le sévoflurane. L'ordre d'apparition du réflexe de toux et de l'impression subjective d'irritation des voies aériennes est identique. Le sévoflurane ne provoque pas de réflexe de toux. On conclut que le sévoflurane est le moins irritant des anesthésiques et qu'on peut le considérer comme celui qui convient le mieux à l'induction de l'anesthésie par inhalation.

Key words
AIRWAY: irritation;
ANAESTHETICS, VOLATILE: enflurane, halothane, isoflurane, sevoflurane;
VENTILATION: anaesthetics, effects of.

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Airway irritation is one of the most important characteristics of the volatile anaesthetic agents, especially when they are used for inhalational induction of anaesthesia. Among the anaesthetic agents used clinically, isoflurane[1-5] and enflurane[5,6] have been reported to induce cough, bronchospasm and breath-holding. In addition, several reports have indicated that desflurane also irritated the airway.[7-9] Airway irritation by sevoflurane has not been assessed, except in a preliminary study by Holaday and Smith.[10] With six healthy male volunteers, the

TABLE I Demographics of the volunteers (mean (SD))

Number	11
Age (yr)	30.2 (3.7)
Height (cm)	170.3 (6.8)
Weight (kg)	65.2 (6.7)

study reported that inhalational induction with sevoflurane had been rapid and smooth and that all subjects had appeared relaxed during exposure.

In our clinical practice, sevoflurane seemed to produce little airway irritation. To confirm this observation, we planned to quantify the amount of the irritation produced by the four volatile anaesthetic agents, halothane, enflurane, isoflurane and sevoflurane, which are available for clinical use in Japan.

Method

This study was approved by the Institutional Human Research Committee and informed consent was given by each subject. Eleven healthy male volunteers were studied. The demographic data are shown in Table I.

A non-rebreathing circuit with one-way valves (#1500, Hans Rudolph Inc. U.S.A.) was used. In the inspiratory circuit, an anaesthetic vaporizer, a reservoir bag and a three-way stop-cock, which was used to switch inspired gas from atmosphere to anaesthetic vapour, were connected consecutively.

Each anaesthetic vaporizer was calibrated using mass spectrometry. A respiratory inductive plethysmograph (Respigraph®, NIMS, U.S.A.) was used to measure tidal volume and respiratory frequency. Change of functional residual capacity was also measured by change of end expiratory level using the Respigraph®. The Respigraph® was calibrated with a pneumotachograph (VM-7000, Fukuda, Japan). The pneumotachograph and a gas analyzer (Capnomac®, Datex, Finland) were inserted between the one-way valves and a mask.

The subjects, in the supine position, breathed spontaneously through the mask attached to the non-rebreathing circuit. After at least five minutes in that position, a vaporizer of one of the four anaesthetic agents, which had been preset at equivalent to one MAC, was connected to the circuit for 15 sec. At least two minutes before connections of the vaporizers, 8 L · min^{-1} air had been passed through them. The MAC values of halothane,[11] enflurane,[12] isoflurane[13] and sevoflurane[14] were assumed to be 0.77, 1.68, 1.15 and 1.71, respectively. At the start of the inhalation of the anaesthetic agents their vapor concentrations were confirmed with a gas analyzer. After 15 sec the inhalational gas was returned to atmosphere. The order of inhalation of the four agents was decided at random. The volunteers were not informed

TABLE II The severity of subjective airway irritation

Subjective airway irritation	*Severity point*
Least	1
Second least	2
Second most	3
Most	4

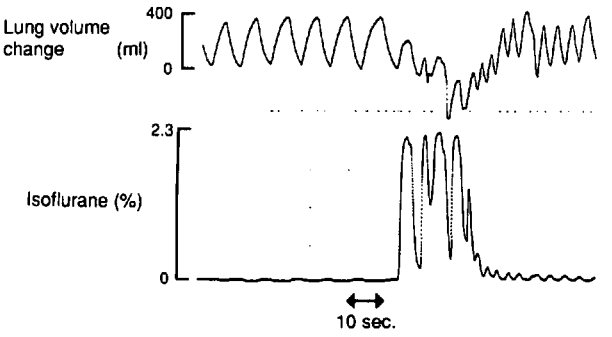

FIGURE 1 An example of lung volume change measured using Respigraph®. Inhalation of 2 MAC isoflurane for 15 sec decreased tidal volume and functional residual capacity, and increased respiratory rate.

of the order. The interval between inhalations was at least three minutes. Before the start of the next inhalation, the end expiratory anaesthetic concentration was confirmed to be zero with the Capnomac. Appearance of the cough reflex was also observed. Following completion of the procedure, the order of the subjective airway irritation among the four agents was evaluated by the volunteers. The subjective airway irritation was described using a four-point scale (Table II).

After an interval of at least 15 min, an identical procedure was followed using an inhaled concentration of the anaesthetic agents, equivalent to two MAC.

In the present study, significant changes were considered to have occurred if the tidal volume and respiratory frequency changed by more than 30% from the resting values for at least 10 sec, and the functional residual capacity changed by more than 30% of its resting tidal volume value for at least ten seconds.

Appearance of the cough reflex, increases or decreases in the respiratory variables, and the subjective airway irritation were statistically analyzed using the Kruskal-Wallis and Tukey's tests. Statistical significance was assumed when $P < 0.05$.

Results

In most cases, inhalation of the anaesthetic agents induced a decrease in tidal volume, increase in respiratory

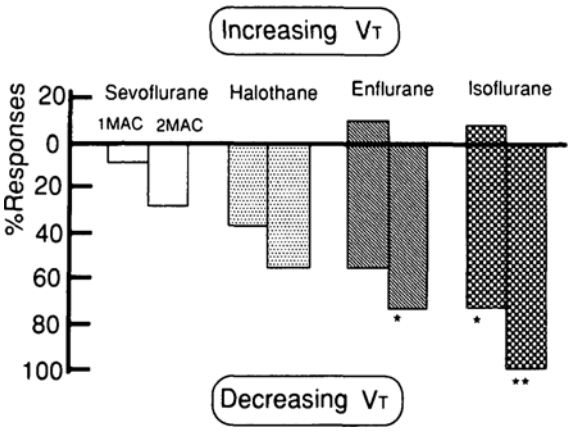

FIGURE 2 Tidal volume changes induced by 15 sec inhalation of the four anaesthetic agents ($n = 11$). * $P < 0.05$; different from the equipotent concentration of sevoflurane. ** $P < 0.01$; different from the equipotent concentration of sevoflurane.

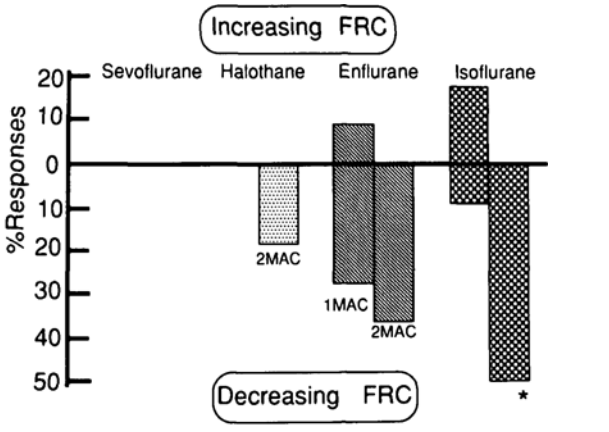

FIGURE 4 Functional residual capacity changes induced by 15 sec inhalation of the four anaesthetic agents ($n = 11$). * $P < 0.05$; different from the equipotent sevoflurane.

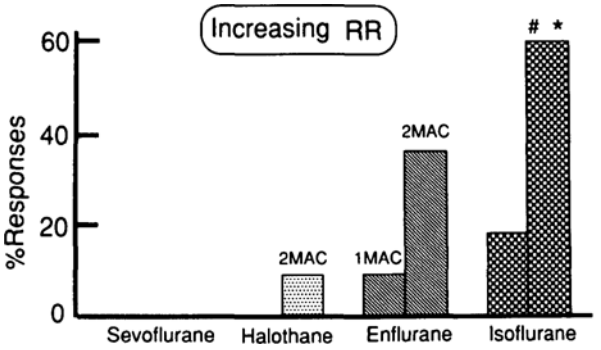

FIGURE 3 Respiratory rate changes induced by 15 sec inhalation of the four anaesthetic agents ($n = 11$). * $P < 0.05$; different from the equipotent sevoflurane. # $P < 0.05$; different from the equipotent halothane.

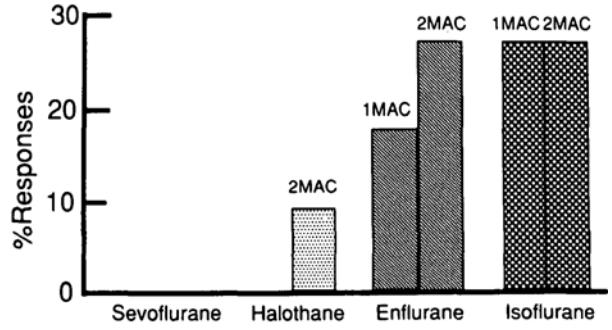

FIGURE 5 Incidence of cough reflex appearance induced by 15 sec inhalation of the four anaesthetic agents ($n = 11$).

frequency and decrease in functional residual capacity (Figure 1). In three subjects, one with 1 MAC enflurane and two with 1 MAC isoflurane, inhalation of the agent induced increases of tidal volume and functional residual capacity without any change in respiratory rate. Changes of each variable were induced most frequently by isoflurane, followed by enflurane, halothane and, least frequently, by sevoflurane (Figures 2, 3, 4). With each agent, change were more frequent at 2 MAC than at 1 MAC, although the differences were not statistically significant.

Decreases in tidal volume appeared more frequently at both concentrations of isoflurane, and at 1 MAC enflurane than with equipotent concentrations of sevoflurane (Figure 2). There were no changes of respiratory rate at either concentration of sevoflurane or at 1 MAC halothane. At 2 MAC isoflurane, respiratory rate increased more frequently than at equipotent concentrations of sevoflurane and halothane (Figure 3). Functional residual capacity did not change at either concentration of sevoflurane or at 1 MAC halothane. Functional residual capacity decreased more at 2 MAC isoflurane than at 2 MAC sevoflurane (Figure 4).

The order of appearance of the cough reflex was similar to the order of changes in the respiratory variables (Figure 5). Sevoflurane did not elicit the cough reflex in any volunteer at either concentration. On the other hand, isoflurane elicited the cough reflex in three of eleven volunteers at both concentrations.

The severity of subjective airway irritation for the four agents is shown in Table III. The severity was least for

TABLE III Severity of subjective airway irritation (mean (SD))

	1 MAC	*2 MAC*
Sevoflurane	1.18 (0.41)*§¶	1.55 (0.69)*§
Halothane	2.09 (0.54)*§	1.91 (0.94)*§
Enflurane	3.09 (0.94)	2.82 (0.87)*
Isoflurane	3.64 (0.51)	3.73 (0.47)

*$P < 0.05$ compared with isoflurane. § $P < 0.05$ compared with enflurane. ¶ $P < 0.05$ compared with halothane.

sevoflurane, followed by halothane and enflurane, and was largest for isoflurane. Sevoflurane produced less irritation than the other three agents at 1 MAC, and less than enflurane and isoflurane at 2 MAC. At both concentrations, halothane produced less irritation than enflurane and isoflurane. At 2 MAC, enflurane produced less irritation than isoflurane. There was no difference between isoflurane and enflurane at 1 MAC, or between sevoflurane and halothane at 2 MAC.

Breath-holding, apnoea or laryngospasm were not induced by any of the four agents.

Discussion

Inhalation of the volatile anaesthetics elicited the cough reflex and changes in respiratory variables. Rapid shallow breathing was also considered to be a response to irritant vapours.[15] A decrease of functional residual capacity was considered to be a protective response. Therefore, these variables were used to quantify the airway irritation produced by the four anaesthetic agents.

There are several limitations of the present study. First, the duration of anaesthetic inhalation was very brief. We could not determine what kind of response might be induced by continuing inhalation beyond 15 sec so that the present study should be considered as an evaluation of the airway responses to the start of anaesthetic inhalation. Second, the intervals between inhalations were of only a few minutes. Although end-tidal anaesthetic concentrations were zero, it is possible that the previously inhaled agent might influence the next measurement. To avoid this influence, the order of inhalation of the four agents was decided at random. Thirdly, the anaesthetic agents were vaporized with dry air which, itself, may have caused airway irritation. Therefore, although the relative comparison among the anaesthetic agents may be acceptable, the absolute extent of airway irritation produced by the individual anaesthetic agents is questionable. Finally, inhalational concentrations of anaesthetic agents were equivalent to one and two MAC. However, the commercially available vaporizers used have maximum dial settings of 5%. Concentrations equivalent to two MAC for halothane, enflurane, isoflurane and sevoflurane were 1.54, 3.36, 2.30 and 3.42, respectively. For sevoflurane and enflurane, conditions of the present study were similar to clinical conditions, but, for halothane and isoflurane, the inhaled concentration of the anaesthetics could be much higher at induction of anaesthesia than in the present study. Since high concentrations of anaesthetics produce greater irritation,[2] the results of the present study may differ from clinical impression.

Despite these limitations, the present study showed that airway irritation produced by sevoflurane was as little or less than that produced by halothane, and much less than by enflurane and isoflurane. An ideal anaesthetic vapour should not irritate airways, particularly when anaesthesia is induced with a mask. In this regard, isoflurane, enflurane and desflurane are not idea.[1-9] Previous studies reported that halothane caused less airway irritation than isoflurane.[1,3,4] Sevoflurane should be considered to be superior to both isoflurane and enflurane.

Inhalational induction of anaesthesia is common in paediatric anaesthesia, especially in outpatient anaesthesia. In these cases, prompt induction and emergence is required. The solubility of sevoflurane is lower than that of halothane (blood/gas partition coefficient of sevoflurane and halothane are 0.60 and 2.3, respectively) and this is of great advantage for prompt induction and emergence of anaesthesia. In addition, sevoflurane is less arrhythmogenic than halothane[16] and this may provide a more stable haemodynamic status during induction. Therefore, we believe that sevoflurane is more suitable for induction of anaesthesia than halothane.

Among the recently introduced volatile anaesthetic agents, sevoflurane is unique in its limited airway irritation. This characteristic is of considerable advantage and suggests that sevoflurane will be widely used, at least for paediatric anaesthesia.

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