Anesthesiology
73:46–51, 1990

Laryngeal and Respiratory Responses to Tracheal Irritation at Different Depths of Enflurane Anesthesia in Humans

Takashi Nishino, M.D., Kazuaki Hiraga, M.D.,† Nobuko Yokokawa, M.D.‡*

The effect of three different depths of enflurane anesthesia (1.0, 1.4, and 1.8 MAC) upon laryngeal and respiratory responses to tracheal instillation of distilled water in nine female patients in whom a double-cuffed endotracheal tube had been inserted was investigated. The laryngeal responses were monitored by measuring the pressure in the saline-filled cuff positioned within the larynx, and the respiratory responses were monitored by measuring ventilatory flow and tracheal airway pressure. Increases in laryngeal cuff pressure in response to tracheal irritation were 19.7 ± 4.5 cmH_2O (mean ± SD) at 1.0 MAC, 13.9 ± 3.6 cmH_2O at 1.4 MAC, and 7.6 ± 1.8 cmH_2O at 1.8 MAC, respectively ($P < 0.01$ for anesthetic dose). At 1.0 MAC of enflurane anesthesia, tracheal instillation of saline caused immediate laryngeal constriction and all components of the tracheal response, such as apnea, expiration reflex, cough reflex, and spasmodic panting. At 1.4 and 1.8 MAC, the same stimulation caused only apnea and constriction of the larynx in the majority of patients. These results indicate that changes in depth of anesthesia can modify the laryngeal and respiratory responses to tracheal irritation. The close association of laryngeal and respiratory responses may be an integral part of the defensive reflex synergism. (Key words: Airways: larynx; trachea. Anesthetics, volatile: enflurane. Reflex: airway.)

CHANGES in laryngeal caliber play a conspicuous part in all airway defensive reflexes. Although it has been shown that in animals stimulation of the airway mucosa causes laryngeal constriction,[1–3] the laryngeal responses to irritation of the respiratory tract have not been fully explored in humans. Our previous studies[4–6] have demonstrated that in anesthetized humans stimulation of tracheal mucosa causes a variety of respiratory reflex responses. However, in these studies the laryngeal responses were not studied. Although the defensive airway reflexes elicited by tracheal irritation are known to be depressed by deep anesthesia,[4] the influence of increasing depths of anesthesia on the laryngeal responses to tracheal irritation is unknown. The aim of the present study was to characterize these responses at different depths of anesthesia. We also attempted to relate the various types of respiratory reflexes to changes in laryngeal wall tension.

* Vice-Director of Operation Theater.

† Chief Anesthesiologist.

‡ Staff Anesthesiologist.

Received from the Department of Anesthesiology, National Cancer Center Hospital, Tokyo, Japan. Accepted for publication February 22, 1990.

Address reprint requests to Dr. Nishino: Department of Anesthesiology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan.

Materials and Methods

Nine female patients 41–49 yr of age were studied. Their average heights and weights were 157.0 ± 3.9 cm and 51.4 ± 7.1 kg, respectively (mean ± SD). All were scheduled for elective radical mastectomy under general anesthesia. None of them had clinical evidence of any respiratory, cardiovascular, or neuromuscular disorder. The protocol of the present study was approved by the Ethics Committee of the hospital, and informed consent was obtained from all the patients.

The patients received 0.5 mg atropine and 50 mg hydroxyzine im 1 h before the induction of anesthesia. Anesthesia was induced with thiamylal (4–5 mg/kg iv) followed by succinylcholine chloride (1 mg/kg iv), and the trachea was intubated with a custom-made double-cuffed endotracheal tube that had an additional fine lumen through the anterior internal wall (Nishino tube, I.D. 7.5 mm, Fuji System Co.). The double-cuffed endotracheal tube was positioned and fixed so that the proximal cuff lay just between the vocal folds, and only the distal cuff was inflated with saline during surgery. Anesthesia was maintained with nitrous oxide and enflurane during the operation, which lasted 3–4 h with a total blood loss of 100–200 ml.

Immediately after the completion of surgery anesthesia was maintained with enflurane in O_2, and spontaneous respiration was allowed to resume while the endotracheal tube was connected to an experimental apparatus incorporated into a semiclosed anesthetic circuit (fig. 1). Ventilatory airflow ($\dot{V}$) was measured through a Fleisch pneumotachograph, and tidal volume (V_T) was obtained by electrical integration of the inspired flow. Tracheal airway pressure (Ptr) was measured from a sidearm of the endotracheal tube with a pressure transducer (DDL-0.05, Toyo Baldwin). End-tidal P_{CO_2} (PET_{CO_2}) and end-tidal enflurane concentration (F_{ENF}) were continuously monitored with an infrared CO_2 analyzer (Normocap, Datex) and a Datex anesthetic monitor (Normac), respectively. All respiratory variables were recorded on an eight-channel recorder (Nihon Kohden RJG-4128). Further details of ventilatory measurements were described previously.[4] To estimate changes in laryngeal wall tension, the proximal cuff of the endotracheal tube was filled with 2–5 ml of saline to a pressure of 10–20 cmH_2O so that changes in cuff pressure reflected laryngeal movements in phase with the respiratory cycle. The cuff pressure was moni-

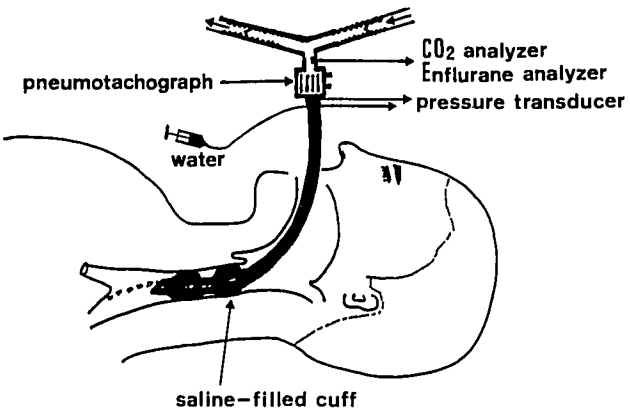

FIG. 1. Schematic illustration of the experimental apparatus.

tored with a Statham-Gould pressure transducer (P 23) and recorded on the recorder together with other respiratory variables. When all the respiratory variables were stable, 0.5 ml of distilled water was injected through the separate lumen of the endotracheal tube, and the laryngeal and ventilatory responses were measured. Each patient was studied in random sequence at three different depths of enflurane anesthesia: 1.0, 1.4, and 1.8 MAC. One MAC for enflurane was taken as 1.68% end-tidal concentration.[7] All measurements were made at least 15 min after establishing a constant end-tidal enflurane concentration. Injections of distilled water were always performed during the expiratory phase and repeated with an interval of 8 min at each depth of enflurane anesthesia. Major respiratory responses observed in this study were apnea, the expiration reflex, the cough reflex, and spasmodic panting. The criterion for apnea is an absence of inspiration >4 s. The expiration reflex is defined as an isolated forceful expiration without prior inspiration, whereas the cough reflex is defined as a sudden and forceful expiration with prior inspiration. Spasmodic panting is defined as a period >10 s when respiratory frequency is >60 breaths/min. Because there was no discernible difference between the two injection trials at each depth of anesthesia in any patient, the mean value from these two trials was used for comparison with all other conditions. Statistical analysis was performed using two-way analysis of variance, followed by Tukey's test, where appropriate.

In addition to injections of 0.5 ml of distilled water, in three of the nine patients the injections of 0.2 ml of distilled water as a subthreshold stimulus for respiratory responses were performed at 1.8 MAC of enflurane anesthesia.

Results

Tracheal instillation of water invariably caused laryngeal and respiratory reflex responses in all patients. Although the expiration reflex, cough reflex, and spasmodic panting were frequently observed at 1.0 MAC of enflurane anesthesia, these responses were rarely seen at deeper depths of enflurane anesthesia; only one of nine patients showed spasmodic panting with the expiration reflex at both 1.4 and 1.8 MAC enflurane anesthesia, whereas the majority of patients showed only apnea at these depths of anesthesia (fig. 2).

Immediately after the tracheal stimulation at 1.0 MAC of enflurane anesthesia, the laryngeal response characterized by a sudden onset of laryngeal constriction was consistently observed in all patients while the subsequent laryngeal response varied among the patients depending on the types of respiratory responses. Figure 3 shows laryngeal responses observed in a patient who showed a series of coughs in response to tracheal stimulation. Although the immediate laryngeal response was characterized by a sudden onset of laryngeal constriction, when vigorous cough efforts were elicited, there was a sudden, transient interruption of sustained laryngeal constriction, coinciding with the peak flow during expiratory efforts of coughing. This indicates that the larynx suddenly dilated during cough. This sudden, transient laryngeal dilatation was consistently observed in other patients who performed vigorous coughing in response to tracheal stimulation. However, when the expiratory efforts during the cough reflex were weak, the cough reflex did not always accompany the apparent laryngeal dilatation.

Figure 4 shows another example of reflex responses observed at 1.0 MAC of enflurane anesthesia. In this case the immediate response after stimulation was laryngeal constriction, which was then followed by the expiration reflex, spasmodic panting, and apnea. Coinciding with the peak flow of the expiration reflex, there was a sudden, transient decrease in laryngeal cuff pressure, indicating that a sudden dilatation of the larynx occurred during

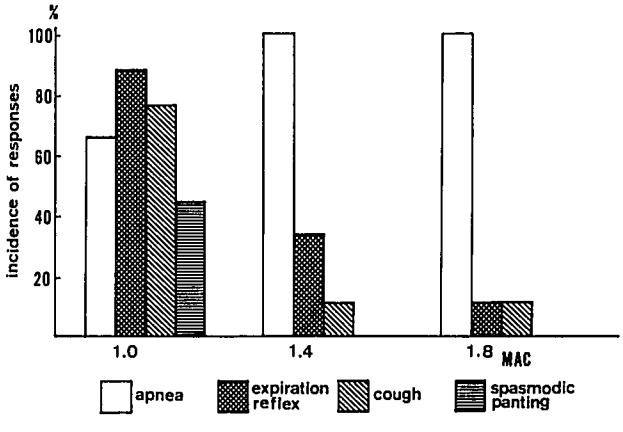

FIG. 2. Incidence (percent of subjects) of various respiratory responses to injection of distilled H_2O at three different depths of enflurane anesthesia.

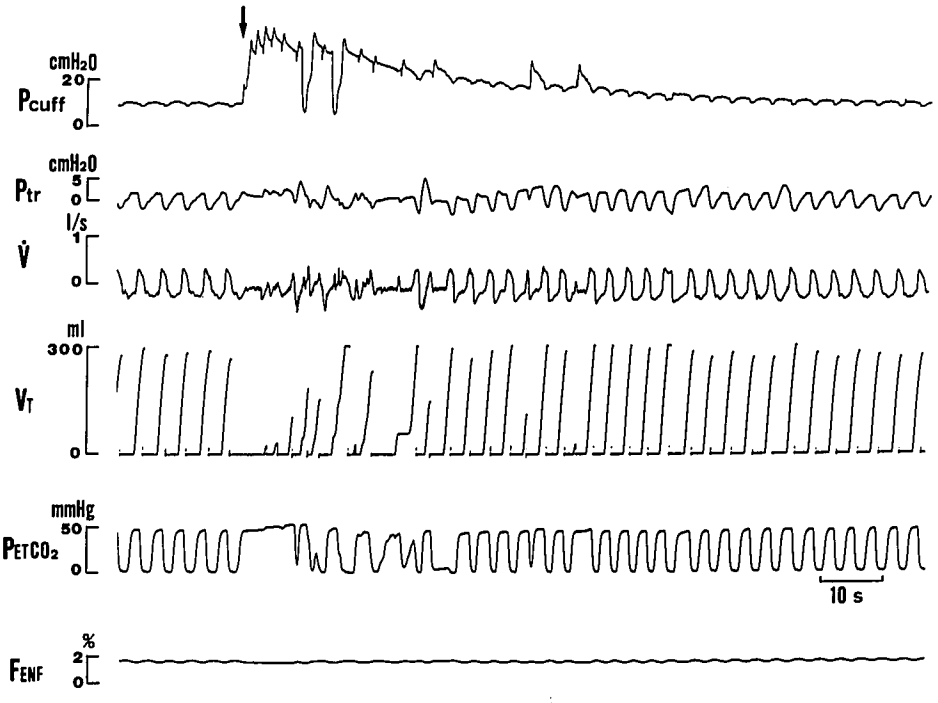

FIG. 3. Experimental records illustrating laryngeal and respiratory responses at 1.0 MAC enflurane. At arrow, 0.5 ml of distilled H_2O was instilled into the trachea. Pcuff = cuff pressure; Ptr = pressure in tracheal airway; $\dot{V}$ = airflow, inspiration upward; V_T = tidal volume, PET_{CO_2} = end-tidal P_{CO_2}.

the expiration reflex. During the subsequent spasmodic panting an oscillatory movement of the larynx was observed.

Figure 5 shows responses of the larynx and respiration observed at 1.8 MAC of enflurane anesthesia in the same patient as in figure 3. Tracheal instillation of water caused

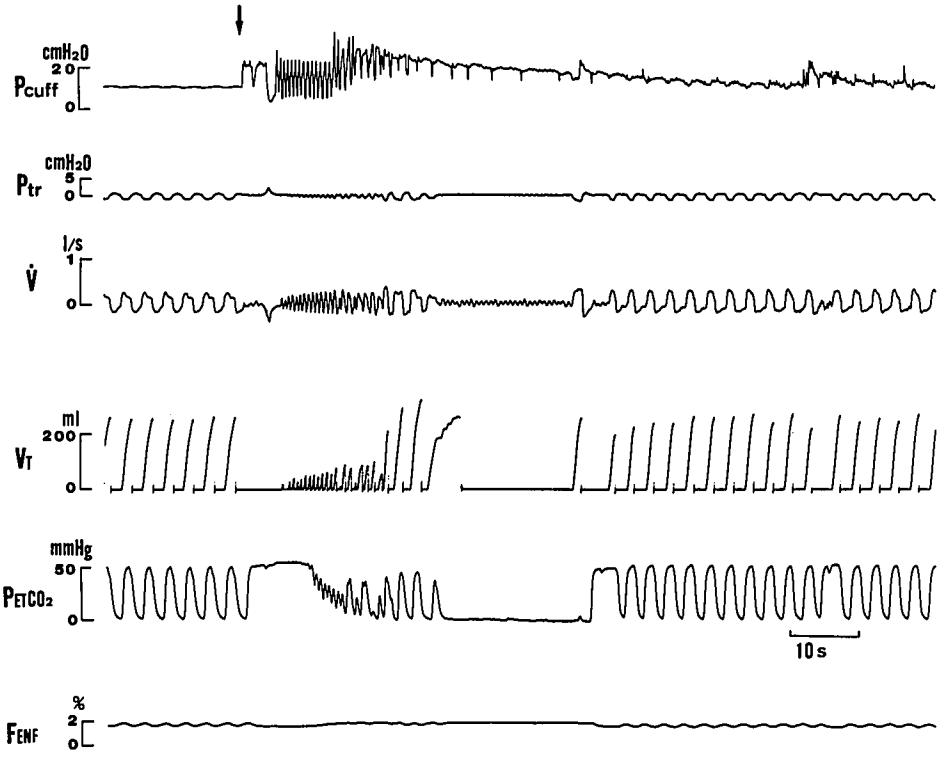

FIG. 4. Laryngeal responses at 1.0 MAC enflurane anesthesia in the presence of expiration reflex and spasmodic panting.

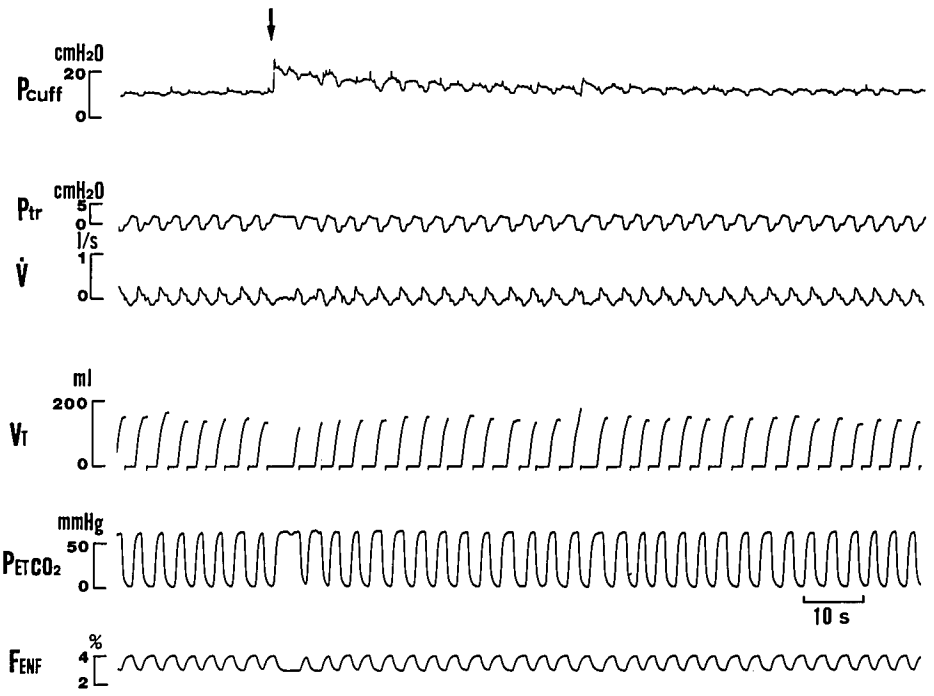

FIG. 5. Experimental records illustrating laryngeal and respiratory responses at 1.8 MAC enflurane anesthesia. The subject is the same as that in figure 3.

immediate laryngeal constriction followed by short apnea. The maximal increase in cuff pressure and the duration of laryngeal response were 10 cmH_2O and 80 s, respectively. These values were less than one-half of those observed in figure 3 at 1.0 MAC enflurane anesthesia. The combination of apnea and laryngeal constriction as observed in figure 5 was the most frequent observation at 1.4 and 1.8 MAC of enflurane anesthesia.

When only 0.2 ml distilled water was instilled into the trachea, there was no change in breathing pattern, whereas immediate laryngeal constriction was consistently observed (fig. 6).

Figure 7 shows maximal increases in laryngeal cuff pressure occurring immediately after tracheal stimulation at three different depths of enflurane anesthesia. The increases in laryngeal cuff pressure were 19.7 ± 4.5 (mean ± SD) cmH_2O at 1.0 MAC of enflurane anesthesia, 13.9 ± 3.6 cmH_2O at 1.4 MAC, and 7.6 ± 1.8 cmH_2O at 1.8 MAC, respectively. There were significant differences between these values ($P < 0.01$).

Figure 8 shows the durations of respiratory and laryngeal responses defined as the time from the onset of responses to the point where the responses returned to prestimulation levels. Durations of both laryngeal and respiratory responses decreased with increasing anesthetic dose, although the duration of respiratory responses was significantly shorter than that of laryngeal responses at all three different depths of anesthesia. These results indicate that both respiratory and laryngeal responses to tracheal stimulation attenuated with increasing anesthetic dose.

Discussion

In the present study we confirmed our previous finding that the types of respiratory reflex responses to tracheal

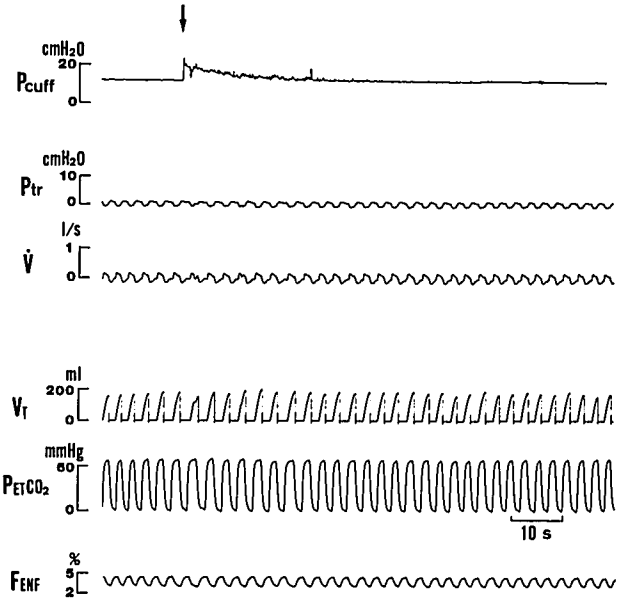

FIG. 6. Responses of the larynx to 0.2 ml distilled H_2O instilled into the trachea.

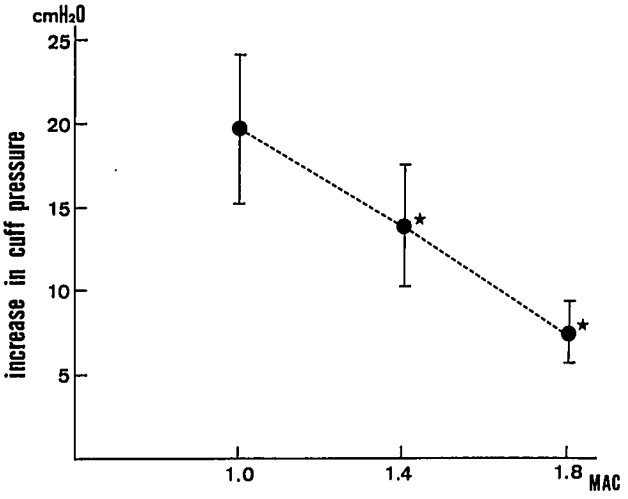

FIG. 7. Maximal increases in cuff pressure immediately after tracheal instillation of 0.5 ml distilled H_2O at three different depths of enflurane anesthesia. Values are mean ± SD. *$P < 0.01$ *versus* preceding value.

irritation depend on the depth of anesthesia.[4] Furthermore, we showed that tracheal irritation causes laryngeal responses and that these responses are associated with the types of respiratory responses; for instance, the response of laryngeal dilatation was associated with the expiration reflex and cough reflex, and the oscillatory movement of the larynx was associated with spasmodic panting. The observed changes may have been modulated by the presence of the endotracheal tube and the saline-filled cuff in the larynx. Although we do not know to what extent this might have contributed to the observed changes, it is possible that the presence of the endotracheal tube and the saline-filled cuff in the larynx might have made the larynx more irritable, exaggerating the laryngeal and respiratory responses.

It has been reported[1-3] that in animals stimulation of the respiratory tract causes laryngeal constriction together with various types of respiratory reflex responses. The present study appears to be the first to simultaneously record the laryngeal and respiratory responses in humans. In the present study we did not directly measure laryngeal caliber. Instead, the changes in laryngeal wall tension were monitored from pressure changes in a saline-filled cuff placed in the larynx. Although the absolute value of cuff pressure by itself is not a meaningful value, changes in cuff pressure do reflect changes in laryngeal wall tension. If it were not for the presence of the cuff, these changes in wall tension would presumably cause changes in laryngeal caliber. Thus, an increase in the cuff pressure indicates laryngeal constriction, whereas a decrease in the cuff pressure represents laryngeal dilatation.

We demonstrated that at relatively deep depths of enflurane anesthesia, *i.e.*, 1.8 and 1.4 MAC of enflurane, stimulation of tracheal mucosa consistently causes apnea and sustained laryngeal constriction in the majority of patients, although the degree and duration at 1.8 MAC of enflurane were much less and shorter, respectively, than those at 1.4 MAC of enflurane. These results are compatible with the general belief that deep depths of anesthesia depress airway reflexes. However, it is somewhat surprising to find that respiratory and laryngeal responses to tracheal irritation continue to be active even at 1.8 MAC of enflurane. Because enflurane at 1.8 MAC produces considerable decreases in ventilation and arterial blood pressure, it seems that total elimination of airway reflex responses to tracheal irritation in a normal clinical situation may not be achieved without possible cardiovascular depression.

When tracheal instillation of water was performed, the laryngeal response occurred rapidly. Compared with the laryngeal response, the duration of respiratory responses was much shorter at all three different depths of anesthesia. Our finding that the laryngeal reflex response can be elicited by stimuli too weak to cause changes in breathing also suggests that the threshold for laryngeal responses is lower than that for respiratory responses.

Although tracheal irritation immediately caused a strikingly strong constriction of the larynx at 1.0 MAC of enflurane, the subsequent responses of the larynx were complicated and quantitative analysis is difficult. Nevertheless, certain qualitative trends are apparent. Major respiratory reflexes observed at this depth of anesthesia

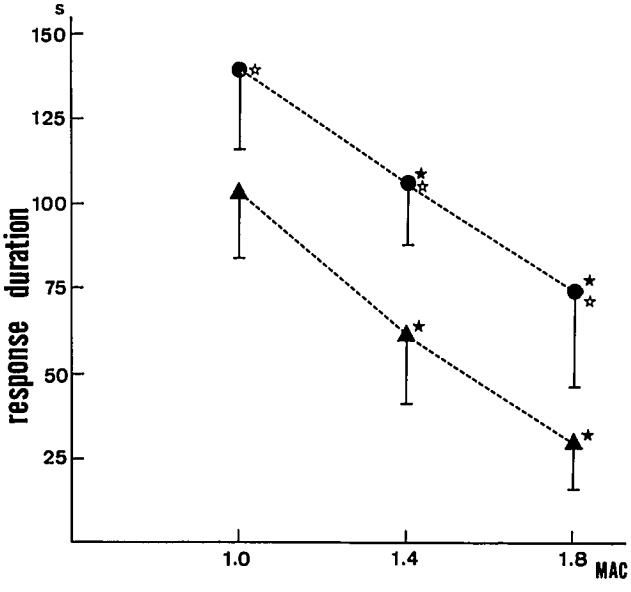

FIG. 8. Durations of laryngeal (●) and respiratory (▲) responses at three different depths of enflurane anesthesia. Values are mean ± SD. *$P < 0.01$ *versus* preceding value. *$P < 0.01$ *versus* corresponding value of respiratory response duration.

are the expiration reflex, cough reflex, and spasmodic panting. During the expiration reflex and cough reflex the laryngeal responses were essentially similar and were characterized by sudden dilatation of the larynx, coinciding with the onset of the forceful expiratory flow. These responses were usually superimposed upon a sustained laryngeal constriction. These findings support the general view that the opening of the glottis at the onset of the expiratory phase of coughing is an active process.[8]

The laryngeal response observed during spasmodic panting is somewhat surprising. Despite the fact that the respiratory frequency during spasmodic panting usually exceeded 100 breaths/min, the oscillatory movement of the larynx was in perfect synchrony with this rapid breathing pattern. This indicates that the laryngeal airway is closely integrated with the function of respiratory muscles by a network of reflex arcs, which uniquely provides for rapid and reversible modification of airway resistance.

The physiologic role of various responses to tracheal irritation observed in the present study is not entirely clear. However, some of these reflex responses are obviously defensive in nature. For example, apnea and laryngeal constriction may be functional in preventing aspiration of foreign materials into the respiratory tract. In clinical terms it is interesting to note that the combination of apnea and laryngeal constriction is the most resistant to deepening anesthesia among various reflex responses. The expiration reflex and cough may tend to remove the irritant stimulus, representing powerful airway clearance mechanisms. It is not clear to what extent spasmodic panting plays a part in the defensive responses to airway irritation. However, oscillatory airflow and/or oscillatory movement of the airway wall during spasmodic panting may facilitate the movement of the stimulants or mucus in the airway surface from where they would be coughed out of the trachea. The close association of laryngeal and respiratory responses may be a part of defensive reflex synergism.

References

1. Stransky A, Szereda-Przestaszewska M, Widdicombe JG: The effects of lung reflexes on laryngeal resistance and motoneuron discharge. J Physiol (Lond) 231:417–438, 1973
2. Szereda-Przestaszewska M, Widdicombe JG: Reflex effects of chemical irritation of the upper airways on the laryngeal lumen in cats. Respir Physiol 18:107–115, 1973
3. Jammes Y, Davies A, Widdicombe JG: Tracheobronchial and laryngeal responses to hypercapnia, histamine and capsaicin in dogs. Bull Eur Physiopathol Respir 21:515–520, 1985
4. Nishino T, Hiraga K, Mizuguchi T, Honda Y: Respiratory reflex responses to stimulation of the tracheal mucosa in enflurane-anesthetized humans. J Appl Physiol 65:1069–1074, 1988
5. Nishino T, Hiraga K, Honda Y: Inhibitory effects of CO_2 on airway defensive reflexes in enflurane-anesthetized humans. J Appl Physiol 66:2642–2646, 1989
6. Nishino T, Sugimori K, Hiraga K, Honda Y: Influence of CPAP on reflex responses to tracheal irritation in anesthetized humans. J Appl Physiol 67:954–958, 1989
7. Gion H, Saidman LJ: The minimum alveolar concentration of enflurane in man. ANESTHESIOLOGY 35:361–364, 1971
8. von Leden H, Isshiki N: An analysis of cough at the level of the larynx. Arch Otolaryngol 81:616–625, 1965