J Anesth (2004) 18:82–88
DOI 10.1007/s00540-004-0231-y

Journal of
Anesthesia

© JSA 2004

Effects of withdrawal of phasic lung inflation during normocapnia and hypercapnia on the swallowing reflex in humans

Toshihito Sai, Shiro Isono, and Takashi Nishino

Department of Anesthesiology, Graduate School of Medicine, Chiba University, 1-8-1 Inohanacho, Chuo-ku, Chiba 260-8760, Japan

Abstract
Purpose. This study was done to test the hypothesis that hypercapnia has a direct, inhibitory effect on swallowing.
Methods. We investigated changes in the frequency and timing of repeated swallows induced by continuous infusion of water into the pharynx before, during, and after transient airway occlusion at normocapnia and hypercapnia in 12 healthy volunteers. Hypercapnia was induced by adding a dead space. Ventilation was monitored using a pneumotachograph, and swallowing was identified by submental electromyogram.
Results. We found that hypercapnia decreased the frequency of swallows (8.2 ± 3.7 vs 11.4 ± 5.3 swallows·min^{-1} [mean ± SD]: hypercapnia vs normocapnia; $P < 0.05$), together with a loss of the preponderant coupling of swallows with expiratory phase observed at normocapnia. We also found that the withdrawal of phasic lung inflation produced by airway occlusion at end-expiration suddenly increased the swallowing frequency, both at normocapnia (from 11.4 ± 5.3 to 16.7 ± 3.7 swallows·min^{-1}; $P < 0.01$) and at hypercapnia (from 8.2 ± 3.7 to 22.0 ± 6.7 swallows·min^{-1}; $P < 0.01$). Although the degree of increased swallowing frequency during airway occlusion was more prominent at hypercapnia than at normocapnia ($P < 0.05$), the distribution of the timing of swallows in relation to the phase of the respiratory cycle during airway occlusion at hypercapnia was similar to that during airway occlusion at normocapnia.
Conclusion. The results of our study strongly suggest that the attenuation of the swallowing reflex during hypercapnia is not due to the direct, inhibitory effect of CO_2 on the swallowing center, but, rather, is due to the increased inhibitory influence of a lung-volume-related reflex.

Key words Swallowing reflex · Hypercapnia · Lung-volume-related reflex

Introduction

Pulmonary aspiration is a major complication during perioperative periods, and the upper airway reflexes, including the swallowing reflex, have obvious protective values against the aspiration of foreign material into the respiratory tract. There is some evidence to suggest that airway protective reflexes interact with background chemical ventilatory drive [1–3]. For example, it has been shown that, in anesthetized humans, an increase in CO_2 ventilatory drive decreases the degree and duration of respiratory responses to airway irritation, whereas a decrease in CO_2 ventilatory drive has the opposite effect [3]. Although the physiological significance of this interaction is not entirely clear, it is conceivable that the automatic respiratory control system may prevail over the airway protective reflexes when the maintenance of ventilation is particularly important in a condition of hypercapnia. Considering that the swallowing reflex functions as a protective reflex, it is likely that the swallowing reflex interacts with background chemical ventilatory drive. In fact, our previous study [4] showed that hypercapnia not only decreased the frequency of the repetitive swallowing induced by continuous infusion of water into the pharynx but also changed the timing of swallows in relation to the phase of the respiratory cycle.

Although the mechanisms that cause these changes in the rate and timing of swallowing are not entirely clear, at least two possible mechanisms might be considered: (1) vagally mediated inhibitory reflexes for swallowing, and (2) direct effects of hypercapnia on the swallowing center in the medulla. Concerning the first possibility, there are several reports [5–8] to support the idea that the vagally mediated reflexes such as lung/pulmonary reflexes and upper airway reflexes play an important role in the control of the swallowing reflex. On the other hand, no substantial evidence to support possibility (2) above has been reported. The purpose of this study was

Address correspondence to: T. Nishino
Received: September 29, 2003 / Accepted: January 30, 2004

to test the hypothesis that hypercapnia, per se, may have a direct effect on the integrative brainstem network underlying the swallowing reflex. We investigated changes in the rate and timing of repetitive swallowing in response to a sudden withdrawal of phasic lung movements during normocapnia and hypercapnia. We reasoned that the sudden withdrawal of phasic vagal influence may disclose the swallowing-respiration relationship produced in the brainstem network.

Subjects, materials, and methods

Study subjects

Twelve healthy male volunteers, aged 21 to 54 years, were studied. None had histories of dysphagia, or of neuromuscular, cardiovascular, or pulmonary disease. Each subject provided informed consent, and the study protocol was approved by the Institutional Ethics Committee. All subjects were told about various procedures that would take place, but none was familiar with the hypothesis being tested.

Study design

Each subject was seated during the experiment and breathed through a tightly fitting face mask connected to a pneumotachograph and then a T-piece system. Details of the experimental setup are given elsewhere [7,8]. In brief, we measured ventilatory airflow, tidal volume (V_T), end-tidal CO_2 tension ($P_{ET_{CO_2}}$), and mask pressure (Pmask). Swallowing was determined by a burst of the submental electromyogram (EMG) with interruption of airflow and visual observation of the characteristic laryngeal movements. Reflex swallows were induced by continuous infusion of water into the pharynx ($2\,ml{\cdot}min^{-1}$) through a thin nasopharyngeal catheter placed without the use of topical anesthesia. During the experiment, hyperoxia was maintained by passing 100% oxygen with a total flow of $10\,l{\cdot}min^{-1}$ through the T-piece.

Methods

Each subject breathed through the face mask with or without an additional dead space (1.3 l), and a period of 5–7 min was allowed for the establishment of stable breathing patterns at normocapnia and hypercapnia. Subsequently, continuous infusion of distilled water into the pharynx ($2\,ml{\cdot}min^{-1}$) was started to induce the repetitive swallowing reflex. When the swallowing response to continuous infusion of water was stable, breathing and swallowing were recorded for 3 min (baseline period). Then, the airway was occluded at end-expiration by inflating a balloon placed near the entrance port of the face mask, and the occlusion was maintained for 15 s. During the occlusion of the airway (airway occlusion period) the subjects were asked to continue their breathing efforts as normally as possible. The changes in respiration and swallowing were analyzed using the data of the last 60 s during the baseline period, the 15 s of airway occlusion, and the first 60 s of a 2-min recovery period following airway occlusion. For quantitative analysis of the effects of sudden changes in ventilation on the swallowing reflex, changes in respiratory variables (airflow, V_T, $P_{ET_{CO_2}}$, Pmask) and swallowing rate during the baseline, airway occlusion, and recovery periods were analyzed. In addition, the timing of the swallows in relation to the phase of the respiratory cycle before and after airway occlusion was determined as described previously [4,7,8]. In brief, swallows preceded by and followed by inspiratory flow were marked as inspiratory (I) swallows, whereas swallows preceded by and followed by expiratory flow were designated as expiratory (E) swallows. Swallows occurring at the transition between inspiration and expiration were designated inspiratory-expiratory (I-E) swallows, and swallows occurring at the transition between expiration and the inspiratory phase of the next breath were designated expiratory-inspiratory (E-I) swallows (Fig. 1). The timing of swallows during airway occlusion was determined by analyzing the relationships between submental EMG signals and negative inspiratory airway pressure developed during airway occlusion (Fig. 2). The submental EMG signal during the swallowing act was easily distinguishable from the EMG activity generated by inspiratory efforts, because the amplitude of EMG activity during the swallowing act was much greater than that generated by inspiratory efforts, even during airway occlusion.

Analysis

Statistical analysis was performed by using repeated measures analysis of variance (ANOVA) (two-way) or Friedman repeated-measures ANOVA on ranks and paired *t*-test, where appropriate. The post-hoc test following ANOVA was performed by using Bonferroni's *t*-test. $P < 0.05$ was considered significant.

Results

All 12 subjects tolerated the continuous infusion of water and transient airway occlusion procedures during normocapnia and hypercapnia, and completed the experimental protocol. A total of 538 swallows were analyzed.

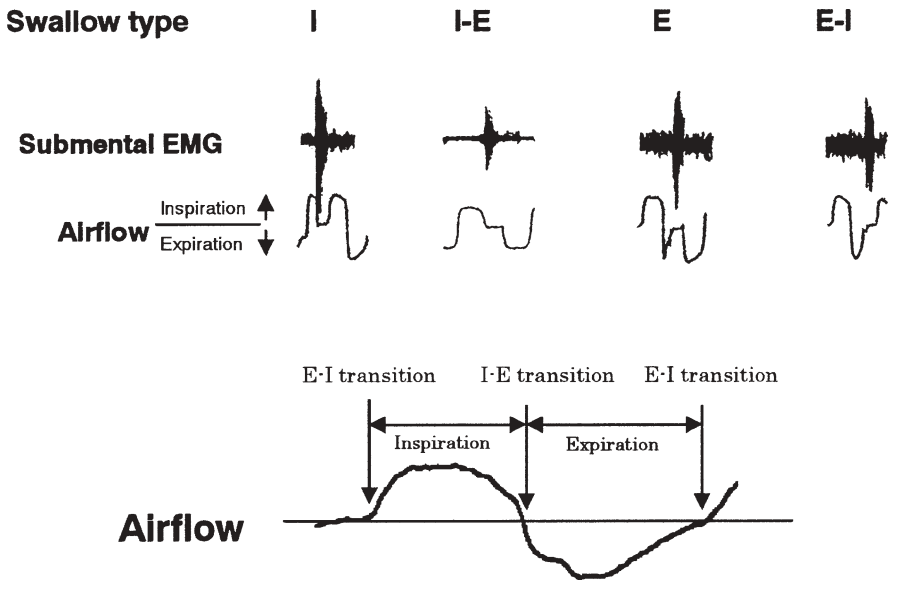

Fig. 1. Definitions of types of swallows. *EMG*, electromyogram; *I*, inspiratory; *E*, expiratory; *I-E*, transition between inspiration and expiration; *E-I*, transition between expiration and the inspiratory phase of the next breath

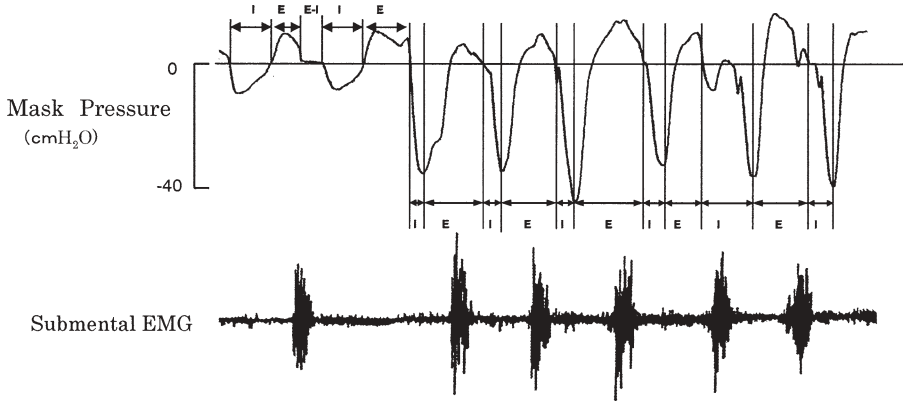

Fig. 2. Changes in airway pressure and the determination of timing of swallows during airway occlusion. Timing of swallows was determined by analyzing the relationship between the submental EMG signal and the airway pressure (*mask pressure*) signal. The phases of the respiratory cycle were judged by the changes in airway pressure. The swallow just before airway occlusion occurred at E-I transition phase and, therefore, was classified as an E-I swallow. The first swallow after airway occlusion occurred at the expiratory phase (expiratory swallow), whereas the fourth swallow occurred at the inspiratory phase (inspiratory swallow). The second, third, and fifth swallows were classified as E-I swallows because these swallows occurred at the E-I transition phase

Table 1 shows the mean values of respiratory variables before and during continuous infusion of water into the pharynx at normocapnia and hypercapnia. Although repetitive swallows induced by continuous infusion of water caused a slight decrease in respiratory frequency at normocapnia, there was no significant difference in the values of other respiratory variables between before and during continuous infusion of water into the pharynx.

Figure 3 shows experimental records illustrating changes in respiration and swallowing in response to airway occlusion at normocapnia (Fig. 3A) and hypercapnia (Fig. 3B) obtained in a single subject. At normocapnia, a one-to-two rhythmic coupling of swallowing and respiration was seen before airway occlusion. In response to airway occlusion, the one-to-two coupling of swallowing and respiration changed to a one-to-one rhythmic coupling, causing an increase in swallowing frequency. Immediately after the release of airway occlusion, there was a slight increase in ventilation and the swallowing frequency decreased considerably. During hypercapnia, the responses of swallowing and respiration to airway occlusion were basically similar to those observed during normocapnia.

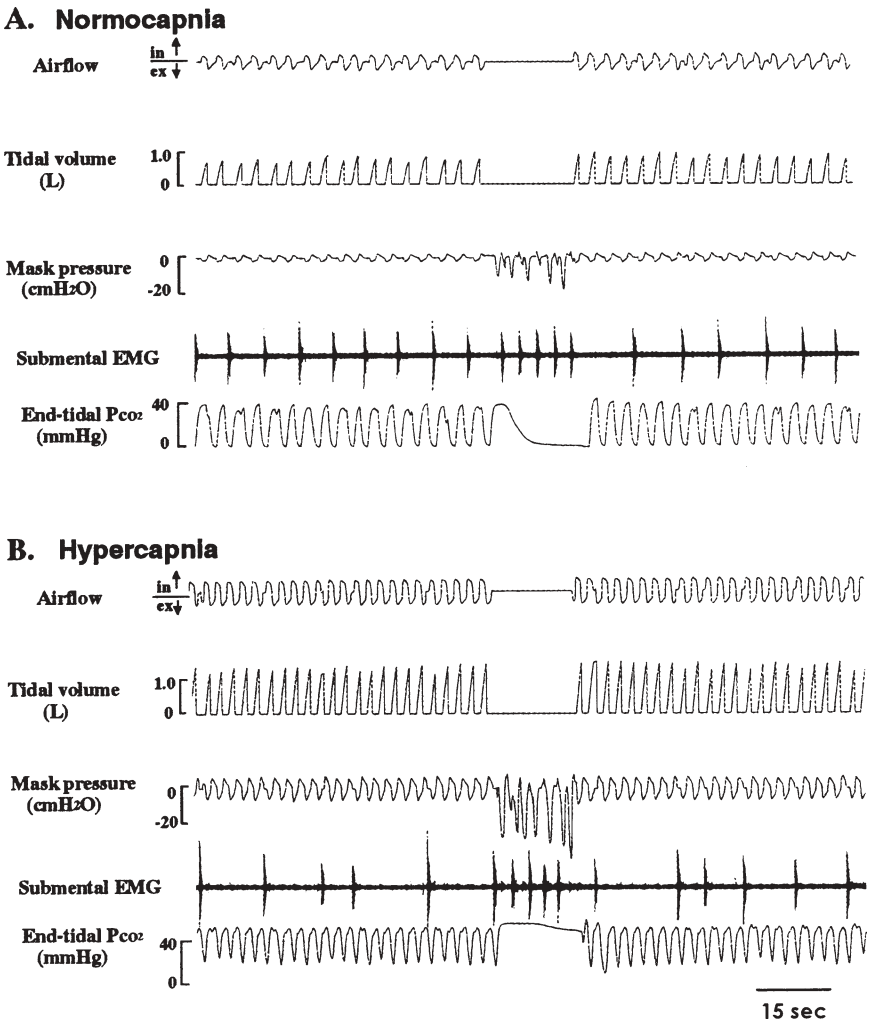

Fig. 3A,B. Experimental records illustrating changes in respiration and swallowing in response to airway occlusion at **A** normocapnia and **B** hypercapnia obtained in a single subject. *in*, inspiration; *ex*, expiration

Table 1. Changes in the values of respiratory variables before and during continuous infusion of water into the pharynx at normocapnia and hypercapnia

	Normocapnia		Hypercapnia	
	Before	During	Before	During
Respiratory rate, breaths·min^{-1}	16.7 ± 3.0	15.7 ± 2.4*	17.2 ± 3.9	16.7 ± 3.6
Tidal volume (l)	0.71 ± 0.10	0.75 ± 0.11	1.51 ± 0.23**	1.55 ± 0.21
Minute ventilation (l·min^{-1})	11.6 ± 1.2	11.5 ± 1.2	25.4 ± 3.1**	25.3 ± 3.7
End-tidal P_{CO_2} (mmHg)	38.4 ± 2.6	38.9 ± 3.0	52.3 ± 2.7**	52.2 ± 2.9

* $P < 0.05$, compared with the value before infusion of water; ** $P < 0.01$, compared with the value during normocapnia
Values are means ± SD

However, the changes appeared to be more exaggerated, because the frequency of swallows was slower before the airway occlusion and was higher during airway occlusion, compared with normocapnia. Figure 4 shows changes in the frequency of swallowing in response to airway occlusion obtained from all 12 subjects. At normocapnia, the values for swallowing frequency before, during, and after airway occlusion were 11.4 ± 5.3, 16.7 ± 3.7, and 7.6 ± 3.6 swallows·min^{-1}, respectively (Fig. 4A). There were significant differences among these values. At hypercapnia, the values for swallowing frequency before, during, and after airway occlusion were 8.2 ± 3.7, 22.0 ± 6.7, and 8.3 ± 3.3 swallows·min^{-1}, respectively (Fig. 4B). The frequency

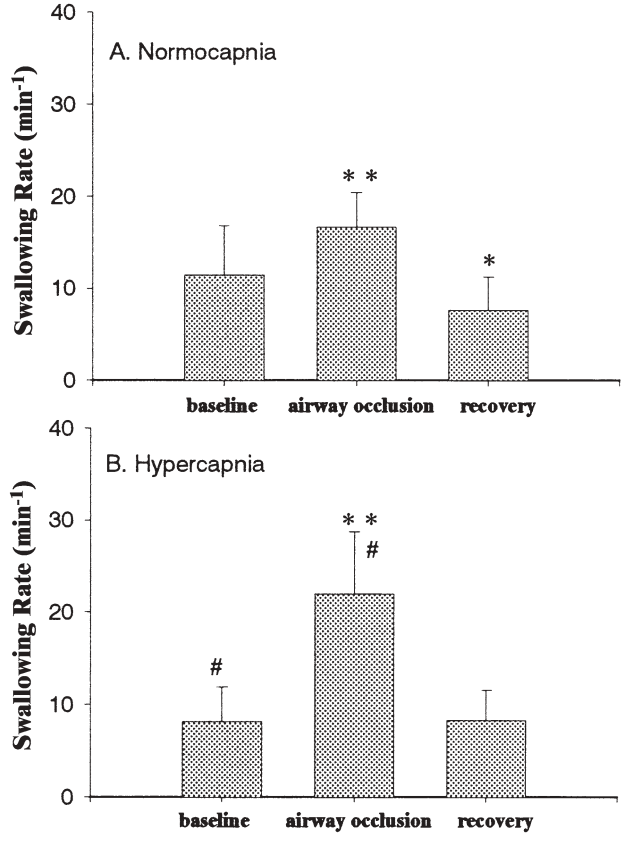

Fig. 4A,B. Changes in swallowing rate in response to airway occlusion at **A** normocapnia and **B** hypercapnia. Values are means ± SD. $^{*}P < 0.05$; $^{**}P < 0.01$, compared with baseline values. $^{\#}P < 0.05$, compared with the corresponding values at normocapnia

of swallows during airway occlusion was significantly higher than those before and after the airway occlusion. In addition, compared with the values for swallowing frequency at normocapnia, the value before airway occlusion was significantly lower ($P < 0.05$) and the value during airway occlusion was significantly higher ($P < 0.05$).

Figure 5 shows changes in the timing of swallows in relation to the phase of the respiratory cycle in response to airway occlusion during normocapnia (Fig. 5A) and hypercapnia (Fig. 5B). Although there was a wide variation among subjects, the majority of swallows occurred at the expiratory phase at normocapnia before airway occlusion. During airway occlusion at normocapnia, expiratory swallows decreased and E-I swallows increased. Under hypercapnic conditions the preponderant occurrence of expiratory swallows was not observed, and I-E as well as E-I transition swallows were more frequently observed. During airway occlusion under hypercapnia, I-E transition swallows decreased and inspiratory swallows increased. Thus, the distribution of timing of swallows in relation to the phase of the respiratory cycle during airway occlusion at hypercapnia was quite similar to that during airway occlusion at normocapnia.

Discussion

In this study we confirmed our previous observation that the swallowing reflex was attenuated during hyperpnea due to hypercapnia. We also demonstrated that airway occlusion caused considerable changes in the frequency and timing of swallows induced by continuous infusion of water into the pharynx. The major findings in this study were that: (1) airway occlusion at end-expiration suddenly increased the frequency of swallows; (2) the degree of increased swallowing frequency during airway occlusion was more prominent at hypercapnia than at normocapnia; (3) the distribution of the timing of swallows in relation to the phase of the respiratory cycle during airway occlusion at hypercapnia was similar to that during airway occlusion at normocapnia, despite the marked difference in the distribution of the timing of swallows between normocapnia and hypercapnia before the airway occlusion. These results suggest that the attenuation of the swallowing reflex during hypercapnia is not due to the direct, inhibitory effect of CO_2 on the swallowing center, but, rather, is due to the increased inhibitory influence of a lung-volume-related reflex.

In the present study we also confirmed our previous observation [4] that hypercapnia not only decreased the frequency of swallowing but also changed the timing of swallows in relation to the phase of the respiratory cycle. It is possible that hypercapnia, per se, may directly inhibit the swallowing center, thereby decreasing the frequency of swallows. However, this possibility is unlikely, because airway occlusion at both normocapnia and hypercapnia considerably increased the swallowing frequency immediately after the start of airway occlusion. Furthermore, the finding that the frequency of swallows during airway occlusion at hypercapnia was higher than that during airway occlusion at normocapnia does not support the possibility that hypercapnia exerts a direct, inhibitory effect on the swallowing center.

The finding that the frequency of swallows increased during airway occlusion suggests that the withdrawal of phasic lung inflation may exert an excitatory effect on the swallowing reflex. Concerning this possibility, it has been shown that nasal continuous positive airway pressure (CPAP) or negative extrathoracic pressure applied in normal adult humans decreases the frequency of repeated swallows [6,7]. Furthermore, our recent study showed that hyperpnea decreased and breath-holding increased the frequency of repeated swallows [8]. All

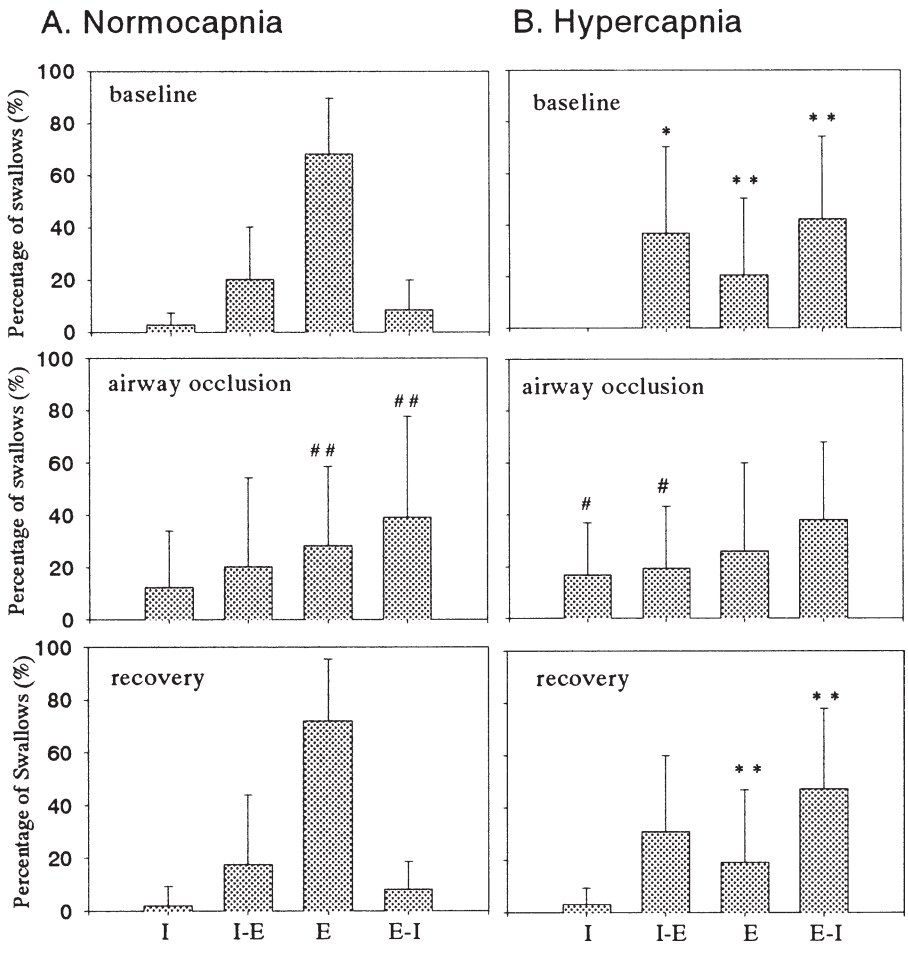

Fig. 5A,B. Distribution of the timing of swallows in relation to the phase of the respiratory cycle during continuous infusion of water at **A** normocapnia and **B** hypercapnia. Values are means ± SD. $^{\#}P < 0.05$; $^{\#\#}P < 0.01$, compared with the corresponding values before airway occlusion. $^{*}P < 0.05$; $^{**}P < 0.01$, compared with the corresponding values at normocapnia

these findings are compatible with the idea that a lung-volume related reflex plays an important role in the control of the swallowing reflex while exerting an inhibitory effect on reflex swallowing. Thus, assuming that a greater phasic vagal activity can be produced by the increases in tidal volume and minute ventilation during hypercapnia [9], the observed decrease in swallowing frequency during hypercapnia can be explained exclusively by the augmented inhibitory effect of a lung-volume related reflex.

The possibility exists that the observed increase in swallowing frequency during airway occlusion may be associated with behavioral and/or emotional responses. For example, Fonagy and Calloway [10] showed that experimental tasks aimed at inducing emotional arousal increased the spontaneous swallowing rate in normal human subjects. Because airway occlusion may cause anxiety and a dyspneic sensation, particularly during hypercapnia, one cannot deny the possibility that the increase in swallowing frequency during airway occlusion may be due to emotional arousal. Another possibility comes from the consideration of a large negative pressure in the upper airway during inspiration that would lead to airway deformation and stimulation of many receptors in the upper airway. Upper airway receptors that initiate swallowing have not been identified histologically, but slowly adapting receptors responding to water and tactile sensation may be responsible for initiating swallow from the upper airway [11].

The marked increase in swallowing frequency during airway occlusion at hypercapnia may indicate that the swallowing center is activated rather than inhibited by hypercapnia in the absence of phasic vagal influence. Although the above-mentioned behavioral/emotional responses may, in part, contribute to the activation of the swallowing center, it is also possible that this activation of the swallowing center may be associated with the simultaneous activation of the respiratory neurons. In this context, it is perhaps no accident that the swallowing center is located at the same site of the brainstem in which the respiratory pattern generator is located. In fact, there is much evidence to indicate that, within the dorsal and ventral medulla, there exists a common pool of neurons that may have a multifunctional role [12–14]. It is possible that some neurons in the respiratory pattern generator may participate in activities of swal-

lowing. Thus, it is conceivable that an increase in respiratory drive due to hypercapnia activates not only the respiratory pattern generator but also the swallowing center.

Several studies [15–18] have shown that swallowing tends to occur preferentially during the expiratory phase of the respiratory cycle during eupneic conditions in normal adult human subjects. In a previous study [4], we have also shown that the preponderant coupling of swallows with expiratory phase is lost during hypercapnia. In the present study, we confirmed these previous observations and showed a marked difference in the timing of swallows between normocapnia and hypercapnia before airway occlusion. Despite the considerably different distributions of timing of swallows at normocapnia and hypercapnia before airway occlusion, the distribution of the timing of swallows at these two different conditions became quite similar during airway occlusion. These observations may suggest that CO_2 cannot be a factor that determines the timing of swallows in relation to the phase of the respiratory cycle. On the other hand, the phasic vagal influence may be a crucial factor determining the timing of swallows. Thus, it is likely that the difference in the timing of swallows observed between normocapnia and hypercapnia may be due to the different degrees of phasic vagal inputs.

A simple extrapolation of our results to clinical situations may not be entirely valid, because hypercapnia does not always accompany hyperpnea in clinical situations. For example, hypercapnia is frequently caused by hypoventilation due to depression of the central nervous system. However, in this situation, the depression of the central nervous system may decrease not only respiratory activity but also the activity of the swallowing center, and the interpretation of the effect of hypercapnia on the swallowing reflex is very difficult. It is also possible that hypercapnia may be produced by changes in respiratory mechanics even in the absence of depression of the central nervous system. In this context, it has been reported that, in conscious subjects, the addition of an external resistive load caused a decrease in minute ventilation with a concomitant increase in $P_{ET_{CO_2}}$, but that no change in the swallowing rate occurred in response to the continuous infusion of water [19]. Thus, it is clear that the swallowing reflex is not attenuated during hypercapnea in the absence of hyperpnea.

Obviously, respiration and swallowing cannot coexist in the upper airway, and the two activities must be coordinated to allow maximal operation of one function without compromising the other function. It has been shown that hypercapnia not only attenuates the swallowing reflex but also changes the timing of swallows, and thereby enhances the chance of laryngeal irritation [4]. The results of the present study strongly suggest that the attenuation of the swallowing reflex during hypercapnia is not due to the direct, inhibitory effect of CO_2 on the swallowing center, but, rather, is due to the increased inhibitory influence of a lung-volume-related reflex.

Acknowledgments. This study was supported in part by Grant-in-Aid for Cancer Research (11-1) from the Ministry of Health, Labour and Welfare of Japan.

References

1. Nishino T, Yonezawa T, Honda Y (1981) Modification of laryngospasm in response to changes in Pa_{CO_2} and Pa_{O_2} in the cat. Anesthesiology 55:286–291
2. Lawson EE (1982) Recovery from central apnea: effect of stimulus duration and end-tidal CO_2 partial pressure. J Appl Physiol 53:105–109
3. Nishino T, Hiraga K, Honda Y (1989) Inhibitory effects of CO_2 on airway defensive reflexes in enflurane-anesthetized humans. J Appl Physiol 66:2642–2646
4. Nishino T, Hasegawa R, Ide T, Isono S (1998) Hypercapnia enhances the development of coughing during continuous infusion of water into the pharynx. Am J Respir Crit Care Med 157:815–821
5. Wilson SL, Thach BT, Brouillette RT, Abu-Osba YK (1981) Coordination of breathing and swallowing in human infants. J Appl Physiol 50:851–858
6. Nishino T, Sugimori K, Kohchi A, Hiraga K (1989) Nasal constant positive airway pressure inhibits the swallowing reflex. Am Rev Respir Dis 140:1290–1293
7. Kijima M, Isono S, Nishino T (2000) Modulation of swallowing reflex by lung volume changes. Am J Respir Crit Care Med 162:1855–1858
8. Yamamoto F, Nishino T (2002) Phasic vagal influence on the rate and timing of reflex swallowing. Am J Respir Crit Care Med 165:1400–1403
9. Sant'Ambrogio G (1982) Information arising from the tracheobronchial tree of mammals. Physiol Rev 62:531–569
10. Fonagy P, Calloway SP (1986) The effect of emotional arousal on spontaneous swallowing rates. J Psychosom Res 30:183–188
11. Storey AT (1968) Laryngeal initiation of swallowing. Exp Neurol 20:359–365
12. Sumi T (1963) The activity of brainstem respiratory neurons and spinal respiratory motoneurons during swallowing. J Neurophysiol 26:466–477
13. Larson CR, Yajima Y, Ko P (1994) Modification in activity of medullary respiratory-related neurons for vocalization and swallowing. J Neurophysiol 71:2294–2304
14. Shiba K, Satoh I, Kobayashi N, Hayashi F (1999) Multifunctional laryngeal motoneurons: an intracellular study in the cat. J Neurosci 19:2717–2727
15. Nishino T, Yonezawa T, Honda Y (1985) Effects of swallowing on the pattern of continuous respiration in human adults. Am Rev Respir Dis 132:1219–1222
16. Selley WG, Flack FC, Ellis RE, Brooks WA (1989) Respiratory patterns associated with swallowing: part 2. Neurologically impaired dysphagic patients. Age Ageing 18:173–176
17. Smith J, Wolkove N, Colacone A, Kreisman H (1989) Coordination of eating, drinking and breathing in adults. Chest 96:578–582
18. Preiksaitis HG, Mayrand S, Robins K, Diamant NE (1992) Coordination of respiration and swallowing: effect of bolus volume in normal adults. Am J Physiol 263:R624–R630
19. Kijima M, Isono S, Nishino T (1999) Coordination of swallowing and phase of respiration during added respiratory loads in awake subjects. Am J Respir Crit Care Med 159:1898–1902