

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

**4,800**

Open access books available

**122,000**

International authors and editors

**135M**

Downloads

Our authors are among the

**154**

Countries delivered to

**TOP 1%**

most cited scientists

**12.2%**

Contributors from top 500 universities



**WEB OF SCIENCE™**

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.

For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# Swallowing, Gastroesophageal Reflux and Sleep Apnea

---

Shinji Teramoto

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/57577>

---

## 1. Introduction

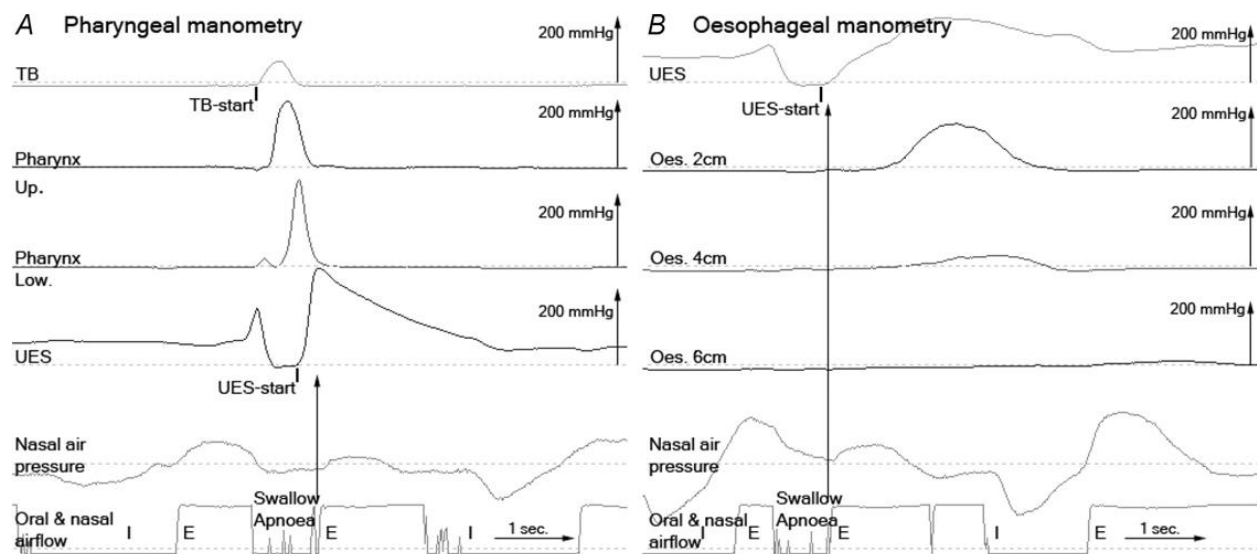
Because the pharynx is a shared conduit for swallowing and respiration, it is known that the breathing cycle is well coordinated with the swallowing in humans [1-3]. The process of inspiration and expiration is very precisely linked with the swallowing reflex via the supra-laryngeal nerve. However, the anatomical configuration of the pharynx may allow for the risk of food aspiration of material into the lower airways during bolus passage, particularly in elderly patients with a history of stroke and dementia [4-11]. The condition and function of the pharynx and upper airways may be considerably affected by nocturnal disturbed breathing including obstructive sleep apnea hypopnea syndrome (OSAHS) [12-14].

Gastro-esophageal reflux (GER) also affects the breathing and respiratory symptom [15]. The coincidence of recurrent respiratory symptoms and gastro-esophageal reflux (GER) is a well-known phenomenon in infants [16]. It has reported that gastro-esophageal reflux (GER) is increased in patients with OSAHS [15]. The GER is also associated with swallowing and breathing. Since the GER, OSAHS, and dysphagia are rapidly increased in adult and elderly patients, this chapter describes the interesting features of sleep apneas in terms of swallowing function and GER.

## 2. Breathing and swallowing

Swallowing function is necessary for eating, and it is coupled with breathing. it is well known that the breathing cycle is well coordinated with the swallowing in humans [1].The adult pattern of breathing-swallowing coordination during eating and drinking is well studied, with 75-95% of swallows beginning in the expiratory phase [2, 3] compared to 39% in newborns [4]. Swallowing elicits inspiratory suppression during breathing (Figure 1). Aspiration related infectious events are prevented by defense mechanisms, such as swallowing reflex, cough

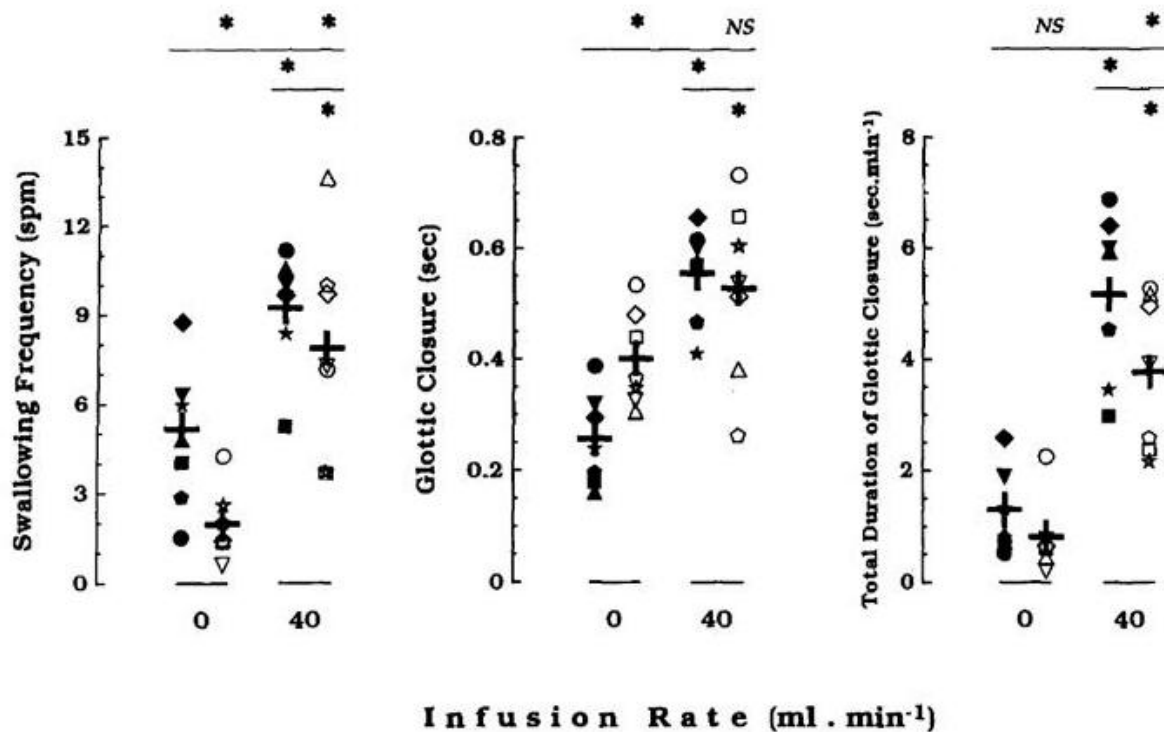
reflex, and mucociliary clearance. Protection of the airway from aspiration requires inhibition of inspiratory airflow throughout the period of laryngeal exposure to the swallowed bolus. This respiratory inhibition is called deglutition apnea and appears to be a universal accompaniment of the normal swallow sequence in man [4-10]. Oral infusion of water at a variable rate of 40 ml/min while the subject breathes through the nose elicits repetitive swallows (rate:  $8.1 \pm 4.1$  swallows/min, mean  $\pm$  SD), but this does not cause a single incidence of coughing or aspiration in normal adults (Figure 2) [10]. The swallows interrupts inspiration and expiration and leads to compensatory changes in tidal volume and breathing frequency. Swallowing also causes respiratory phase resetting with a pattern that is characteristic of the strong perturbations of an attractor-cycle oscillator [11]. The threshold for initiation of swallowing in awake subjects is influenced by, but not strongly coupled to, the phase of respiration. The respiratory timing, in addition to anatomical barriers within the upper airway, influences the vulnerability for aspiration during deglutition. Swallows initiated near the expiratory-inspiratory transition may be the most likely to result in bolus aspiration, especially in pathological conditions that weaken the impact of swallowing on respiratory rhythm or slow the transport of the bolus through the pharynx [11]. Breathing and swallowing are well-controlled by the interaction of neuronal groups co-localized in the brainstem [12, 13]. This central neuronal control, combined with local anatomical conditions and sensory input from the pharynx, permit safe and directed passage of air and food materials. Ventilatory control as indicated by arterial partial pressure of CO<sub>2</sub> affects swallowing [14, 15]. The dysphagia due to anatomical disorders or diseases may also affect breathing patterns [16-18]. The changes in pharyngeal function by surgical conditions may be concerned. However, the coupling between the swallowing and respiratory pattern generators is highly stable even in the post-laryngectomized patients [19].



(cited by Hårdemark Cedborg A I et al. *Exp Physiol* 2009;94:459-468)

**Figure 1. Pharyngeal and esophageal swallowing and swallowing apnea One swallow preceded and followed by expiration (respiratory phase pattern E-E).** One swallow preceded and followed by expiration (respiratory phase pattern E-E). Recordings of pharyngeal (A) and oesophageal manometry (B), nasal air pressure and oral and nasal airflow by the bidirectional gas flow discriminator. The end of swallowing apnea is marked with arrows ( $\uparrow$ ). The start of pharyngeal swallowing is defined as the start of pressure rise at the tongue base (TB-start) and the end of pharyngeal

swallowing as the start of pressure rise at the upper esophageal sphincter (UES-start), which also defines the start of the esophageal phase of swallowing. Pharyngeal manometry was recorded at the tongue base (TB), upper/lower level of the pharynx (Pharynx Up./Low.) and upper oesophageal sphincter (UES). Oesophageal manometry was recorded at 2, 4 and 6 cm below the UES. Inspiration (I), expiration (E).



(Cited by Issa FG, Porostocky S. Control of ventilation during continuous swallowing. Am J Respir Crit Care Med 1994;150:1274-8.)

**Figure 2. Changes in swallowing pattern during quiet breathing and CO<sub>2</sub> rebreathing.** Swallowing pattern during quiet breathing (closed circles) and hypercapnic tests (open symbols) in control (no infusion, 0 ml/min) and continuous swallowing (40 ml/min) in seven subjects participating in the study. Different symbols represent mean data of different subjects, with bold crosses representing the mean data of all tests. Note that the number of swallows per minute (spm), duration of the swallow (glottic closure), and the total duration of glottic closure were higher during rebreathing tests than during control tests. Note also that the pattern of swallowing was different during quiet breathing than during CO<sub>2</sub> rebreathing. Asterisks (p < 0.05) and NS (not significant) denote statistical difference between CO<sub>2</sub> rebreathing and quiet breathing (top asterisks), between 40 and 0 infusion rates during quiet breathing (middle asterisks), and between 40 and 0 infusion rates during CO<sub>2</sub> rebreathing (bottom asterisks).

### 3. Swallowing function in sleep apnea

The condition and function of the pharynx and upper airways is affected by nocturnal disturbed breathing and obstructive sleep apnea (OSA) [20]. Although the mechanisms of apnea termination in obstructive sleep apnea have not been fully elucidated, mechanoreceptor feedback from the respiratory muscles or pharynx has been thought to play an important role in apnea termination [21]. The influence of chemoreceptor information may be mediated

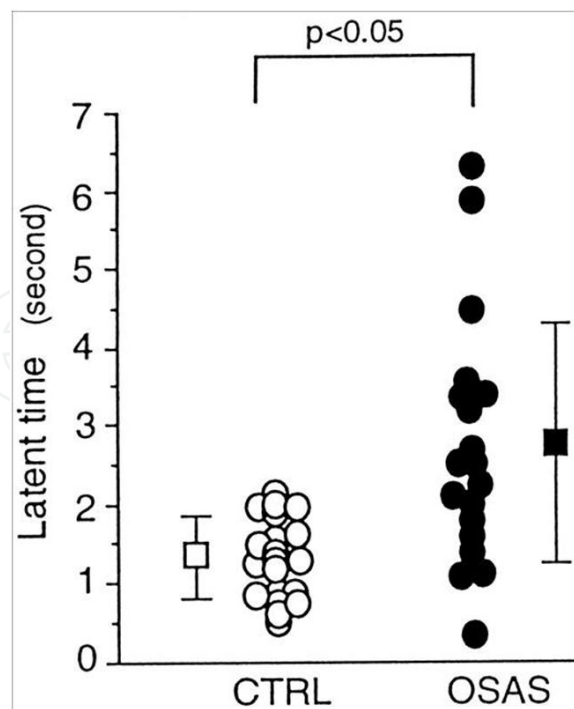
indirectly through an effect on ventilatory effort. The constant positive airway pressure applied via a nose mask through the nares (nasal CPAP, nCPAP) has been established as the first line of therapy for obstructive sleep apnea hypopnea syndrome (OSAHS). It has been reported, however, that nCPAP exerts an inhibitory influence on the water-induced swallowing reflex [22].

Several investigators have reported that gastroesophageal reflux (GER) is increased in adult and child patients with OSAHS [23, 24]. It appears that the swallowing mechanism may be affected by mechanical and/or chemical stimuli, including apnea and positive pressures in the upper airways. Because abnormalities of neural networks in the area of the suprapharynx are implicated in the cause and/or results of obstructive sleep apneas, it is possible that patients with OSAHS have an abnormal swallowing reflex due to impaired neural/muscular function at the upper airways.

The phenomenon was observed. The swallowing reflex was determined according to the following criteria: latent time (LT), the time following a bolus injection of distilled water at the suprapharynx to the onset of swallowing; inspiratory suppression time (IST), the time from the termination of swallowing to the next onset of inspiration; and threshold volume, the minimum volume of water (range, 0.4 to 2 mL) that could evoke the swallowing response. Whereas the LT values in patients with OSAS were larger than the LT values in the control subjects, the IST values (which may reflect the switching mechanism from deglutition apnea to breathing) were actually shorter (Figure 3). In addition, a greater bolus volume was necessary to elicit swallowing in patients with OSAHS than was necessary in the control subjects. Thus, patients with OSAHS are likely to exhibit an impaired swallowing reflex, probably due to the perturbed neural and muscular function of the upper airways [25]. However, Jobin and others have reported that threshold volume did not differ between the OSAHS and control groups with obesity. Although the swallowing latency was shorter for OSA patients, IST were similar for OSA patients and control subjects. Since there was a significant inverse relation between vibratory sensation threshold (VST) and IST, oropharyngeal sensory impairment in OSA may be associated with an attenuation of inhibitory modulating inputs to reflex and central control of upper airway swallowing function [26].

#### **4. Clinical implication of swallowing dysfunction in sleep apnea**

Sleep apnea caused swallowing dysfunction may lead to susceptibility to upper airway infection in child patients and older patients [27-29]. The increased respiratory effort to breath against a closed airway may facilitate pulmonary aspiration in the patients. It is known that children with sleep-disordered breathing experience more respiratory infections. Sleep apnea associated swallowing abnormality is possibly a predisposing risk factor for community-acquired pneumonia (CAP) in children [27]. In the frail elderly, sleep apnea considered to be a significant risk factor for the development of pneumonia [28-30]. Further, immune perturbations secondary to disrupted sleep may render them susceptible to invasion of pathogens [31]. The impaired immune function caused by sleep-disturbed breathing may also potentiate the emergence of pneumonia.



(Cited by Teramoto et al. Chest. 1999;116(1):17-21. doi:10.1378/chest.116.1.17)

**Figure 3.** Swallowing reflex in OSAS patients and control subjects. A presentation of the latency for the swallowing reflex induced by a bolus of water in 20 patients with OSAS and in 20 age-matched control subjects (CTRL). The latency for swallowing initiation was judged using LT on the recording of submental EMG activity.

From treatment viewpoints of sleep apnea, nCPAP therapy may have favorable effects on the risk reduction of airway infection. The treatment of OSAHS with CPAP may be effective for the improvement of awakens and daytime activity as well as the prevention of nocturnal aspiration and pneumonia. On the other hand, poor maintenance of the CPAP machine and the humidifier leads to bacterial growth. Although this does not cause an infection, it can result in the introduction of bacteria to the patient's respiratory system. Keeping the machine and its components clean decreases the opportunity for bacterial growth. The only infection clearly associated with CPAP use may be meningitis. It has been reported that meningitis occurred in patients using CPAP only following a skull trauma [31]. In the elderly, OSA and central type apnea was associated with an increase in mortality from pneumonia in addition to increased risk of cardiovascular related and all-cause mortality. However, there was no relationship between mortality and severity of sleep apnea [32].

## 5. Breathing and gastroesophageal reflux (GER)

Acid reflux events are very different between the awake period and the sleep period. During sleep, acid reflux events tend to be less frequent and of a longer duration as compared with acid reflux events during the awake period [33]. This is due to the profound effect of sleep on esophageal response to acid reflux events. During sleep, there is a significant reduction in



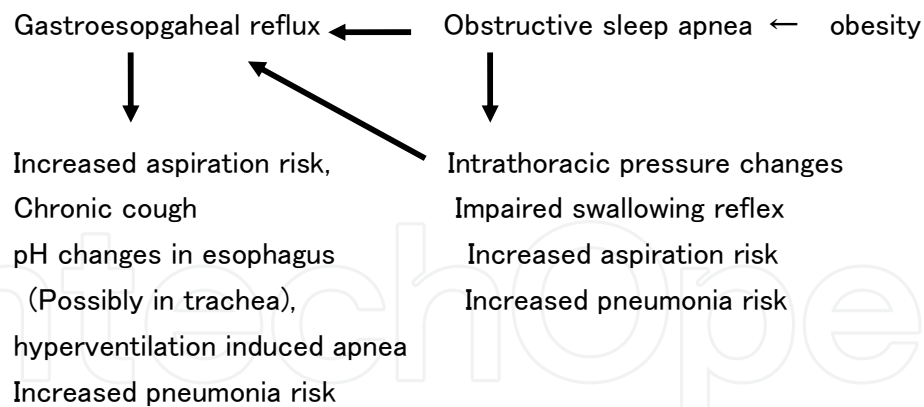
voluntary swallowing and thus primary peristalsis. In addition, diminished saliva production during sleep results in delayed normalization of the distal esophageal pH after an acid reflux event has occurred. Loss of gravitation effect as well as alteration in perception of acid reflux events and thus less symptom generation may all adversely affect physiological response to GER. Consequently, nocturnal GER has been demonstrated to be associated with esophageal inflammation, GER-related complications and extra-esophageal manifestations of gastroesophageal reflux disease (GERD) [34, 35]. It is well known that GERD, besides its classical symptoms, is associated with extra esophageal symptoms and complications as well (Table 1). The most common ones are respiratory symptoms, no cardiac chest pain, and physiatrist symptoms including nocturnal disturbed breathing [36-38].

Organ specialty	Symptoms /complications
Cardiology	non-cardiac chest pain
Pulmonologist	bronchial asthma, chronic cough
Otolaryngology	Posterior laryngitis, reflux laryngitis,
Psychiatry	sleep disorders, sexual disorders, anxiety
Pediatrics	recurrent lower respiratory tract infection, apnea (sudden death), otitis media
Geriatrics	sleep disorders, recurrent lower respiratory tract infection

**Table 1.** Extra-esophageal complications of GERD

## 6. Gastroesophageal reflux in sleep apnea

Gastroesophageal reflux disease (GERD) is a very common disorder defined as various symptoms or esophageal mucosal damage generated by the abnormal reflux of gastric contents into the esophagus [39]. Patients with OSAHS have been reported to have a high prevalence of gastroesophageal reflux (GER) symptoms [40]. The increase of transdiaphragmatic pressure in parallel with the large negative intrathoracic pressure produced during apnea events may directly lead to GER (Figure 4) [41]. Some studies have demonstrated that the application of nCPAP for OSAHS also improve GER symptoms. However, GER does not occur with every apnea [42]. Because the common conditions observed in patients with OSAHS, including obesity or alcohol ingestion, are also predisposing factors for GER, the direct pathologic association between OSAHS and GER has not been established. In fact, a recent investigation in over 1000 subjects failed to show a causal link between both diseases [43]. Thus, there is a common pathology between OSAHS and GERD, but the direct causal relationships between two disorders remains controversial. Further, a temporal relationship between cough and reflux events has been suggested by studies utilizing impedance-pH monitoring of reflux events and objective cough recording. However, consensus is lacking in terms of whether this temporal relationship proves a causal link between reflux and cough [44].



**Figure 4.** Possible pathologic link between gastroesophageal reflux (GER) and sleep apnea

## 7. Clinical implication of GER in sleep apnea

Extraesophageal complications of GERD have been concerned in patients with sleep apnea. The GER may be associated with cardiovascular, pulmonologic, laryngeal, and dental complications [45]. The most recognized manifestations are non-cardiac chest pain, bronchial asthma, chronic bronchitis, chronic cough, and posterior laryngitis, as well as the acidic damage of dental enamel [45].

Heartburn during sleep is very common in the general population. This type of symptom of GERD is strongly associated with increased body mass index (BMI), carbonated soft drink consumption, snoring, daytime sleepiness, insomnia, hypertension, bronchial asthma, and usage of benzodiazepines. These factors are also strong risk factors for sleep apnea. Thus, heartburn during sleep may be associated with the severity of OSA related negative intrathoracic pressure, resulting in increased sleep complaints and excessive daytime sleepiness [46]. It has been suggested that sleep deprivation is hyperalgesic in patients with GERD and provides a potential mechanism for increase in GERD symptom severity in sleep-deprived patients [47].

## 8. Possible links among dysphagia, GER and sleep apnea

Chronic cough is a common problem in patients who visit physicians. The cough is associated with deterioration in patients' quality of life. The three most common causes of chronic cough in those who are referred to pulmonary specialists are postnasal drip, asthma and gastroesophageal reflux. It has been reported that asthma, postnasal drip syndrome (PNDS), and gastroesophageal reflux disease (GERD), alone or in combination, were responsible for > 90% of the causes of chronic cough [48]. The chronic cough may lead to true asthma and asthma is exacerbated by the gastroesophageal reflux [49, 50]. The initial treatment of patients with cough



is often empiric and may involve a trial of decongestants, bronchodilators or histamine H<sub>2</sub> antagonists, as monotherapy or in combination [51]. If a therapeutic trial is not successful, sequential diagnostic testing including chest radiograph, and barium swallow may be indicated. The chronic cough could be caused by repeated GER, aspiration, and OSA [52]. The pathologic link between chronic cough and sleep apneas has been considered. The chronic cough is a symptom of GER and dysphagia. The daytime symptom may affect the night time symptom including sleep apneas. One possible explanation for the risk of chronic cough in OSA patients may be related to easy pulmonary aspiration. Since high collapsibility of the upper airway is characteristic to OSA, resultant hypoxemia may stimulate such patients to breath against a closed airway, therefore generating a more negative intra-thoracic pressure [53-55]. The more negative intra-thoracic pressure induces a higher pressure gradient and a vacuum pressure through the upper airway, facilitating aspiration of pharyngeal secretions, saliva or oral contents into the lower respiratory tract[56]. Because the fundamental mechanism of sleep-disordered breathing in children may not be the same as that of sleep apneas in adults and the elderly, the inter-relationships among chronic cough, sleep apnea, and GER in younger subjects and children is different from those in adult and elderly patients. Post-swallow apnea and post-swallow inspiration occur significantly more frequently in infants suffering from acute bronchiolitis than healthy infants [57]. It is interesting to know the swallowing function in child patients and older patients with sleep apneas or GERD. Because the swallowing function is impaired in patients with OSAHS, and because the swallowing function is associated with cough reflex thorough substance P, the abnormality in swallowing function in OSAS may be associated with chronic cough in children and adults [58, 59]. It has been suggested that excessive daytime sleepiness seen in some OSAHS patients may be associated with various pathophysiological mechanisms including changes in substance P levels [60]. Although many patients with adults OSAHS complain of sleep-related heartburn and regurgitation of gastric contents into the pharynx, the complaint is rarely heard in children with apneas. Therefore, the similarities and differences in swallowing function, cough reflex, and GER between children and adult patients with SAS may lead to further knowledge regarding the coupling mechanism between respiration and deglutition [61, 53]. However, as GERD manifests a spectrum of conditions, including asthma, posterior laryngitis, and chronic coughing, the pathologic link among chronic cough, OSAS, and GERD is not simply determined in children.

## 9. Summary

Breathing and swallowing is tightly coupled. Disruption of breathing-swallowing coordination causes aspiration, which facilitates several pulmonary complications including lower respiratory tract infection.

Swallowing is also affected by the gastroesophageal reflux (GER). Thus, GER affects respiratory symptom including aspiration, cough, and dysphasia. The coincidence of recurrent respiratory symptoms and GER is important in infants as well as elderly patients. The GER related respiratory symptoms are considerably influenced by nocturnal disturbed breathing including OSAHS. The intrathoracic pressure changes during obstructive apnea and compen-

sated hyperinflation are associated with the occurrence of GER and aspiration. We should seriously consider that the swallowing, breathing and GER are dependently and independently linked in various clinical condition during daytime and nighttime.

## Author details

Shinji Teramoto\*

Address all correspondence to: [shinjit-ky@umin.ac.jp](mailto:shinjit-ky@umin.ac.jp)

Department of Pulmonary Medicine, Hitachinaka Medical Education and Research Center, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Japan

## References

- [1] Smith J, Wolkove N, Colacone A, et al. Coordination of eating, drinking and breathing in adults. *Chest* 1989; 96:578–582
- [2] 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(3 Pt 2), R624-630.
- [3] Hiss SG, Treole K, Stuart A. Effects of age, gender, bolus volume, and trial on swallowing apnea duration and swallow/respiratory phase relationships of normal adults. *Dysphagia*, 2001; 16(2): 128-135.
- [4] Bamford O, Taciak V, Gewolb IH. The relationship between rhythmic swallowing and breathing during suckle feeding in term neonates. *Pediatr Res*, 1992;31(6): 619-624.
- [5] Wilson SL, Thach BT, Brouillette RT, Abu-Osba YK. Coordination of breathing and swallowing in human infants. *Journal of Applied Physiology*, 1981;50: 851-858.
- [6] Nishino T, Yonezawa T, Honda Y. Effects of swallowing on the pattern of continuous respiration in human adults. *Am Rev Respir Dis*. 1985;132(6):1219-22.
- [7] Selley WG, Flack FC, Ellis RE, Brooks WA. Respiratory patterns associated with swallowing: Part 1. The normal adult pattern and changes with age. *Age Ageing*. 1989;18(3):168-72.
- [8] Nishino T, Tanaka A, Ishikawa T, Hiraga K. Respiratory, laryngeal, and tracheal responses to nasal insufflation of volatile anesthetics in anesthetized humans. *Anesthesiology*. 1991;75:441-444.

- [9] 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: G750-755.
- [10] Issa FG, Porostocky S. Control of ventilation during continuous swallowing. *Am J Respir Crit Care Med*. 1994;150:1274-1278.
- [11] Paydarfar D, Gilbert RJ, Poppel CS, et al. Respiratory phase resetting and airflow changes induced by swallowing in humans. *J Physiol (Lond)* 1995; 483:273–288
- [12] Dick TE, Oku Y, Romaniuk JR & Cherniack NS. Interaction between central pattern generators for breathing and swallowing in the cat. *J Physiol* 1993; 465, 715–730.
- [13] Saito Y, Ezure K, Tanaka I. Swallowing-related activities of respiratory and non-respiratory neurons in the nucleus of solitary tract in the rat. *J Physiol* 2002; 540: 1047–1060.
- [14] Sai T, Isono S, Nishino T. Effects of withdrawal of phasic lung inflation during normocapnia and hypercapnia on the swallowing reflex in humans. *J Anesth* 2004; 18: 82–88.
- [15] Nishino T, Hasegawa R, Ide T, Isono S. Hypercapnia enhances the development of coughing during continuous infusion of water into the pharynx. *Am J Respir Crit Care Med* 1998; 157, 815–821.
- [16] Nilsson H, Ekberg O, Bülow M, Hindfelt B. Assessment of respiration during video fluoroscopy of dysphagic patients. *Acad Radiol* 1997; 4: 503–507.
- [17] Hadjikitidis S, Pickersgill TP, Dawson K, Wiles CM. Abnormal patterns of breathing during swallowing in neurological disorders. *Brain* 2000;123, 1863–1873.
- [18] Terzi N, Orlikowski D, Aegerter P, Lejaille M, Ruquet M, Zalzman G, Fermanian C, Raphael JC, Lofaso F. Breathing–swallowing interaction in neuromuscular patients: a physiological evaluation. *Am J Respir Crit Care Med* 2007; 175: 269–276.
- [19] Charbonneau I, Lund JP, McFarland DH. Persistence of respiratory–swallowing coordination after laryngectomy. *Journal of Speech, Language and Research* 2005; 48: 34-44
- [20] Radwan L, Maszczyk Z, Koziorowski A, Koziej M, Cieslicki J, Sliwinski P, Zielinski J. Control of breathing in obstructive sleep apnea and in patients with the overlap syndrome. *Eur Respir J* 1995; 8:542–545
- [21] Kimoff RJ, Cheong TH, Olha AE, Charbonneau M, Levy RD, Cosio MG, Gottfried SB. Mechanisms of apnea termination in obstructive sleep apnea. Role of chemoreceptor and mechanoreceptor stimuli. *Am J Respir Crit Care Med*. 1994;149:707-714.
- [22] Nishino T, Sugimori K, Kohchi A, Hiraga K. Nasal constant positive airway pressure inhibits the swallowing reflex. *Am Rev Respir Dis*. 1989;140:1290-3.

- [23] Ing AJ, Ngu MC, Breslin AB. Obstructive sleep apnea and gastroesophageal reflux. *Am J Med.* 2000;108 Suppl 4a:120S-125S.
- [24] Noronha AC, de Bruin VM, Nobre e Souza MA, de Freitas MR, Araújo Rde P, Mota RM, de Bruin PF. Gastroesophageal reflux and obstructive sleep apnea in childhood. *Int J Pediatr Otorhinolaryngol.* 2009;73:383-389.
- [25] Teramoto S, Sudo E, Matsuse T, Ohga E, Ishii T, Ouchi Y, Fukuchi Y. Impaired swallowing reflex in patients with obstructive sleep apnea syndrome. *Chest.* 1999;116:17-21.
- [26] Jobin V, et al, Swallowing function and upper airway sensation in obstructive sleep apnea. *J Appl Physiol* 2007; 102:1587–1594
- [27] Goldbart AD, Tal A, Givon-Lavi N, Bar-Ziv J, Dagan R, Greenberg D. Sleep-disordered breathing is a risk factor for community-acquired alveolar pneumonia in early childhood. *Chest.* 2012;141:1210-1215.
- [28] Ishii M, Yamaguchi Y, Yamamoto H, Ouchi Y, Osumi S, Nakamura T. Relationship between sleep apnea and respiratory infections in bedridden elderly individuals on tube feeding. *J Am Geriatr Soc.* 2012 ;60:790-792
- [29] Sanner BM, Fluerebrock N, Kleiber-Imbeck A, et al. Effect of continuous positive airway pressure therapy on infectious complications in patients with obstructive sleep apnea syndrome. *Respiration* 2001;68:483-487
- [30] Morimoto S, Takahashi T, Okaishi K, Okuro M, Nakahashi T, Sakamoto D, Mizuno T, Kanda T, Takahashi M, Toga H. Sleep apnoea syndrome as a risk for mortality in elderly inpatients. *J Int Med Res* 2012;40:601-11.
- [31] Besedovsky L, Lange T, Born J. Sleep and immune function. *Pflugers Arch* 2012;463:121-137
- [32] Kuzniar TJ, Gruber B, Mutlu GM. Cerebrospinal fluid leak and meningitis associated with nasal continuous positive airway pressure therapy. *Chest.* 2005;128:1882-1884.
- [33] Orr W, Johnson L, Robinson M. Effect of sleep on swallowing, esophageal peristalsis, and acid clearance. *Gastroenterology* 1984; 86: 814–819.
- [34] Cuttitta G, Cibella F, Visconti A, et al. Spontaneous gastroesophageal reflux and airway patency during the night in adult asthmatics. *Am J Respir Crit Care Med* 2000; 161: 177–181
- [35] Jacob P, Kahrilas P, Herzon G. Proximal esophageal pH-metry in patients with 'reflux laryngitis'. *Gastroenterology* 1991; 100: 305–310.
- [36] Demeter P, Pap A. The relationship between gastroesophageal reflux disease and obstructive sleep apnea.-*J Gastroenterol* 2004;39:815-820

- [37] Teramoto S, Ohga E, Matsui H, et al. Obstructive sleep apnea syndrome may be a significant cause of gastroesophageal reflux disease in older people. *J Am Geriatr Soc* 1999;47, 1273-1274
- [38] Teramoto S, Yamamoto H, Ouchi Y. Gastroesophageal reflux is common in patients with sleep apnea rather than snorers without sleep apnea. *Chest* 2003;124:767-768.
- [39] Itomare A, Guarino MP, Cocca S, Emerenziani S, Cicala M. Gastroesophageal reflux disease: Update on inflammation and symptom perception. *World J Gastroenterol*. 2013;19(39):6523-6528.
- [40] Guilleminault C. Obstructive sleep apnea: the clinical syndrome and historical perspective. *Med Clin North Am* 1985;69:1187-1203,
- [41] Kerr P, Shoenuit JP, Millar T, Buckle P, Kryger MH. Nasal CPAP reduces gastroesophageal reflux in obstructive sleep apnea syndrome. *Chest*. 1992;101:1539-1544.
- [42] Penzel T, Becker H, Brandenburg U, et al. Arousal in patients with gastro-oesophageal reflux and sleep apnoea. *Eur Respir J* 1999; 14:1266-1270
- [43] Mizuta Y, Takeshima F, Shikuwa S, Ikeda S, Kohno S. Is there a specific linkage between obstructive sleep apnea syndrome and gastroesophageal reflux disease? *Digestive Endoscopy* 2006;18: 88-97
- [44] Kahrilas PJ, Smith JA, Dicpinigaitis PV. A Causal Relationship Between Cough and Gastroesophageal Reflux Disease (GERD) has been Established: A Pro/Con Debate. *Lung*. 2013 Nov 13. (Epub ahead of print)
- [45] Poelmans J, Tack J. Extraoesophageal manifestations of gastro-oesophageal reflux. *Gut*. 2005;54:1492-9.
- [46] Bytzer P. Assessment of reflux symptom severity: methodological options and their attributes. *Gut*. 2004;53:iv28-34.
- [47] Fass R, Quan SF, O'Connor GT, Ervin A, Iber C. Predictors of heartburn during sleep in a large prospective cohort study. *Chest* 2005;127:1658-66.
- [48] Schey R, Dickman R, Parthasarathy S, Quan SF, Wendel C, Merchant J, Powers J, Han B, van Handel D, Fass R. Sleep deprivation is hyperalgesic in patients with gastroesophageal reflux disease. *Gastroenterology*. 2007;133:1787-95.
- [49] Palombini, BC, Villanova, CAC, Araujo, E, et al. A pathologic triad in chronic cough: asthma, postnasal drip syndrome, and gastroesophageal reflux disease. *Chest* 1999; 116: 279-284.
- [50] Stein, MR Advances in the approach to gastroesophageal reflux (GER) and asthma. *J Asthma* 1999;36, 309-314.
- [51] Bruno, G, Graf, U, Andreozzi, P Gastric asthma: an unrecognized disease with an unsuspected frequency. *J Asthma* 1999;36, 315-325.



- [52] Irwin RS, Madison JM: The Diagnosis and Treatment of Cough, *N. Eng. J. Med*, 343, 1715-1721, 2000
- [53] Teramoto S, Ouchi Y. A possible pathologic link between chronic cough and sleep apnea syndrome through gastroesophageal reflux disease in older people. *Chest* 2000; 117(4):1215-1216.
- [54] Morrell MJ, Arabi Y, Zahn B, et al. Progressive retropalatal narrowing preceding obstructive apnea. *Am J Respir Crit Care Med* 1998;158:1974-1981
- [55] Schwab RJ, Gupta KB, Gefer WB, et al. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing: Significance of the lateral pharyngeal walls. *Am J Respir Crit Care Med* 1995;152:1673-1689
- [56] Schwab RJ, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. *Am J Respir Crit Care Med* 2003;168:522-530
- [57] Dempsey JA, Veasey SC, Morgan BJ, et al. Pathophysiology of sleep apnea. *Physiol Rev* 2010;90:47-112
- [58] Pinnington L L, Smith CM, Ellis RE, Morton RE. Feeding efficiency and respiratory integration respiratory integration in infants with acute viral bronchiolitis. *J Pediatrics*, 2000;137:523-526.
- [59] Sekizawa, K, Ujiie, Y, Itabashi, S, et al Lack of cough reflex in patients with aspiration pneumonia(letter).*Lancet*1990;335, 1228-1229
- [60] Hatipoğlu U. Rubinstein I. Inflammation and Obstructive Sleep Apnea Syndrome Pathogenesis: A Working Hypothesis. *Respiration* 2003;70:665–671
- [61] Ursavas A. Upregulating substance P levels to treat obstructive sleep apnea. *Expert Opin Ther Targets*. 2008;12:583-8.



