Laryngeal inputs in defensive airway reflexes in humans

T. Nishino*, S. Isono, A. Tanaka, T. Ishikawa
Department of Anesthesiology, Graduate School of Medicine, Chiba University, 1-8-1 Inohanacho, chuo-ku, 260 8670 Chiba, Japan

Received 8 September 2004; accepted 13 September 2004

Abstract

Stimulation of laryngeal receptors is the natural starting point of defensive airway reflexes including the cough reflex, expiration reflex, spasmodic panting, and apnoea with laryngospasm. Although several different types of laryngeal receptors have been reported, the laryngeal irritant receptors are considered to play the most essential role in elicitation of defensive airway reflexes. Based on the knowledge that the laryngeal irritant receptors are stimulated by water solutions lacking chloride anions, we have developed an experimental method to elicit defensive airway reflexes with a direct instillation of distilled water onto the laryngeal mucosa in humans. Using this experimental method, we studied the characteristics of defensive airway reflexes in lightly anaesthetized patients with multiple system atrophy (MSA). The reflex responses to water stimulation observed in these patients were characterized by apnoea with laryngospasm while the cough reflex was never elicited. Endoscopic images of the larynx in these patients were also characterized by laryngeal oedema. Considering the pathological changes occurring in the central nervous system and the laryngeal mucosa, it is possible that the defensive airway reflexes may be modified by central and/or peripheral mechanisms in patients with MSA.

© 2004 Elsevier Ltd. All rights reserved.

Keywords: Laryngeal receptors; Laryngeal reflexes; Cough; Multiple system atrophy

1. Introduction

The larynx is innervated by the recurrent laryngeal nerve (RLN), the internal branch of the superior laryngeal nerve (SLN), and the external branch of the SLN. While the RLN provides the afferent innervation of the subglottal portion of the larynx, the RLN innervates all muscles of the larynx except the cricothyroid muscle. On the other hand, the internal branch of the SLN is mainly composed of afferent fibres from the cranial portion of the larynx whereas the external laryngeal branch carries mostly motor fibres which innervate the cricothyroid muscle. The results of several previous studies [1–3] showed that coughing due to inhaled irritants is not much affected by laryngeal denervation and raised the question about the importance of the larynx as a source of respiratory reflexes. However, the preservation of the cough reflex after laryngeal denervation does not necessarily deny the importance of the larynx as a reflexogenic site. In fact, the study of Higenbottam et al. [1] showed that in heart–lung transplantation patients, the cough response to the nebulized distilled water was strikingly diminished whereas the cough response to instillation of distilled water onto the laryngeal mucosa remained active. Considering that the main function of the larynx is to prevent the entrance of pharyngeal contents into the lower airways, it could be possible that the larynx is relatively insensitive to inhaled irritants but is quite sensitive to mechanical or chemical stimulation induced by solid or liquid materials. In any case, there is no doubt that the larynx is an important reflexogenic site and the reflex responses elicited from the larynx require a well-coordinated activation of both the afferent and the efferent pathways.

2. Laryngeal receptors

Based on morphology and location, laryngeal receptors can be classified into (1) mucosal receptors, (2) articular (joint) receptors, and (3) muscular receptors [4]. However,
this classification does not provide us with much information as to the correlation between reflex responses and receptor activity since receptors of a given category include functionally different types of receptors, which behave differently in response to the same stimulus. On the other hand, Sant’Ambrogio et al. [5] emphasized the functional aspects of laryngeal receptors and showed that in the larynx of the dog there are four different groups of receptors classified on the basis of their responses to airflow, chemical and mechanical stimuli. These are: (1) cold (flow) receptors which are affected by changes in laryngeal temperature; (2) irritant receptors which not only show a rapidly adapting response to maintained mechanical deformation but also respond to a wide variety of irritant gases and aerosols; (3) pressure receptors which are sensitive to changes in laryngeal transmural pressure, and (4) drive receptors which are affected by laryngeal motion. Among these receptors, irritant receptors activated by known tussigenic stimuli are generally considered as the probable source of defensive airway reflexes. Laryngeal irritant receptors usually respond not only to irritant stimuli like cigarette smoke but also to water instilled in the laryngeal lumen [6]. Volatile anaesthetic agents such as halothane, isoflurane and enflurane also activate laryngeal irritant receptors in a dose-related manner [7].

3. Stimulation of laryngeal mucosa for elicitation of defensive reflexes

In 1950, Hoglund and Michaelsson described a technique for eliciting the upper airway reflexes using small concentrations of ammonia vapour in humans [8]. Several investigators used a similar technique and clarified the effects of ageing [9], codeine [10], and prolonged tracheal intubation [11] on laryngeal reflexes. However, inhalation of irritant vapour may stimulate not only the upper airway including the larynx but also the lower airways, causing the interpretation of the upper airway reflexes due to inhaled irritants more difficult. In order to elicit airway defensive reflexes in humans, we usually instill a small amount of distilled water directly onto the laryngeal mucosa since this is a very simple and reliable method for eliciting defensive airway reflexes [12]. Mechanical stimulation of the laryngeal mucosa can also elicit defensive reflexes but water stimulation seems to be more effective in eliciting reflex responses. Furthermore, when it comes to reproducibility, water stimulation is more consistent in terms of types of reflex responses elicited and the duration of reflex responses. The use of distilled water is based on the study of Boggs and Bartlett who showed instillation of water into the larynx elicits reflex apnoea in puppies and that this response is mediated by the laryngeal receptors that are stimulated by low chloride ion concentrations [13]. In addition, the study of Anderson et al. [14] showed that the majority of laryngeal irritant receptors are sensitive to solutions lacking chloride ion. Although water-responsive laryngeal receptors are not specialized endings and some of respiratory-modulated mechanoreceptors respond to water, it is unlikely that both the pressure and drive receptors contribute to elicitation of defensive airway reflexes since they are activated regularly during normal respiratory events. It is also unlikely that the cold receptors are associated with defensive airway reflexes elicited by water instillation into the larynx, since the cold receptors do not respond to water.

4. Studies on patients with multiple system atrophy

Recently, we had an opportunity to study the defensive airway reflex in patients with multiple system atrophy (MSA). MSA is a neurodegenerative disorder including Shy-Drager syndrome, olivopontocerebellar atrophy, and striatonigral degeneration. Patients with MSA are known to frequently develop pulmonary aspiration during the disease process [15]. Although it is possible that impairment of defensive airway reflexes including the cough reflex may be responsible for the development of pulmonary aspiration, little information is available as to the defensive airway reflexes in patients with MSA. In order to clarify the characteristics of defensive airway reflexes in patients with MSA, the defensive airway reflexes elicited by water stimulation in patients with MSA were compared with those in patients without MSA. Preparation of the subjects and methods in this study are as follows.

4.1. Methods

Twelve patients (8 males and 4 females) with MSA and 14 female patients without MSA were studied. The patients of the latter group were fit and had no history of cardiovascular, respiratory, and neuromuscular disorders. All patients were premedicated with 0.5 mg atropine given intramuscularly 30–45 min before anaesthesia. Anaesthesia was induced with a bolus injection of 1.5–2.0 mg/kg propofol and maintained with continuous infusion of propofol at a rate of 5–10 mg/kg per h. Details of the experimental setup used have been described elsewhere [12]. In brief, placement of a laryngeal mask airway (LMA) was conducted after induction of anaesthesia, and the distal end of the LMA was connected to an elbow connector and then to an experimental apparatus incorporated into a semiclosed anaesthetic circuit. A fiberoptic endoscope was passed through a self-sealing diaphragm of the elbow connector down to the end of LMA to visualize laryngeal airway. Laryngeal images of the larynx were recorded with a video recording system. Ventilatory airflow was measured using a pneumotachograph and a differential pressure transducer.

A thin catheter was placed through a suction channel of the endoscope so that the tip of the catheter lay just above the glottis. To elicit the defensive airway reflexes, 0.5 ml of
distilled water was injected through the catheter onto the laryngeal mucosa around the vocal cords, and the respiratory responses were evaluated. The respiratory responses elicited by the laryngeal stimulation were classified into the following four categories: (1) cough reflex, which is a forceful expiration with prior inspiration; (2) expiration reflex, defined as a forceful expiration without a preceding inspiration; (3) spasmodic panting, defined as a rapid shallow breathing; and (4) apnoea with laryngospasm, which defined as a complete closure of the glottis lasting >10 s on the video images.

Statistical analysis of the data was performed using Student’s t-test and Fisher’s exact probability test, where appropriate. \( P < 0.05 \) was considered significant.

4.2. Results

Endoscopic images of the larynx showed that the laryngeal mucosa was considerably oedematous in patients with MSA whereas an oedematous change of the larynx was never observed in patients without MSA (Fig. 1). The values of vocal cord angle at the end of expiration in patients with MSA were significantly smaller than that in patients without MSA, reflecting oedema formation in these patients (Fig. 2).

Fig. 3a shows a typical example of respiratory changes observed in a patient without MSA in response to laryngeal stimulation. The laryngeal stimulation with water instillation immediately caused complex and forceful responses including the expiration reflex, spasmodic panting, cough reflex, and apnoea with laryngospasm. On the other hand, the responses observed in a patient with MSA were simple and less vigorous since apnoea with laryngospasm was the only reflex response observed (Fig. 3b). Similar observations were obtained in most of these patients. Incidence of various reflex responses observed in patients with MSA and in patients without MSA is summarized in Fig. 4. None of patients with MSA showed a cough reflex and spasmodic panting, and the expiration reflex was observed in only 3 of 12 patients with MSA.

Fig. 1. Endoscopic images of laryngeal mucosa. Compared with the patient without MSA, the laryngeal mucosa of the patient with MSA is apparently oedematous.

Fig. 2. Difference in vocal cord angle between patients with MSA and patients without MSA. Values are mean ± SD. ** \( P < 0.01 \), compared with patients without MSA. Vocal cord angle is defined as the angle produced by lines connecting anterior and posterior commissures was measured at the end of expiration in each patient.

Fig. 3. Examples of respiratory responses. (a) Patient without MSA; (b) patient with MSA. Note that laryngeal stimulation elicits various types of reflex responses in a patient without MSA whereas the same stimulation causes only apnoea in a patient with MSA. At arrow, 0.5 ml of water was injected into the larynx.
possible that the characteristics of reflex responses observed are characterized by laryngeal oedema. Thus, it is quite likely that pathological changes occurring in the laryngeal receptors.

Assuming that no change in the central state occurs during prolonged intubation, the observed change may be ascribed to the peripheral level. In this context, the predominant occurrence of apnoea with laryngospasm was kept unchanged. The reflex responses observed in patients with MSA were rarely elicited whereas in patients with MSA these reflex responses were frequently elicited. It is unlikely that the difference in reflex responses between the two groups of patients is due to the difference of anaesthesia since patients in both groups were anaesthetized with the same agent and the same dose. The mechanisms responsible for the predominant occurrence of apnoea in patients with MSA are unclear. Considering the fact that MSA is a sporadic neurodegenerative disease involving several olivary and pontine nuclei [15], it is quite possible that the predominant occurrence of apnoea in patients with MSA is due solely to central mechanisms. In fact, the predominant occurrence of apnoea has been observed by increasing depth of anaesthesia [16] or by intravenous administration of local anaesthetics [17], suggesting that a depression of the central nervous system contributes to this response. However, it is also possible that the alterations in laryngeal responses may involve some mechanisms occurring at the peripheral receptor level. In this context, the predominant occurrence of apnoea with laryngospasm has been observed to occur in surgical patients after prolonged tracheal intubation at a constant depth of anaesthesia [12]. In these patients with prolonged tracheal intubation, the incidence of forceful inspiratory efforts markedly decreased whereas the incidence of apnoea with laryngospasm was unchanged. Assuming that no change in the central state occurs during prolonged intubation, the observed change may be ascribed to pathological changes occurring in the laryngeal receptors.

Endoscopic images of the larynx in patients with MSA are characterized by laryngeal oedema. Thus, it is quite possible that the characteristics of reflex responses observed in patients with MSA may involve pathological changes occurring not only in the central nervous system but also in the laryngeal mucosa. The reason why the patients with MSA have laryngeal oedema is unclear. However, we can speculate that laryngeal stridor commonly observed in MSA patients is associated with the development of laryngeal oedema. In this context, it is possible that prolonged and progressive trauma to the laryngeal structures induced by stretching of the structures during stridor may lead to the development of chronic laryngeal oedema. A similar damage to the upper airway structures due to vibration induced by snoring has been proposed to occur in patients with obstructive sleep apnoea syndrome [18].

In conclusion, we studied defensive airway reflexes in patients with MSA using the experimental method of eliciting defensive airway reflexes with a direct instillation of distilled water onto the laryngeal mucosa. The reflex responses observed in patients with MSA were characterized by apnoea with laryngospasm and the cough reflex was never elicited. Endoscopic images of the larynx in patients with MSA were also characterized by laryngeal oedema. Pathological changes occurring in the central nervous system and laryngeal mucosa may be responsible for the predominant occurrence of apnoea with laryngospasm while suppressing the responses of coughing and other types of forceful expiratory effort. These changes may also contribute to the development of pulmonary aspiration in patients with MSA.

Acknowledgements

This study is supported in part by a grant or the strategy for Cancer Control from the Ministry of Health, Labour and Welfare of Japan.

References


