

## Differences in Respiratory Reflex Responses from the Larynx, Trachea, and Bronchi in Anesthetized Female Subjects

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**Background:** Animal studies show that airway receptors responsible for eliciting respiratory protective reflexes are not uniformly distributed in the airways. Based on this information, it is possible that the protective reflex responses to airway irritation in humans may vary, depending on the site of stimulation. The purpose of this study is to examine whether the protective reflex responses evoked from the larynx are different from those evoked from the lower airways and to see how change in depth of anesthesia modifies the protective reflex responses evoked from individual sites.

**Methods:** The airway mucosa of the larynx, tracheal carina, and bronchi were stimulated by injection of distilled water (0.5 ml) at two different depths of sevoflurane anesthesia (1.2 and 1.8 MAC) in 11 female subjects breathing spontaneously through the laryngeal mask airway. The respiratory responses were monitored by measuring ventilatory flow and airway pressure.

**Results:** At 1.2 MAC of sevoflurane anesthesia, both laryngeal and tracheal stimulation caused protective responses, such as forceful expiratory efforts, apnea, and spasmodic panting, whereas bronchial stimulation caused little or no such responses. There was no significant difference in the incidence of different types of reflex responses between the larynx and the trachea. At 1.8 MAC of sevoflurane, the nature of the elicited responses was very similar to that observed at 1.2 MAC of sevoflurane, showing little dose-dependence of anesthetic effect.

**Conclusions:** The respiratory reflex responses evoked by injection of water vary, depending on the site of stimulation. The incidence of various reflex responses was not affected by the changing depth of anesthesia. The sensitivity to airway

irritation seems to be greater at the larynx and trachea than at the more peripheral airways. (Key words: Airways: bronchus; larynx; trachea. Anesthetics, volatile: sevoflurane. Reflex: airway.)

THE protective reflexes from the respiratory tract, particularly those from the larynx, trachea, and bronchi, are of great practical importance to physicians. Airway receptors responsible for eliciting airway reflexes do not appear to be uniformly distributed in the airways.<sup>1</sup> Animal studies showed that the types of reflex response to stimulation of airway mucosa vary with the site of stimulation.<sup>2</sup> Although, in general, the airway protective reflexes are susceptible to general anesthesia, the susceptibility to anesthesia of the reflexes evoked from different parts of the airways has not been explored in humans. Considering the striking differences in the anatomy and afferent innervation of the larynx and the lower airways, we hypothesized that respiratory reflexes evoked from the larynx may be qualitatively different from those elicited from the lower airways in humans and that there may be differences in the susceptibility to general anesthesia between the reflex responses elicited from different parts of the airways.

To test these hypotheses, in the current study, we investigated respiratory reflex responses to injection of water into the larynx, trachea, and bronchi at two different depths of sevoflurane anesthesia.

### Methods and Materials

After obtaining approval from the Institutional Ethics Committee and informed consent, 11 female patients whose ages ranged from 27 to 56 yr were studied. Their average heights and weights were  $157 \pm 3.7$  cm and  $52 \pm 5.7$  kg, respectively (mean  $\pm$  SD). All were scheduled for elective surgery, including mastectomy (nine patients) and minor orthopedic procedures (two patients). None of them had clinical evidence of respi-

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ratory, cardiovascular, or neuromuscular disorders. The patients received atropine (0.5 mg, intramuscular) 45 min before induction of anesthesia. Anesthesia was induced with sevoflurane (4–5%) in conjunction with 60% N<sub>2</sub>O. When a sufficient depth of anesthesia was achieved, the laryngeal mask airway (LMA, size 3 or 4) was inserted blindly or with the use of a laryngoscope. The distal tube part of the LMA was connected to an elbow connector and then to an experimental apparatus incorporated into a semiclosed anesthetic circuit.

After insertion of the LMA, anesthesia was maintained with sevoflurane in oxygen while the patients were breathing spontaneously. To ascertain that the LMA was in proper position, a pediatric-size fiberoptic bronchoscope (3.6 mm OD) was passed through a self-sealing diaphragm in the elbow connector down to the end of the shaft of the laryngeal mask, and the larynx was visualized. When the LMA was in proper position, there was no gas leak with airway pressure of 20 cmH<sub>2</sub>O.

Ventilatory airflow ( $\dot{V}$ ) was measured with a Fleisch pneumotachograph (no. 2) and a differential pressure transducer (TP-602; Nihon Koden); tidal volume ( $V_T$ ) was obtained by electrical integration of the inspired flow. Airway pressure ( $P_{aw}$ ) was continuously measured with a pressure transducer (Uniflow, Baxter, Japan). End-tidal  $P_{CO_2}$  ( $P_{ETCO_2}$ ) was monitored continuously with a mainstream capnometer (Nihon Koden TG-706P).  $\dot{V}$ ,  $V_T$ ,  $P_{aw}$ , and  $P_{ETCO_2}$  were recorded on a thermal array recorder (Nihon Koden WS 800R).

Each patient was studied at two different depths of sevoflurane anesthesia (end-tidal concentrations 2.5% (1.2 MAC) and 3.7% (1.8 MAC)). The order of two different depths of anesthesia was randomized. The end-tidal sevoflurane concentration was monitored with an anesthetic gas analyzer (Ohmeda RJA 2125). All measurements were made at least 10 min after establishing a constant end-tidal sevoflurane concentration. The experimental protocol was as follows.

When all the respiratory variables were stable, the fiberoptic was passed through the central compartment of the grille of the LMA into the larynx. Then, 0.5 ml of distilled water with 5 ml of air was injected through the suction channel of the fiberoptic onto the vocal cords; the fluid was observed as it bathed the cords, and the respiratory responses were measured. The fiberoptic was further advanced into the tracheal lumen with the tip located 1–2 cm above the carina. While the carina and the two mainstem bronchial orifices were in view, 0.5 ml of distilled water was injected, and the respiratory responses were measured. The tip of the

fiberscope was further advanced to the origin of the left or right lower lobe bronchus, and the respiratory responses to injection of 0.5 ml distilled water were measured. The fiberoptic was withdrawn to the level of the carina and the larynx while the order of injections of water into the three different sites was reversed. Thus, at each location, the two injection trials were performed with an interval of at least 5 min.

The respiratory responses to water stimulation were divided into four categories, depending on different changes in breathing pattern: (1) apnea, an absence of inspiration for >10 s; (2) forceful expiratory efforts, including the cough reflex and expiration reflex; (3) spasmodic panting, a period >10 s when respiratory frequency is >60 breaths/min; and (4) irregular breathing, a period >5 s when respiratory frequency and/or tidal volume were <70% or >130% of the prestimulation values. Among these four responses, the first three responses (e.g., apnea, forceful expiratory efforts, and spasmodic panting) can be viewed as protective in nature, because they may be functional in preventing aspiration of foreign materials into the respiratory tract or facilitating the removal of the irritant stimulus.<sup>3</sup> Concerning the elicitation of protective responses, different types of reflex response have been thought to be mediated by the same type of receptor.<sup>4</sup>

To determine whether there was a significant difference in the incidence of the different types of respiratory responses based on the site of stimulation, statistical analysis was performed with a  $\chi^2$  test and Fisher's exact test where appropriate, and  $P < 0.05$  was considered significant.

## Results

Figures 1 and 2 show examples of changes in reflex responses to stimulation of different sites of the respiratory tract at two different depths of anesthesia observed in a single subject. In this subject, at 1.2 MAC of sevoflurane anesthesia, injections of distilled water into the larynx (fig. 1A) and the trachea (fig. 1B) elicited vigorous protective responses, including forceful expiratory efforts, spasmodic panting, and apnea, which were followed by irregular breathing, whereas injections of distilled water into the bronchus (fig. 1C) caused only a slight change in breathing pattern.

At 1.8 MAC of sevoflurane anesthesia (fig. 2), the nature of the responses was similar to those observed at 1.2 MAC of sevoflurane, although recovery of regular breathing appeared to be much faster.



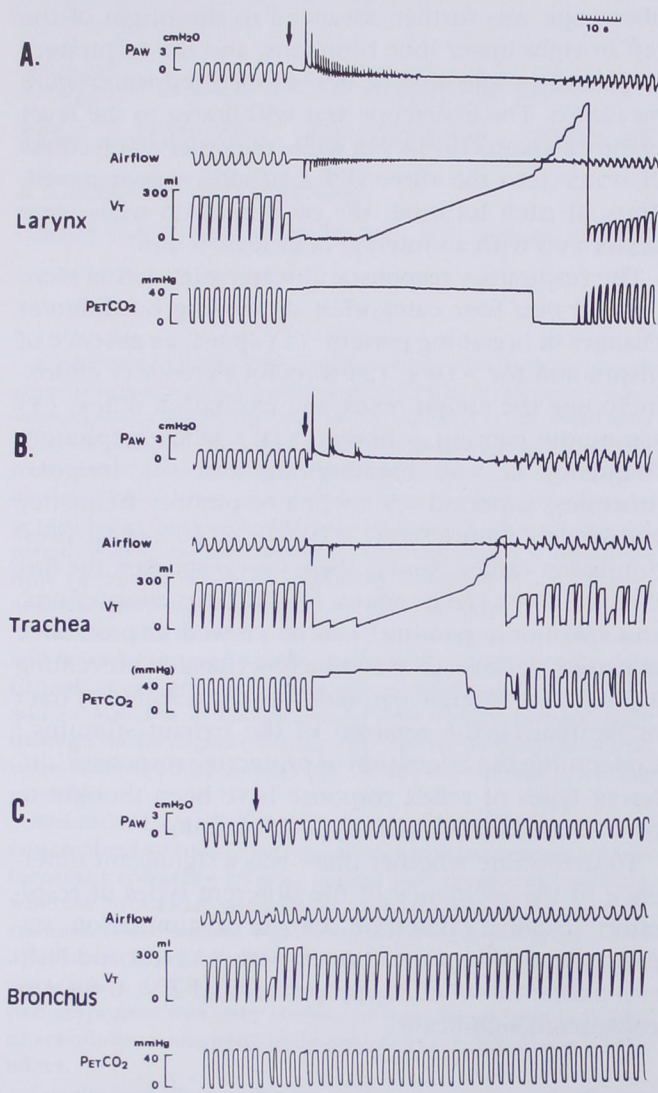


Fig. 1. Experimental records illustrating respiratory responses to airway stimulation at 1.2 MAC of sevoflurane anesthesia. At arrow, 0.5 ml of distilled water was instilled.  $P_{AW}$  = airway pressure;  $V_T$  = tidal volume;  $P_{ETCO_2}$  = end-tidal  $P_{CO_2}$ .

The types and occurrence of respiratory responses evoked from the three different sites under two different depths of anesthesia are shown in figure 3. Although forceful expiratory efforts and spasmodic panting were occasionally observed at 1.2 and 1.8 MAC of sevoflurane anesthesia in response to stimulation of the larynx and trachea, these responses were never observed in response to bronchial stimulation, regardless of the depth of anesthesia. The occurrence of forceful expiratory efforts in response to stimulation of the larynx and trachea was significantly higher ( $P < 0.05$ ) than that after

bronchial stimulation at 1.2 MAC of sevoflurane anesthesia. In the majority of patients, stimulation of the larynx and trachea elicited the apneic response. Stimulation of the bronchi caused apnea in only one subject at 1.2 MAC of sevoflurane, and at 1.8 MAC, no subject experienced apnea. The occurrence of apneic response after stimulations of the larynx and trachea was significantly higher ( $P < 0.01$ ) than that after bronchial stimulation at 1.2 and 1.8 MAC of sevoflurane anesthesia. Comparison between the larynx and the trachea revealed there was no significant difference in the incidence of four different responses between the two

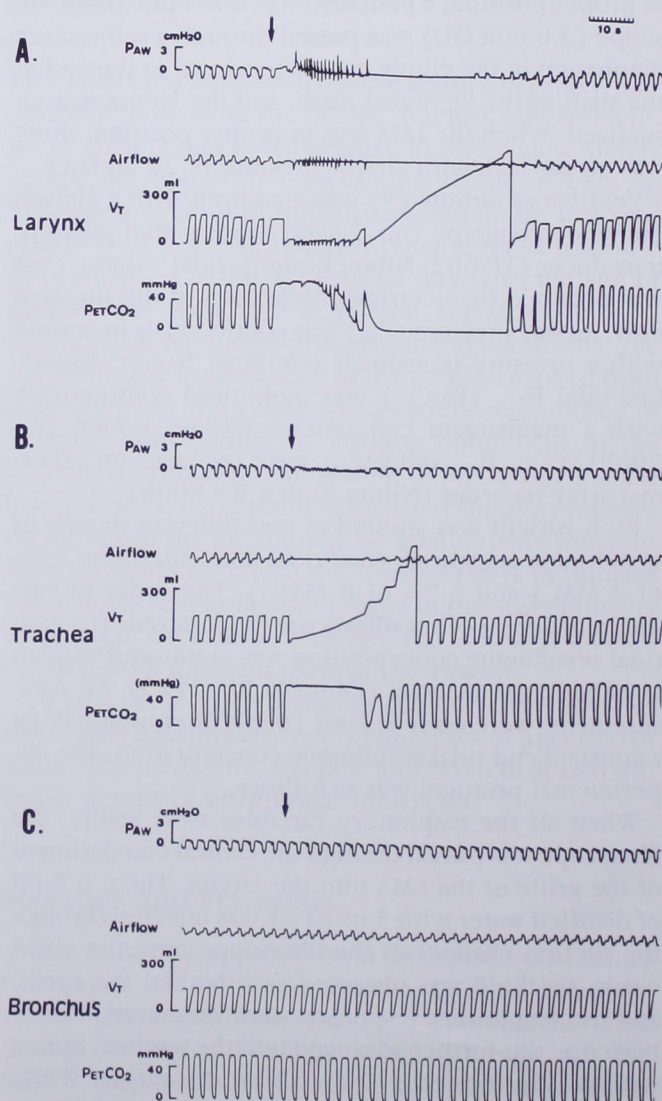


Fig. 2. Experimental records illustrating respiratory responses to airway stimulation at 1.8 MAC of sevoflurane anesthesia. The subject is the same as in figure 1.



## REFLEX RESPONSES FROM THE AIRWAYS

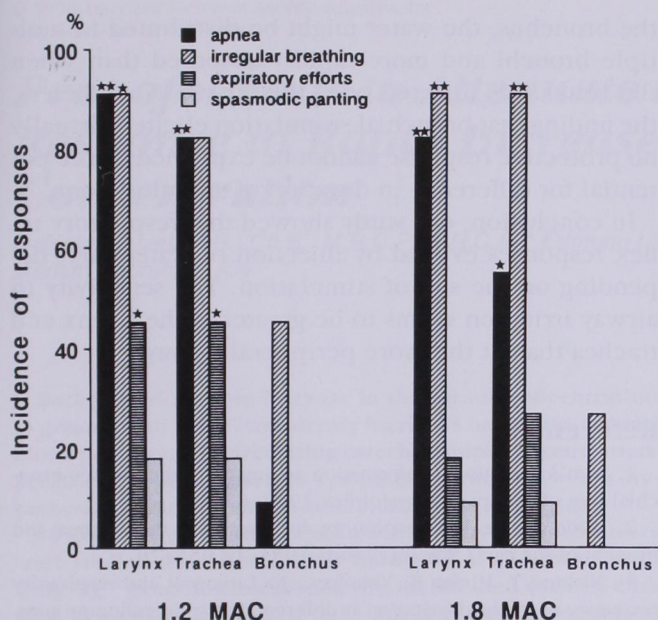


Fig. 3. Incidence (percent of subjects) of various respiratory responses evoked from different parts of the respiratory tract. \* $P < 0.05$  and \*\* $P < 0.01$  compared with the responses elicited from bronchial stimulation at the same anesthetic concentration.

different sites at 1.2 and 1.8 MAC of sevoflurane anesthesia, indicating that the types of respiratory responses elicited by stimulation of the larynx were similar to those elicited by stimulation of the trachea at 1.2 and 1.8 MAC of sevoflurane anesthesia.

## Discussion

This study demonstrated that the site of stimulation is crucial for determining the pattern of respiratory responses elicited by injection of a small amount of distilled water in human subjects and that there is little dose-dependence of anesthetic effect. We observed that, at a moderate depth of sevoflurane anesthesia (1.2 MAC), laryngeal stimulation caused vigorous protective responses that are qualitatively similar to those elicited by tracheal stimulation, whereas bronchial stimulation caused little or no response. These findings are compatible with the general belief that the most important reflexogenic areas are at the level of the larynx and the trachea, especially in its caudal portion around the carina, whereas the more peripheral bronchial branches are less important as reflexogenic areas.<sup>5</sup> To this effect, Jackson<sup>6</sup> observed that, whereas a small mechanical ir-

ritant in the larynx or trachea causes vigorous coughing, mechanical stimulation of the finer subdivisions of the tracheobronchial tree causes less cough production during bronchoscopic procedures in awake patients.

The differences in reflex responses from different sites may be explained in part by an uneven distribution of airway receptors responsible for the reflex responses, because the number of the receptors excited for a given volume of water may depend on the concentration of the receptors in individual sites. In this context, the larynx has the richest afferent supply among airways, as indicated by the number of afferent fibers constituting the internal branch of the superior laryngeal nerve. It has been reported that, in the cat, the superior laryngeal nerve contains 2,200 myelinated afferent fibers,<sup>7</sup> whereas the whole cervical vagus nerve contains only 3,000 myelinated afferent fibers.<sup>8</sup> The animal studies<sup>9,10</sup> also showed that rapidly adapting receptors, which play a major role in defensive airway reflexes, are nonuniformly distributed in the tracheobronchial tree and are more concentrated in the larger airways. Although no data regarding the distribution of rapidly adapting receptors are available for humans, it is likely that their concentration is higher in the larynx and trachea than in the more peripheral airways. In contrast with the distribution of rapidly adapting receptors, the majority of vagal fibers originating from the lung and lower airways are nonmyelinated (C-fibers). In fact, vagal degeneration experiments in cats have established that nonmyelinated afferents outnumber myelinated in pulmonary vagal branches, with the ratio of unmyelinated to myelinated fibers being 9:1.<sup>11</sup>

In contrast with our results on the relative reactivity of the larynx and the tracheal carina, a study by Tatar *et al.*<sup>12</sup> showed that stimulation of the tracheobronchial region is more effective and prompt in eliciting cough than is stimulation of the larynx in anesthetized dogs. Also, our finding that bronchial stimulation causes little or no reflex response does not easily reconcile with the results obtained in anesthetized dogs.<sup>13</sup> Thus, Pisarri *et al.*<sup>13</sup> showed that injection of water into a lobar bronchus stimulates both rapidly adapting receptors and airway C-fibers and evokes vigorous respiratory responses, including apnea and rapid, shallow breathing, emphasizing that the lower airways are important as reflexogenic areas. The difference between our observation and those of Tatar *et al.*<sup>12</sup> and Pisarri *et al.*<sup>13</sup> may be related to a species difference. However, it is more likely that the difference is related to the difference in methodology. For instance, in the study by Tar-



tar *et al.*,<sup>12</sup> the cough reflex was elicited by either mechanical stimulations or citric acid inhalations in experimental preparations with the functionally isolated upper airway.

Although Pisarri *et al.*<sup>13</sup> stimulated the bronchial mucosa with distilled water, they injected a greater amount of water (0.25–0.5 ml/kg) into the lobar bronchus, compared with the volume of water used in our study (0.5 ml/50–60 kg). It is also possible that differences in the type and/or level of anesthesia caused the difference. In the studies by Tartar *et al.*<sup>12</sup> and Pisarri *et al.*,<sup>13</sup> anesthesia was maintained with intravenous  $\alpha$ -chloralose, whereas anesthesia was maintained with sevoflurane in our study. Because most of commonly used volatile anesthetics are known to stimulate the laryngeal irritant receptors<sup>14</sup> and inhibit the pulmonary irritant receptors,<sup>15</sup> the difference between the animal studies and our study may be due to the different effects of anesthetics on the activities of the receptors.

The presence of the fiberoptic during tracheal and bronchial stimulation might have influenced the observed responses. For example, injections of water into the trachea or the bronchus in the presence of fiberoptic might stimulate not only the target site but also other sites because of mechanical irritation with the fiberoptic. It is also possible that the presence of the fiberoptic may fundamentally alter the response to airway stimulation because of the adaptation of the receptor system to the continuing stimulation, particularly for a lesser response through bronchial stimulation. However, in each patient, the responses to repeated injections of water into the trachea and the bronchi were reproducible, and the evoked responses were always lesser with bronchial stimulation, regardless of the order of stimulation. Therefore, it is unlikely that the presence of the fiberoptic altered the responses to airway stimulation.

In the current study, the patients received atropine as premedication. It is possible that atropine may cause changes in bronchomotor tone, which in turn lead to secondary influences on protective responses. However, it is unlikely that the small dose of atropine used in our study might have influenced the observed respiratory changes.

Finally, the potential for differences in duration of stimulus depending on the sites of water injection has to be considered. It is possible that, after injection into

the bronchus, the water might be distributed to multiple bronchi and more rapidly absorbed than when the water was injected onto the larynx. Nonetheless, the finding that bronchial stimulation elicited virtually no protective response cannot be explained by the potential for difference in duration of stimulus alone.

In conclusion, our study showed that respiratory reflex responses evoked by injection of water vary, depending on the site of stimulation. The sensitivity to airway irritation seems to be greater at the larynx and trachea than at the more peripheral airways.

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