Respiratory, Laryngeal, and Tracheal Responses to Nasal Insufflation of Volatile Anesthetics in Anesthetized Humans

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In order to determine whether or not irritation of the nasal passage with commonly used volatile anesthetics can elicit airway reflexes, we investigated respiratory, laryngeal, and tracheal responses to nasal insufflation of three volatile anesthetics (enflurane, isoflurane, and halothane) in 18 patients anesthetized with flunitrazepam, pentazocine, and nitrous oxide. The trachea of each patient was intubated with a saline-filled double-cuffed endotracheal tube. Changes in breathing pattern were measured with a pneumotachograph while changes in laryngeal wall tension and tracheal wall tension were assessed by measuring changes in the proximal cuff pressure and the distal cuff pressure, respectively. In 8 of 13 patients, the dose-response relationship for each anesthetic was determined by administering different concentrations (1, 3, and 5%) of gas mixtures. In these patients, nasal insufflation of 1 and 3% of each anesthetic did not produce any reflex response, whereas reflex responses were evident during nasal insufflation of 5% enflurane, isoflurane, and halothane. In all 13 patients, nasal insufflation of all three anesthetics at a concentration of 5% invariably produced changes in breathing pattern characterized by prolongation of expiratory time (T_E). However, prolongation of T_E was the most pronounced for enflurane (from a control value of 2.1 ± 0.5 to a maximum value of 4.8 ± 2.2 s [mean ± standard deviation]), less for isoflurane (from 2.2 ± 0.5 to 3.9 ± 1.7 s), and the least for halothane (from 2.2 ± 0.6 to 2.9 ± 0.9 s). These differences in T_E between the three anesthetics were all statistically significant (P < 0.05). In 6 of 13 patients, nasal insufflation of either enflurane or isoflurane or both caused a marked prolongation of T_E (T_E > 5 s), during which time there was a small but consistent increase in laryngeal wall tension. No measurable change occurred in tracheal smooth muscle tone during insufflation of any anesthetic. Our results suggest that the nose may be an important reflexogenic site. The reflex responses elicited by nasal insufflation of volatile anesthetics may partly explain the breathing-holding observed occasionally during induction of anesthesia with high concentrations of volatile anesthetics. (Key words: Anesthetics, volatile; enflurane; halothane; isoflurane. Reflexes: nasal. Ventilation: breathing pattern.)

Stimulation of the nasal mucosa can be shown to stimulate various airway reflex responses in humans. The nature and strength of the stimulus used determines to some extent the type of reflex response obtained. For example, it has been shown that inhalation of very low concentrations of sulfur dioxide causes rapid shallow breathing, whereas other irritants, such as ammonia vapor or cigarette smoke, produce depression of breathing or even apnea.

Induction of anesthesia with volatile anesthetic agents such as enflurane and isoflurane, which possess a mild pungent odor, may cause breath-holding, coughing, and laryngospasm. Although it is possible that stimulation of the nasal mucosa with these agents may contribute to some of these responses, little is known about the effects of nasal mucosal stimulation with volatile agents on respiratory reflex responses in humans. To test the hypothesis that mild pungent volatile anesthetics can elicit airway-defensive reflexes from the nose, in the current study we examined respiratory, laryngeal, and tracheal responses to nasal insufflation of enflurane, isoflurane, and halothane in lightly anesthetized humans.

Materials and Methods

After obtaining approval from the Institutional Ethics Committee and informed consent, 13 patients, women aged 27–45 yr, were studied. Their average heights and weights were 158.2 ± 3.5 cm and 52.2 ± 5.0 kg (mean ± standard deviation [SD]), respectively. All were scheduled for elective mastectomy under general anesthesia. None had clinical evidence of any respiratory, cardiovascular, neuromuscular, or rhinologic disorders. The patients received 50–75 mg hydroxyzine (intramuscularly) 1 h before induction of anesthesia. Anesthesia was induced with flunitrazepam§ (0.04 mg/kg, intravenously [iv]) and pentazocine (0.3 mg/kg iv) followed by succinylcholine chloride (1 mg/kg iv). Additional doses of pentazocine (0.3 mg/kg iv) were given every 40 min.

The trachea was then intubated with a custom-made double-cuffed endotracheal tube (Nishino tube, ID 7.5 mm, Fuji System Co.) after the larynx and the trachea were sprayed with 5 ml of 4% lidocaine using a "laryngotracheal anesthesia" set (TOP, Tokyo). The double-cuffed endotracheal tube was positioned and fixed so that the proximal cuff lay just between the vocal folds. Both proximal and distal cuffs could be filled with as much as 6 ml of saline without causing a change in cuff pressure. To seal the trachea, the distal cuff was inflated with 2–5 ml of saline to obtain a pressure of about 20 cmH2O.

After intubation of the endotracheal tube, spontaneous respiration was allowed to resume while the patients breathed 50% nitrous oxide in oxygen. Then, the endotracheal tube was connected to an experimental ap-

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§ Flunitrazepam (Rohypnoi®, Roche) is a benzodiazepine with a plasma half-life of 10–20 h. It has the chemical formula of 5-(O-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2H-1,4-benzodiazepine-2-one.
paratus incorporated into a semiclosed anesthetic circuit. The proximal cuff of the endotracheal tube was filled with 2–4 ml of saline to a pressure of about 10 cmH2O so that changes in cuff pressure reflected respiratory phasic movements of the larynx.

Ventilatory airflow was measured using a Fleisch pneumotachograph (no. 2), and tidal volume (VT) was obtained by electrical integration of the inspired flow. Tracheal airway pressure was measured from a sidearm of the endotracheal tube with a pressure transducer (DDL-0.05, Toyo Baldwin). End-tidal carbon dioxide tension (PETCO2) was continuously monitored with an infrared carbon dioxide analyzer (Normocap, Datex). The cuff pressures of the proximal and distal cuffs were monitored with a Statham-Gould pressure transducers (P23). A soft nasal tube that fit snugly in the patient's nostril was inserted 5 mm into the nostril, and nasal insufflation of oxygen at a constant flow rate (3 ml/min) was started through this nasal tube.

When all of the respiratory variables were stable, enflurane, isoflurane, or halothane were administered through the nasal tube using precalibrated vaporizers (Enflurane [Cyprane] for enflurane, Forawick [Muraco] for isoflurane, and Fluotec Mark 3 [Cyprane] for halothane, respectively) incorporated in the insufflation system, while the concentration of each agent was monitored with a Datex anesthetic monitor (Normac). All respiratory variables were recorded on a Nihon Kohden eight-channel recorder (RJG-4128).

In 8 of 13 patients, a dose-response relationship for each anesthetic was obtained by administering different concentrations (1, 3, and 5%) of the gas mixtures. In the other 5 patients, only a concentration of 5% of enflurane, isoflurane, and halothane was administered. The order of administration of each agent was randomized, and the administration of each agent was continued for 30–40 s, with an interval of 10 min before the administration of the next agent. Respiratory, laryngeal, and tracheal responses to insufflation of each of the three agents into the nose were analyzed and compared with respect to changes in the inspiratory time (TI), expiratory time (TE), VT, laryngeal cuff pressure, and tracheal cuff pressure. Control values for TI, TE, and VT were obtained by averaging the values for the three breaths immediately before nasal insufflation of volatile agents. The breath immediately after insufflation of each agent was designated as the first experimental breath, and subsequent breaths were designated as the second, third, fourth, and fifth experimental breaths (b1, b2, b3, b4, and b5 in fig. 2), and so forth.

Statistical analysis was performed using Student’s t test and analysis of variance (two-way) followed by Dunnett's test (for comparisons between control and experimental breaths for each anesthetic) and Tukey's test (for comparisons between three anesthetics), where appropriate. P < 0.05 was considered statistically significant.

**Results**

In the eight patients whose nose was insufflated with three different concentrations (1, 3, and 5%) of enflurane, isoflurane, and halothane, there was no visible response to 1 and 3% of all three anesthetics, whereas changes in breathing pattern was observed in all eight patients when 5% of any of the anesthetics was administered. Since reflex responses to nasal insufflation were evident only when 5% of any of the anesthetics was administered, further analysis of data was limited to the responses to nasal insufflation of each anesthetic at a concentration of 5%.

Figure 1 shows an example of the respiratory responses to nasal insufflation of three volatile anesthetics in a single patient. With the start of insufflation of enflurane or isoflurane into the nose, there was a sudden decrease in VT with a prolongation of TE, although these responses rapidly attenuated with time. During the disturbed respiration there was a small increase in proximal (laryngeal) cuff pressure but no change in distal (tracheal) cuff pressure. In contrast to the changes observed during nasal insufflation of enflurane and isoflurane, the changes in breathing pattern during nasal insufflation of halothane were less remarkable.

Figure 2 shows changes TI, TE, VT, and PETCO2 of five experimental breaths during nasal insufflation of enflurane, halothane, and isoflurane. Compared to the control value, a significant prolongation of TE (P < 0.05) was observed in the first, second, and third experimental
breathe during insufflation of enfurane. During insufflation of isoflurane, TE in the second and third experimental breaths was significantly prolonged ($P < 0.05$), whereas a significant prolongation of TE was observed only in the first experimental breath during halothane insufflation. There were no significant changes in T1 or VT during insufflation of any of the three anesthetics. A small but significant increase ($P < 0.05$) in PETCO2 was observed after insufflation of enfurane and isoflurane.

In 6 of 7 of 13 patients during nasal insufflation of enfurane and in 4 of these 6 patients during isoflurane insufflation, there was a marked prolongation of $T_E$, such prolongation of $T_E$ was never seen during insufflation of halothane. During this prolonged $T_E$, there was a small but consistent increase in laryngeal cuff pressure (enfurane, 0.4 ± 0.1 cmH2O; isoflurane, 0.4 ± 0.1 cmH2O [mean ± SD]), whereas no change in tracheal cuff pressure was discernible. In all the patients, during nasal insufflation of halothane, the maximal effect was seen on either the first or the second experimental breath, whereas the maximal effect occurred on either one of the five experimental breaths during nasal insufflation of enfurane or isoflurane. When the effects of nasal insufflation of the three anesthetics were compared in terms of the maximal prolongation of $T_E$ observed during five experimental breaths, there were significant differences ($P < 0.05$) between the effects of the three anesthetics (enfurane, 4.8 ± 2.2 s; isoflurane, 3.9 ± 1.7 s; and halothane: 2.9 ± 0.9 s [mean ± SD]).

**Discussion**

In the current study we tested the effects of nasal insufflation of three commonly used volatile anesthetics on respiration. Our results showed that nasal insufflation of all three anesthetics with a concentration of 5% invariably caused changes in the breathing pattern, characterized by prolongation of $T_E$. Although the precise site of action was not explored systematically in this study, our preliminary studies showed that topical lidocaine applied to the nasal mucosa abolished the responses to nasal insufflation of enfurane and isoflurane. Therefore, our results indicate that during induction of anesthesia with a high concentration of anesthetic gas mixtures, all three anesthetics stimulate the nasal mucosa and thereby elicit nasal reflexes. Our findings are compatible with those of Allen, who observed that in anesthetized humans, the inhalation of strong irritants such as wintergreen and ammonia produced marked depression and slowing or complete arrest of respiration.

Our results demonstrated that nasal insufflation of enfurane caused the most marked influence on the breathing pattern, that halothane had the least effect, and that the effect of isoflurane was intermediate.

It is quite possible that the concentration of each anesthetic agent greatly affected the results, since it is conceivable that the higher the concentration of volatile anesthetics, the stronger the stimulation of the nasal mucosa. Thus, the differences in reflex responses might be due simply to the differences in strength of stimuli. The dose-response relation for each anesthetic obtained in 8 of 13 patients showed that reflex responses were evident only when a high concentration (5%) of anesthetics was administered, suggesting that with doses normally used for clinical anesthesia there might be no graded dose-response effect but that there might be a certain threshold concentration for elicitation of nasal reflexes. The relatively small effects of enfurane and isoflurane in comparison with the effect of halothane may be related to the fact that enfurane and isoflurane are mildly pungent, whereas halothane is not.

Alternatively, the different in reflex responses might be due to the differences in the inspired concentration/MAC multiple since it is possible that a high inspired concentration/MAC ratio may result in almost instantaneous "anosmia." In fact, in the current study the inspired concentration/MAC multiple for halothane was substantially greater than that for enfurane. Likewise, this ratio was higher for isoflurane than for enfurane. If lower anesthetic concentrations had been used, with a smaller degree of anosmia the reflex effects of isoflurane and halothane might have been greater than those observed in the current study. However, the observation that nasal insufflation of lower concentrations (1 and 3%) of halothane and isoflurane were not effective for eliciting reflex responses is incompatible with this notion.
During continued insufflation of volatile anesthetics, in the majority of patients, the inhibition of breathing attenuated with time. This observation is consistent with either an adaptation of receptors mediating the response or a central adaptation, or both. Coleridge et al. studied the effects of volatile anesthetics on pulmonary receptors and showed that a high concentration of volatile anesthetics produces an immediate excitation of pulmonary stretch receptors followed by a marked depression of receptor activity. It is possible that a similar response may occur at the site of nasal receptors. An increase in chemical drive during decreased breathing may also play some role in the phenomenon of adaptation. In this connection, there is some evidence that in anesthetized humans an increase in alveolar carbon dioxide tension decreases the degree and duration of airway defensive reflexes.

In experimental animals, stimulation of the nasal mucosa is known to produce various reflex responses, including sneezing, changes in breathing pattern, laryngeal constriction, bronchodilatation, and possibly bronchoconstriction. In agreement with the responses observed in experimental animals, our patients consistently showed changes in breathing pattern in response to nasal mucosa stimulation. However, changes in laryngeal wall tension during the nasal mucosa stimulation were less consistent, and changes in tracheal wall tension were never observed. These results suggest that there may be some difference between humans and other species in the types of nasal reflexes.

Alternatively, it is possible that the stimulation of nasal mucosa with volatile anesthetics is not strong enough to cause reflex responses other than changes in breathing pattern. In this context, a possibility exists that the threshold for laryngeal constriction and changes in airway smooth muscle may be higher than the threshold for changes in breathing pattern.

Induction of anesthesia with enflurane or isoflurane, particularly when a high concentration is used, may be associated with breath-holding, coughing, and laryngo-spasms. Although it is most likely that these responses are elicited from stimulation of the upper airway, the site of stimulation has not been explored. Obviously, the larynx and its associated structures, rich in sensory afferent nerves and extremely sensitive, may be a source of these reflex responses. The results of our experiments suggest that the nose may also be an important reflexogenic area and that stimulation of the nasal mucosa alone can cause at least the response of breath-holding during inhalation of enflurane or isoflurane.

It is worthy to note that the nasal reflexes may be abolished during deep anesthesia and that the effects of nasal reflexes can be masked by psychological stimulation in unanesthetized subjects. Although our experiments were performed under light anesthesia, the possibility exists that the nasal reflexes may have been modified by this light anesthesia. It is also possible that exaggeration of nasal reflexes may occur upon induction with a high concentration of volatile anesthetic, during the excitement stage prior to surgical depth of anesthesia.

In conclusion, our results show that the nose is an important reflexogenic site in humans and that the stimulation of the nasal mucosa with commonly used volatile anesthetics causes considerable changes in the breathing pattern that may or may not be accompanied by an increase in laryngeal wall tension but that are not accompanied by changes in tracheal smooth muscle tone. Our results also demonstrated that the potency of the elicitation of nasal reflexes differs among different anesthetics.

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