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The mandible advancement may alter the coordination between breathing and the non-nutritive swallowing reflex

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SUMMARY The coordination between nasal breathing and non-nutritive swallowing serves as a protective reflex against potentially asphyxiating material, i.e. saliva and secretions, entering the respiratory tract. Although this protective reflex is influenced by positional changes in the head and body, the effect of mandible position on this reflex is not fully understood. We examined the effect of mandible advancement associated with mouth opening on the coordination between nasal breathing and non-nutritive swallowing induced by continuous infusion of distilled water into the pharyngeal cavity. The combination of mandible advancement and mouth opening increased the duration of swallowing apnoea and submental electromyographic burst duration. When the mandible was advanced with the mouth open, the duration of swallowing apnoea increased significantly compared with the centric position (0·79 ± 0·23 vs. 0·64 ± 0·12 s, $P < 0{\cdot}05$, $n = 12$), and the duration of submental electromyographic activity increased significantly (2·11 ± 0·63 vs. 1·46 ± 0·25 s, $P < 0{\cdot}05$, $n = 12$). Mandible advancement with mouth opening altered the respiratory phase resetting during swallowing and the timing of swallow in relation to respiratory cycle phase. We conclude that mandible re-positioning may strongly influence the coordination between nasal breathing and non-nutritive swallowing by altering respiratory parameters and by inhibiting movement of the tongue–jaw complex.

KEYWORDS: mandible advancement, mouth opening, respiratory parameters, swallowing apnoea, timing of swallow

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Introduction

The coordination between nasal breathing and non-nutritive swallowing serves as a protective reflex to shield the upper airways from saliva in the mouth, secretions in the pharynx, and liquids refluxed from the stomach during sleep in the supine position (1, 2). It has been generally recognized that this protective reflex of human adult and infants (31, 32) during sleep does not require arousal response. However, it has been postulated that this protective reflex may be altered by changes in head and upper body posture (3) and by changes in respiratory function because of reduction of lung volume (4). If these altered protective reflex become much laborious with non-physiological function during sleep in the night-time, a possible occurrence of frequent arousal may cause significant influence on the sleep structure and circadian cycle in awake.

On the other hand, it has been recognized that mandible position is a dominant factor for both controlling the swallowing function during the oral phase and maintaining upper airway patency, because the mandible anchors the tongue, hyoid bone and several muscles related to swallowing and respiratory function in the pharyngeal region. Restricted mandible

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advancement is one of the most effective therapies in patients with moderate obstructive sleep apnoea (OSA) (5). There is strong evidence suggesting that mandible advancement improved upper airway obstruction during anaesthesia in the supine position (6–9). However, it has been reported that the physiological mandible position during the ''swallowing saliva'' manoeuvre (10) was located 2 mm anterior to the centric relation position (11). It can be predicted that non-physiological range of mandible position, i.e. mandible advancement position, may affect swallowing function, because the suprahyoid muscles are attached to several craniofacial landmarks, specific elements of swallowing such as tongue and hyoid movement may be affected by craniofacial morphology (12).

Therefore, we hypothesized that if change in mandible position affects respiratory function and upper airway patency, mandible position might also influence the coordination between non-nutritive swallowing and nasal breathing in the supine position. Furthermore, we also hypothesized that sleep structure may be modified because of interference of normal coordination between non-nutritive swallowing and nasal breathing. However, to date, no studies have examined the effect of mandible position on the coordination between non-nutritive swallowing and nasal breathing in the supine condition. The aim of this study was to investigate the influence of mandible advancement associated with mouth opening on the coordination between nasal breathing and the non-nutritive swallowing reflex induced by continuous infusion of distilled water into the pharyngeal cavity in the supine condition.

Subjects and methods

The experimental protocol was approved by the Human Investigation Committee of the Nagasaki University Graduate School of Biomedical Science (number: 29-2, certificated on 2007.4.5), and written informed consent was obtained from all subjects.

Subjects criteria

Fourteen healthy young subjects of Nagasaki University in both gender were recruited for this study. These volunteers are not representative of a particular social or physical category and paid to participate. Subjects require criteria (i) average build and healthy, (ii) ability for nasal breathing without any congestion or abnormality of nose, (iii) none had a history of upper airway and pharyngeal disease, such as OSA, dysphagia or other gastrointestinal, neurological disease and any respiratory disease such as chronic obstructive pulmonary disease (COPD) or asthma. (iv) had normal orthodontic skeletal characteristics, with normal overjet (2∼3 mm), normal overbite (2∼3 mm), and no apparent retrognathia.

Experimental set-up

Figure 1 illustrates the experimental set-up. All subjects underwent oxygen saturation (SpO_2) monitoring by pulse oximetry.

We performed submental electromyography (EMG) by placing a surface electrode 1 cm posterior to the genu of the mandible over the midline suprahyoid

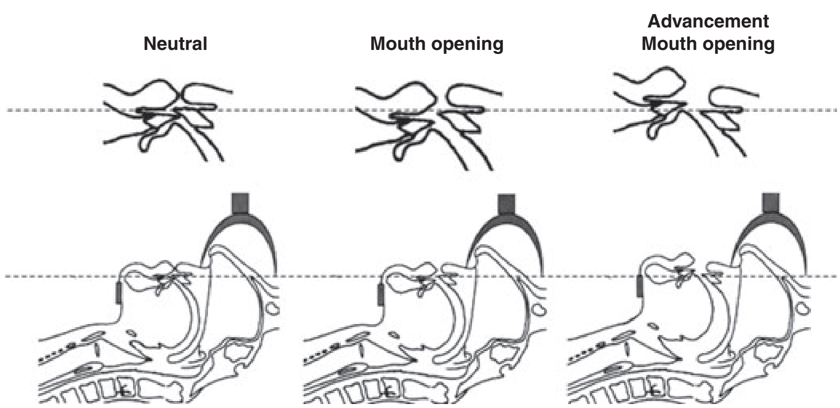

Fig. 1. Three experimental conditions are shown. Coordination between nasal breathing and non-nutritive swallowing was evaluated in three different conditions in random order: (i) neutral mandible position; (ii) mouth open position; (iii) mandible advancement position.

muscle complex. This signal was differentially amplified (Bioamp CF*) relative to a surface recording over the left zygomatic arch. An electrode over the right zygomatic arch served as the ground lead. The EMG signal was also whole-wave rectified and integrated in 50 ms intervals.

Nasal airflow and nasal pressure (Pn) were monitored with a pneumo-tachometer and differential pressure transducer, respectively (model 3830 and model 1100†). The dead space of this system was 150 mL. The airflow signal was filtered (low bandpass filter 100 Hz) and amplified, and zero flow was calibrated by removing the pneumotachograph from the mask. To calibrate volume, 3 L of air was passed through the pneumotachograph. All measurement signals were digitally recorded with a sampling frequency of 1000 Hz on Power Lab data acquisition software and analysed simultaneously (Chart 5, model 8sp‡).

Induced non-nutritive swallowing reflex

Non-nutritive swallowing was induced by continuous infusion of distilled water (3 mL min^{-1}) for a 3-minute period using a syringe pump via a flexible polyethylene tube placed on the mouth floor. A swallowing act was identified by a burst of submental activity on the EMG with a transient interruption of airflow (swallowing apnoea). The occurrence of swallowing was confirmed by the submental EMG burst and swallowing apnoea, which were determined from the EMG tracing and airflow tracing, respectively. The end of the pharyngeal phase of swallowing was marked as the termination of the brief inspiratory airflow signal at the end of the swallowing apnoea (zero flow interval).

Experimental protocol

Effect of mandible advancement

The coordination between nasal breathing and non-nutritive swallowing was evaluated in same subject under three different conditions in random order (Fig. 1). (i) neutral mandible position: lip closure and mouth closure, free anterior–posterior movement; (ii) mouth open position: the mandible was fixed with no advancement in the centric position with an oral appliance 5 mm in height, with no anterior–posterior movement; (iii) mandible advancement position: 65∼75% of the maximum protrusion of the mandible (approximately 6∼8 mm advancement, achieved with an oral appliance 5 mm in height), based on the value reported in previous studies (7, 13, 14). In our previous study (7), we used the criteria to assess the degree of mandible advancement position (minimally effective mandible advancement position = eMAP) defined as the minimal level of mandible advancement required to prevent inspiratory airflow limitation using the same method. We obtained the value of 7·1 ± 1·2 mm from centric occlusion position (normal over jet) for eMAP.

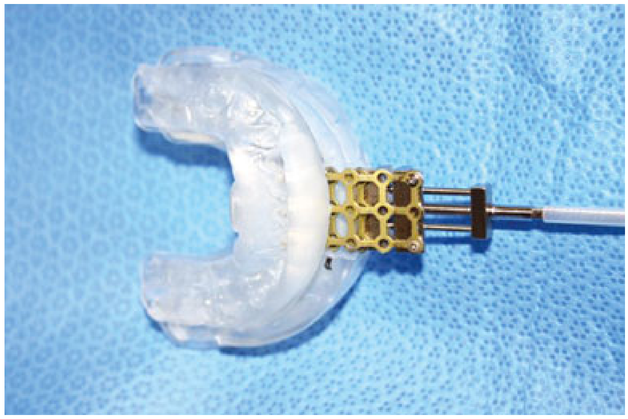

Fig. 2. View of the mandibular positioner showing the device used to modify and adjust the mandible–maxilla relation.

The mandible re-positioning device

Prior to the study, a mandible positioner was constructed from clear acrylic resin and a 2-mm polyethylene plate (Erkodur§) for each subject as described in a previous study (14) (Fig. 2). In brief, a stepping screwed device (Modular Internal Distraction System¶) was attached to a strut extending from lower and upper arch splints. The distance between the upper and lower arch splints was approximately 5∼6 mm. One rotation of the screw enables 0·5 mm extension of the lower splint, thus advancing the mandible by 0·5 mm. The basal standard point was defined as 0 mm advancement

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in the centric occlusion position. The magnitude of mandible advancement was 6~8 mm.

Data analysis

The subjects were explained about the experimental protocol using water infusion and trained before the measurement without insertion of any device in mouth. The respiratory parameters were evaluated in the different mandible positions under two conditions: (i) first condition was performed in the pre-swallowing phase (without water infusion) for 5 min, followed by second condition (ii) the swallowing phase (with water infusion) for 5 min.

Respiratory parameters

The respiratory parameters evaluated were: respiratory rate (*f*), tidal volume (*VT)*, minute ventilation ($\bar{V}_E$), inspiratory duty cycle (IDC; IDC = T_I/T_{TOT}) where T_I is the duration of inspiration and T_{TOTAL} is the duration of the inspiration and expiration. Dead space volume (V_{DS}) was calculated with the formula, height^2 (in cm)/189 mL (Table 1). Alveolar ventilation ($\bar{V}_{ALV}$) was calculated by subtracting dead space ventilation, which is the product of dead space volume (V_{DS}) and respiratory frequency (*f*), from minute ventilation, as shown in the following equation:

$$\bar{V}_{ALV} = \bar{V}_E - (V_{DS} \times f)$$

Duration of swallowing apnoea was assessed by measuring the plateau phase (inspiratory zero airflow) on the respiratory trace (nasal inflow) (Fig. 3a,b). The onset of swallowing was defined as explained above. Respiratory phase resetting during swallowing was analysed by the method described in a previous study (15). Old phase was defined as the time from inspiratory onset to onset of the rapid rise in submental EMG activity associated with swallowing. Co-phase of the first reset breath was the time from the EMG onset to the onset of the first inspiration following the swallow. The co-phase of subsequent breaths was likewise measured relative to EMG onset. The resulting data were normalized by assigning a value of one to the average period of three control breaths preceding the swallow. Thus, old phase and co-phase were expressed as fractions of one cycle rather than units of time. At least five breaths were allowed to elapse after each swallow before recording the next run of three control breaths. We should point out that the interval between any marker of deglutition and reset respiratory timing is a valid measure of co-phase, provided that the markers are applied consistently in a given experiment. The respiratory phase resetting calculated by summation of co-phase and old phase represents degree of respiratory phase resetting during swallow.

Table l. The effects of mandible advancement and mouth open on respiratory and EMG parameters

Control phase pre-swallow (no water infusion)	Neutral	Open	Advance
Respiratory rate (=f, breath min^{-1})	14·3 ± 2·6	17·9 ± 2·4*	17·1 ± 2·7*
Tidal volume = V_T (mL s^{-1})	438 ± 117	375 ± 69*	369 ± 71*
Minute ventilation = V_E (mL s^{-1})	6115 ± 980	6098 ± 1160*	6374 ± 1165*
Estimated alveolar ventilation = V_{ALV} (mL s^{-1})	3751 ± 952	3329 ± 1078*	3508 ± 1104*
Total respiratory cycle duration (=T_{TOT} s)	4·31 ± 0·82	3·62 ± 0·85*	3·51 ± 0·63*
Inspiratory duration (=T_I, s)	1·97 ± 0·53	1·59 ± 0·41*	1·54 ± 0·31*
Inspiratory duty cycle (T_I/T_{TOT})	0·46 ± 0·06	0·44 ± 0·04	0·44 ± 0·07
Swallowing phase (water infusion)			
Swallowing apnea (s)	0·64 ± 0·12	0·59 ± 0·08	0·79 ± 0·23*
Old phase	0·47 ± 0·24	0·51 ± 0·10	0·56 ± 0·19
Co-phase	0·51 ± 0·10	0·71 ± 0·1 8	0·71 ± 0·1 6
Respiratory phase resetting	0·97 ± 0·85	1·24 ± 0·80*	1·29 ± 0·78*
Swallowing count (counts min^{-1})	8·5 ± 3·8	8·4 ± 2·1	6·9 ± 1·5*
EMG burst duration (s)	1·46 ± 0·25	1·51 ± 0·20	2·11 ± 0·63 *
Maximum integrated EMG activity (microVs)	4·6 ± 3·6	4·2 ± 2·1	4·8 ± 3·2
Average integrated EMG activity (microVs)	0·77 ± 0·2	0·72 ± 0·08	0·59 ± 0·27 *

EMG, electromyography.
**P* < 0·05 vs. value in neutral position.

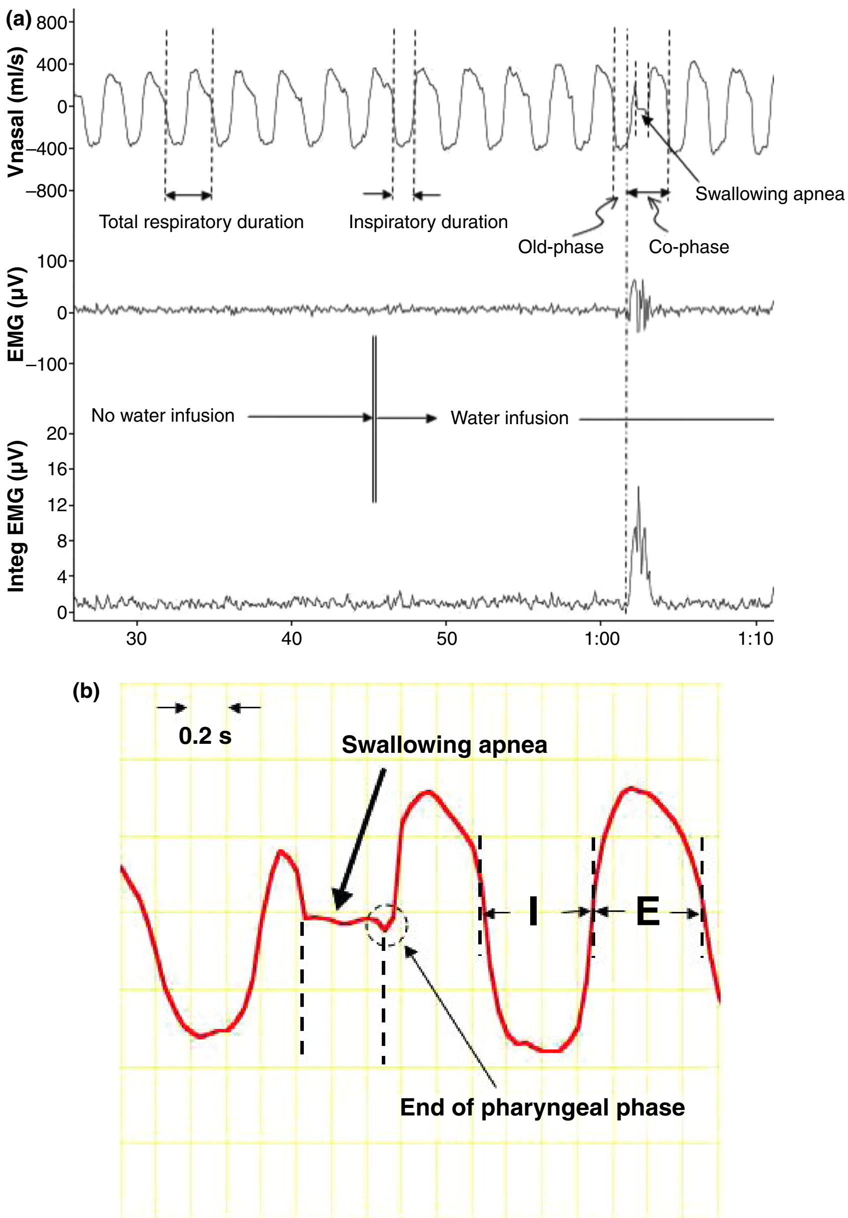

Fig. 3. a. Representative recording of the swallowing reflex. The occurrence of swallowing was confirmed by the submental electromyography (EMG) burst and swallowing apnoea, which were determined from the EMG tracing and airflow tracing, respectively. Inspiratory nasal airflow (VI) (top channel), submental EMG activity (second channel from top) and integrated submental EMG (third channel) are shown. b. Detail of the Fig. 3a, showing first the swallowing apnoea and the end of pharyngeal phase of swallowing and second, the brief inspiratory airflow signal at the end of the swallowing apnoea. The letter I represents inspiration phase and the letter E represents expiration phase.

Timing of swallows in relation to respiratory cycle phase were evaluated in each condition (Table 2). Swallows preceded by and followed by inspiratory flow were marked as inspiratory swallows (I-I), whereas swallows preceded by and followed by expiration flow were designated expiratory swallows (E-E). Swallows occurring at the transition between inspiration and expiration were designated inspiratory–expiratory (I-E) transition swallows, and those occurring at the transition between expiration and the inspiratory phase of the next breath were designated expiratory–inspiratory (E-I) transition swallows.

Statistical analysis

All statistical analyses were performed using SPSS version 16.0**. On the basis of our previous study of the effects of reclining and chin-tuck position on the coordination between respiration and swallowing (3), we estimated (one-way ANOVA) that twelve volunteers would provide a 80% power to detect with an α-error *P* of 0·05 a change in swallowing apnoea of 0·19 s (27%) with average standard deviation of 0·14 at the

**SPSS Japan Inc., Tokyo, Japan.

Table 2. Timing of swallow

	Neutral	Centric	ad
E-Etype(%)	80·9 ± 22·9	64·3 ± 20·8	57·5 ± 19·8*
E-I type(%)	12·5 ± 10·8	27·2 ± 18·6	37·2 ± 21·8*
I-E type(%)	6·6 ± 5·2	8·5 ± 8·7	5·3 ± 9·5
I-I type(%)	0·0	0·0	0·0

*P < 0·05 vs. value in neutral position.

different mandible position. Effects of mandible position for each outcome variable were studied using ANOVA with post-hoc Bonferroni. P values of <0·05 were considered significant. All values are reported as mean ± SD.

Results

Two subjects were excluded because they could not breath nasally. Twelve subjects (9 men, 3 women) aged between 21 and 35 (mean, 27·2 ± 1·6 years) matched for subject criteria were studied and completed measurements.

Respiratory parameters in the pre-swallow phase

The effect of mandible opening on the coordination between respiration and swallowing is shown in Table 1. In the pre-swallow phase, respiratory rate increased significantly from 14·3 ± 2·6 breaths min^{-1} in the neutral position to 17·9 ± 2·4 breaths/min in the mouth open position and 17·1 ± 2·7 breath min^{-1} in the mandible advancement position. Respiratory cycle duration decreased significantly in the mouth open position and mandible advancement position (3·62 ± 0·85 s, 3·51 ± 0·63 s, respectively) compared with the mouth closed position (4·31 ± 0·82 s). Inspiratory duration decreased significantly in the mouth open position and mandible advancement position (1·59 ± 0·41 s, 1·54 ± 0·31 s, respectively) compared with the mouth closed position (1·97 ± 0·53 s). Inspiratory duty cycle (IDC) did not change.

Tidal volume decreased significantly from 438 ± 117 mL s^{-1} in the neutral position to 375 ± 69 ml/sec in the mouth open position and 369 ± 71 mL s^{-1} in the mandible advancement position. Minute ventilation decreased from 6115 ± 980 mL s^{-1} in the neutral position to 6098 ± 1160 mL s^{-1} in the mouth open position. Minute ventilation significantly increased to 6374 ± 1165 mL s^{-1} in the mandible advancement position compared to both neutral and mouth open positions. Estimated alveolar ventilation decreased significantly from 3751 ± 952 mL s^{-1} in the neutral position to 3329 ± 1078 mL s^{-1} in the mouth open position and 3508 ± 1104 mL s^{-1} in the mandible advancement position.

Swallowing apnoea and EMG activity in the swallow phase

The duration of swallowing apnoea increased significantly in the mandible advancement position (0·79 ± 0·23 s) compared with the neutral position (0·64 ± 0·12 s) and mouth open position (0·59 ± 0·08 s). There was no significant difference in respiratory phase resetting during swallowing. The duration of submental EMG activity in the mandible advancement position increased significantly (2·11 ± 0·63 s) compared with the neutral position (1·46 ± 0·25 s) and mouth open position (1·51 ± 0·20 s). The average integrated EMG activity decreased significantly in the mandibular advancement condition (0·59 ± 0·27 μV) compared with the neutral position (0·77 ± 0·20 μV) and mouth open position (0·72 ± 0·08 μV).

Respiratory phase resetting

There was no significant difference of co-phase and old-phase among the three conditions. The respiratory phase resetting was 0·97 ± 0·85 in the neutral position and was significantly higher in the mouth open position (1·24 ± 0·80) and in the mandible advancement position (1·29 ± 0·78).

Timing of swallow in relation to respiratory cycle phase

In the neutral position, 80·9 ± 22·9% of swallows were E-E type, 12·5 ± 10·8% were E-I type, and 6·6 ± 5·2% were I-E type (Table 2). There were no I-I type swallows in the neutral position. In the mandible advancement position, E-E type swallows decreased significantly (57·5 ± 19·8%), E-I type increased significantly (37·2 ± 21·8%), while I-E type did not change (5·3 ± 9·5%).

Discussion

The aim of the present study was to investigate the influence of mandible advancement and mouth opening on the coordination between nasal breathing and the non-nutritive swallowing reflex. There were two major findings in this study. The mandible advancement associated with mouth opening caused (i) significant prolongation in duration of swallowing apnoea associated with alteration of respiratory phase resetting during swallow, (ii) a significant decrease in swallows occurring in the E-E transition and a significant increase in swallows occurring in the I-E transition. These findings indicate that the change in mandible position may significantly influence the coordination between nasal breathing and non-nutritive swallowing.

The effects of mandible position on respiratory parameters in pre-swallow phase

Mouth opening (5∼6 mm) with no mandible advancement was associated with significantly altered respiratory parameters in the pre-swallowing phase. Mouth opening increased the respiratory rate, and this was associated with reduction in tidal volume and therefore a reduction in estimated alveolar ventilation. Previously, we have shown that mouth opening increased upper airway collapsibility in the supine position during sleep (6). The data in this study indicate that even a small amount of mouth opening may increase upper airway collapsibility in the supine position, activating the inspiratory drive.

In contrast, mandible advancement did not cause further modification to respiratory parameters compared with the mouth open condition. Consistent with a previous study (7), mandible advancement is very beneficial in maintaining upper airway patency.

As the upper airway collapses, an increase in respiratory drive (inspiratory effort) and a prolongation of inspiratory duty cycle have an important role in maintaining and stabilizing ventilation. In this study, we found a significant increase in respiratory drive in the mouth open and mandible advancement conditions, but no difference in inspiratory duty cycle (IDC). For a given inspiratory duty cycle, an increase in respiratory rate would decrease the tidal volume. As the tidal volume falls, the dead space fraction increases, and alveolar ventilation will decrease accordingly. Thus, inspiratory duty cycle and respiratory rate responses to a given level of upper airway obstruction may determine the degree of hypoventilation during sleep.

The effects of mandible position on swallowing apnoea and timing of swallows in swallow phase

In this study, when compared with the neutral position, mandible advancement with mouth opening significantly caused a shift of swallows occurring in the expiratory phase (E-E type) to later in the respiratory cycle (E-I type). We believe that the prolongation of swallowing events caused the changes in the swallowing patterns, e.g. from E-E to E-I. A similar change in the timing of swallows has been observed during hypercapnia and with the addition of respiratory loads. Kijima *et al.* (4) recently suggested that added respiratory loads can modulate patterns of respiration and swallowing elicited by continuous infusion of water into the pharynx. Consistent with Kijima's study, we found an increase in respiratory rate and a reduction in alveolar ventilation in the mouth open position and mandible advancement position. Therefore, change in swallow timing may in part depend on the change in lung volume, i.e. alveolar ventilation.

We observed significant prolongation in respiratory phase resetting during swallowing in the mouth open and mandible advancement positions. It has been suggested that if the sum of old phase and co-phase is larger than one, respiratory phase resetting is elicited and activated. The present data indicate that respiratory phase resetting occurred in the mouth open and mandible advancement positions, affecting the coordination between breathing and swallowing.

Taken together, we speculate that an increase in upper airway collapsibility elicited by mouth opening may activate the compensatory respiratory response to maintain minute ventilation and alveolar ventilation. But this change in respiratory parameters may severely disrupt the coordination between nasal breathing and non-nutritive swallowing. In addition, mandible advancement may inhibit normal physiological movement of the tongue–jaw complex, because mandible advancement may modify both the inter-arch contacts and the proprioceptive afferent input coming from the temporo-mandibular joints. Even though mandible advancement has the advantage of improving upper airway collapsibility, it may inhibit the tongue–jaw connection. It is clear that mandible advancement mechanically disturbs this movement of tongue–jaw complex. A recent study by Johal *et al.* (16) reported that a highly significant increase in the EMG activity of the genioglossus, geniohyoid, and masseter muscles accompanied the insertion of a mandibular advancement appliance in awake patients with OSA. Furthermore, Mays *et al.* (12) revealed that craniofacial morphology may influence hyoid movement and therefore affect swallowing physiology.

Thus, we speculate that the combination of increased upper airway collapsibility and mechanical disturbance in muscle movement may have a major influence on swallowing apnoea and the timing of swallows.

Mandible advancement with mouth opening is likely to considerably improve airway patency by activating respiratory drive (inspiratory effort) and enlarging anatomical airway size and increasing EMG activity of dilator muscles. However, at the same time, these changes in respiratory function and EMG activity may adversely affect the coordination between nasal breathing and non-nutritive swallowing.

Methodological limitations

The present study has several methodological limitations. First, we performed these evaluations in limited numbers of normal healthy volunteers in the awake supine condition. It is clear that the simple extrapolation of our results to the sleep state may not be entirely valid: for instance, the effect of mandible position on the coordination between respiration and non-nutritive swallowing during the awake state may differ from that observed in sleep. In normal subjects, it has been reported that 1000∼1500 mL per day (0·5∼1·0 mL min^{-1}) of saliva is secreted in the mouth (17, 18). The non-nutritive swallowing reflex occurs during sleep with a reported frequency of 2·1∼9·1 swallows per hour of sleep, reduced from the more than 25 swallows per hour that occur normally during the day (19). This reduced swallowing reflex during sleep may be related to the reduced salivary flow during sleep. Interestingly, it has been reported that excessive salivation is one of major side effects reported by patients with OSA who have oral appliances (20–22). Several researchers have studied swallowing function using similar protocols of 3 mL min^{-1} infusion of distilled water (4, 23) and 4∼6 mL min^{-1} (15, 24). In consideration of the reduced secretion volume in sleep, we used a 3-mL min^{-1} infusion of distilled water for the experimental protocol in this study.

Second, the validity of measuring swallowing apnoea during swallowing phase with water infusion in the supine position must be considered. We found that swallowing apnoea was 0·64 s in the neutral position and 0·79 s in the mandible advancement position associated with mouth opening. The duration of swallowing apnoea has been measured in several studies, and mean duration appears to be between 0·6 and 0·76 s in young subjects (25, 26). Recently, we found that excessive chin-tuck position increased the duration of swallowing apnoea by 14% to 0·89 s compared with the sitting position (0·78 s) (14). Therefore, we believe that the duration of swallowing apnoea is consistent with previous data.

Third, we should consider the timing of swallowing. In accord with results of several previous studies (27–30), we observed that the majority of swallows interrupted breathing in the expiratory phase (E-E) in the neutral position. The occurrence of this interruption in the I-E transition increased in the mandible advancement position. Although we do not know whether this evaluation is a useful method for assessing the timing of swallow in the supine position, this information may have important clinical implications.

Clinical implications and future research

The present findings may have significant clinical implications for patients who have OSA. Restricted mandible advancement is one of the most effective therapies in patients with moderate OSA (5). To date, several studies have evaluated the side effects of such oral appliances. Although several studies have reported side effects such as temporomandibular joint noise, temporomandibular joint pain, dental discomfort, xerostomia, myofacial discomfort, bite changes and occlusal changes, none have investigated the effect of mandible advancement on non-nutritive swallowing function during sleep. As mentioned above, excessive salivation is one of the major side effects in patients with OSA who have oral appliances (20–22). We do not know the exact amount of saliva secretion during sleep; however, if excessive amount of saliva was produced, the risk for aspiration would be significantly increased. We should therefore carefully evaluate non-nutritive swallowing function during sleep, as we do for other side effects seen in patients with OSA treated with oral appliances. It has been suggested that arousal from sleep has no effect on the coordination between non-nutritive swallowing and breathing of human infants and adult (31, 32) during sleep. However, our finding may lead the speculation that the much laborious non-nutritive swallowing with mandible advancement position may elicit frequent EEG arousal response during sleep in the nighttime. Even though upper airway collapsibility was significantly improved by mandible appliance, a possible occurrence of frequent arousal may worsen the quality of sleep and cause daytime sleepiness.

Furthermore, previous studies have revealed neuromuscular dysfunction activity in patients with OSA. Miyamoto *et al.* (33) suggested that mouth opening during sleep occurs more frequently in patients with OSA than in those without it. Huxley *et al.* (2) suggested that aspiration of pharyngeal secretions easily occurs in normal adults during deep sleep in the supine position, presumably because of depression of the non-nutritive swallowing reflex. Beal *et al.* (34) suggested that there is an apparent risk of increased pharyngeal aspiration in patients with OSA during sleep. These studies indicate that patients with OSA have a pre-existing dysfunction in the activity of muscles related to maintaining upper airway patency and to generating swallowing function. Furthermore, it is reasonable to consider increased risk of aspiration during sleep in elder patients compared to young patients. We suppose that future study will be needed to test the effects of age, gender and BMI on the coordination between breathing and non-nutritive swallowing which may cause major influence during sleep stage. We do not have enough data to prove whether this apparent risk factor of aspiration is because of inhibition of the coordination between breathing and non-nutritive swallowing. However, if excessive mandible re-positioning occurred during non-REM sleep and was associated with reduction of neuromuscular activity, this may further impair the coordination between breathing and non-nutritive swallowing reflex, increasing the risk of aspiration.

In this study, we used 6∼8 mm mandible advancement which was reported to be 65∼75% of maximum protrusion in individual subjects as recommended for OSA treatment in previous studies (7, 13, 14). However, it is reasonable to suppose that the duration of swallowing apnoea may depend on the degree of mandible advancement and mouth opening. It has been reported that the physiological mandible position during the ''swallowing saliva'' manoeuvre (10) was located 2 mm anterior to the centric relation position (11). Therefore, we should carefully decide the thickness of the mouth opening device and the degree of mandible advancement. Future research is encouraged to perform direct comparison between patients with OSA and normal controls subjects to evaluate the effects of age, gender and severity of OSA symptoms. It is worthwhile to establish the potential characteristics and clinical implications of disorganized coordination between respiration and non-nutritive swallowing during sleep stage.

In conclusion, whatever the mechanism may be, our data demonstrate that mandible re-positioning may significantly influence the coordination between respiration and non-nutritive swallowing.

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References

1. Nishino T. Swallowing as a protective reflex for the upper respiratory tract. Anesthesiology. 1993;79:588–601.
2. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. Am J Med. 1978;64:564–568.
3. Ayuse T, Ayuse T, Ishitobi S, Kurata S, Sakamoto E, Okayasu I *et al.* Effect of reclining and chin-tuck position on the coordination between respiration and swallowing. J Oral Rehabil. 2006;33:402–408.
4. Kijima M, Isono S, Nishino T. Coordination of swallowing and phases of respiration during added respiratory loads in awake subjects. Am J Respir Crit Care Med. 1999;159:1898–1902.
5. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. Sleep. 2006;29:244–262.
6. Ayuse T, Inazawa T, Kurata S, Okayasu I, Sakamoto E, Oi K *et al.* Mouth opening increases upper airway collapsibility without changing resistance during midazolam sedation. J Dent Res. 2004;83:718–722.
7. Inazawa T, Ayuse T, Kurata S, Okayasu I, Sakamoto E, Oi K *et al.* Effect of mandibular position on upper airway collapsibility and resistance. J Dent Res. 2005;84:554–558.
8. Isono S, Tanaka A, Tagaito Y, Ishikawa T, Nishino T. Influences of head positions and bite opening on collapsibility of the passive pharynx. J Appl Physiol. 2004;97:339–346.
9. Tamura M, Ishikawa T, Kato R, Isono S, Nishino T. Mandibular advancement improves the laryngeal view during direct laryngoscopy performed by inexperienced physicians. Anesthesiology. 2004;100:598–601.
10. Shanahan TE. Physiologic vertical dimension and centric relation. 1956. J Prosthet Dent. 2004;91:206–209.
11. Millet C, Jeannin C, Vincent B, Malquarti G. Report on the determination of occlusal vertical dimension and centric

relation using swallowing in edentulous patients. J Oral Rehabil. 2003;30:1118–1122.
12. Mays KA, Palmer JB, Kuhlemeier KV. Influence of craniofacial morphology on hyoid movement: a preliminary correlational study. Dysphagia. 2009;24:71–76.
13. Hiyama S, Tsuiki S, Ono T, Kuroda T, Ohyama K. Effects of mandibular advancement on supine airway size in normal subjects during sleep. Sleep. 2003;26:440–445.
14. Ayuse T, Hoshino Y, Inazawa T, Oi K, Schneider H, Schwartz AR. A pilot study of quantitative assessment of mandible advancement using pressure-flow relationship during midazolam sedation. J Oral Rehabil. 2006;33:813–819.
15. Paydarfar D, Gilbert RJ, Poppel CS, Nassab PF. Respiratory phase resetting and airflow changes induced by swallowing in humans. J Physiol. 1995;1:273–288.
16. Johal A, Gill G, Ferman A, McLaughlin K. The effect of mandibular advancement appliances on awake upper airway and masticatory muscle activity in patients with obstructive sleep apnoea. Clin Physiol Funct Imaging. 2007;27:47–53.
17. Thie NM, Kato T, Bader G, Montplaisir JY, Lavigne GJ. The significance of saliva during sleep and the relevance of oromotor movements. Sleep Med Rev. 2002;6:213–227.
18. Rudney JD, Ji Z, Larson CJ. The prediction of saliva swallowing frequency in humans from estimates of salivary flow rate and the volume of saliva swallowed. Arch Oral Biol. 1995;40:507–512.
19. Lichter I, Muir RC. The pattern of swallowing during sleep. Electroencephalogr Clin Neurophysiol. 1975;38:427–432.
20. Dort LC, Hussein J. Snoring and obstructive sleep apnea: compliance with oral appliance therapy. J Otolaryngol. 2004;33:172–176.
21. Schmidt-Nowara WW, Meade TE, Hays MB. Treatment of snoring and obstructive sleep apnea with a dental orthosis. Chest. 1991;99:1378–1385.
22. Pantin CC, Hillman DR, Tennant M. Dental side effects of an oral device to treat snoring and obstructive sleep apnea. Sleep. 1999;22:237–240.
23. Nishino T, Sugimori K, Kohchi A, Hiraga K. Nasal constant positive airway pressure inhibits the swallowing reflex. Am Rev Respir Dis. 1989;140:1290–1293.
24. Jafari S, Prince RA, Kim DY, Paydarfar D. Sensory regulation of swallowing and airway protection: a role for the internal superior laryngeal nerve in humans. J Physiol. 2003;550:287–304.
25. Perlman AL, Ettema SL, Barkmeier J. Respiratory and acoustic signals associated with bolus passage during swallowing. Dysphagia. 2000;15:89–94.
26. Klahn MS, Perlman AL. Temporal and durational patterns associating respiration and swallowing. Dysphagia. 1999;14:131–138.
27. Preiksaitis HG, Mayrand S, Robins K, Diamant NE. Coordination of respiration and swallowing: effect of bolus volume in normal adults. Am J Physiol. 1992;263:R624–R630.
28. Shaker R, Li Q, Ren J, Townsend WF, Dodds WJ, Martin BJ *et al.* Coordination of deglutition and phases of respiration: effect of aging, tachypnea, bolus volume, and chronic obstructive pulmonary disease. Am J Physiol. 1992;263:G750–G755.
29. Smith J, Wolkove N, Colacone A, Kreisman H. Coordination of eating, drinking and breathing in adults. Chest. 1989;96:578–582.
30. Nishino T, Yonezawa T, Honda Y. Effects of swallowing on the pattern of continuous respiration in human adults. Am Rev Respir Dis. 1985;132:1219–1222.
31. Kelly BN, Huckabee ML, Frampton CM, Jones RD. Arousal has no effect on non-nutritive breathing-swallowing coordination during the first year of human life. Int J Dev Neurosci. 2008;26:385–390.
32. Kelly BN, Huckabee ML, Jones RD, Carroll GJ. The influence of volition on breathing-swallowing coordination in healthy adults. Behav Neurosci. 2007;121:1174–1179.
33. Miyamoto K, Ozbek MM, Lowe AA, Sjoholm TT, Love LL, Fleetham JA *et al.* Mandibular posture during sleep in patients with obstructive sleep apnoea. Arch Oral Biol. 1999;44:657–664.
34. Beal M, Chesson A, Garcia T, Caldito G, Stucker F, Nathan CA. A pilot study of quantitative aspiration in patients with symptoms of obstructive sleep apnea: comparison to a historic control group. Laryngoscope. 2004;114:965–968.

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