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Analysis of the dynamic changes in the soft palate and uvula in obstructive sleep apnea-hypopnea using ultrafast magnetic resonance imaging

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ABSTRACT. Apnea and the respiratory cycle are dynamic processes in obstructive sleep apnea-hypopnea (OSAH), which occur only during sleep. Our study aimed to observe the dynamic changes in the soft palate and the uvula during wakefulness and sleep using ultrafast magnetic resonance imaging (UMRI) to provide reference data for the pathogenesis and treatment of OSAH. The dynamic changes in the soft palate and uvular tip of 15 male patients (average age: 50.43 ± 9.82 years) with OSAH were evaluated using UMRI of the upper

airway while asleep and awake after 1 night of sleep deprivation. A series of midline sagittal images of the upper airway were obtained. The distance from the center of the soft palate to the x-axis (an extended line from the anterior nasal spine to the posterior nasal spine), from the uvular tip to the x-axis, from the center of the soft palate to the y-axis (a perpendicular line from the center of the pituitary to the x-axis), and from the uvular tip to the y-axis (designated as PX, UX, PY, and UY, respectively) were measured during sleep and wakefulness. The minimum PX, PY, UX, and UY were shorter during sleep than during wakefulness, whereas the maxima were longer during sleep ($P < 0.01$), the differences between the maximum and minimum PX, PY, UX, and UY were larger during sleep ($P < 0.01$). The upward, downward, forward, and backward ranges of movement of the soft palate and the uvular tip were larger during sleep in OSAH patients. This increased compliance may trigger each airway obstructive event.

Key words: Ultrafast magnetic resonace imaging; sleep apnea; Obstrutive sleep apnea-hypopnea

INTRODUCTION

Patients with obstructive sleep apnea-hypopnea (OSAH) have abnormal structures and neurobiological mechanisms of the upper airway (Schellenberg et al., 2000; Hsu et al., 2004; Smith et al., 2006; Lee et al., 2010). Understanding the upper airway structure and function in OSAH patients is needed to gain insight into the pathogenesis of this disorder to improve the selection of both appropriate therapies and treatment success (Halme et al., 2010). The velopharynx is one of the main sites of airway obstruction in OSAH (Liu et al., 1999; Ciscar et al., 2001; Rama et al., 2002). We assumed that the soft palate and the uvula are involved in upper airway obstruction while asleep because of their specific locations. The lengths of the soft palate and uvula have been studied through various methods (Trudo et al., 1998; Liu et al., 1999), including direct physical examination (Liu et al., 1999), cephalometric analysis (Sanner et al., 2002), computed tomography (CT), and magnetic resonance imaging (MRI) (Trudo et al., 1998; Tsuiki et al., 2004). However, most of these methods were performed on awake patients (Liu et al., 1999) or with an image obtained within 3 min (Lowe et al., 1995; Trudo et al., 1998). Given that apnea and the respiratory cycle are dynamic processes, information about the soft palate and uvula is overlooked or is not fully considered by some diagnostic imaging methods because of their low temporal resolution (Lowe et al., 1995; Trudo et al., 1998). Moreover, considering that OSAH occurs only during sleep, findings among conscious patients (Lowe et al., 1995; Liu et al., 1999) are not necessarily applicable to patients during spontaneous physiological sleep. The dynamic alterations in the soft palate and the uvula during sleep remain unreported. Ultrafast MRI (UMRI) is a recently developed technique that can obtain images at multiple locations with sufficient quality and temporal resolution (<1 s) to assess the upper airway and surrounding soft tissues dynamically (Ciscar et al., 2001; Rama et al., 2002; Piskin et al., 2012). The aim of this report is to study the dynamic alterations of the soft palate and uvula

during wakefulness and sleep using UMRI to provide reference data for the pathogenesis and treatment of OSAH.

MATERIAL AND METHODS

Subjects

Between February 2003 and March 2005, 15 male patients were selected for inclusion in the study. Only male subjects were selected to avoid a potential influence of gender on the dynamic motion of the upper airway. The average age was 50.43 ± 9.82 years, and the average body weight was 74.53 ± 7.76 kg. The average body mass index was 28.45 ± 3.11 kg/m^2, and all subjects had OSAH. Of the 18 original cases, 3 were excluded because they did not fall asleep. All patients agreed to participate in the study. All subjects were diagnosed with OSAH using nocturnal polysomnography at the First Hospital Affiliated to Wenzhou Medical University. The average apnea-hypopnea index (AHI) was 25.55 ± 13.50/h. Each subject provided a thorough history (including the Epworth somnolence questionnaire) and underwent a physical examination. They did not undergo any treatment. The protocol was approved by the Ethical Review Committee of the participating hospitals to ensure accordance to the Helsinki Declaration. After full explanation of the procedure, each subject gave written informed consent before entering the study.

Polysomnography

All patients underwent overnight polysomnography in a quiet dark room using a 19-channel polygraph (Rembrandt Embla Polysomnography System, Monet 16; Medcare Flaga, Sidumuli 24, 108; Reykjavik, Iceland). Sleep was documented using standard electroencephalographic, electrooculographic, and electromyographic criteria. The electroencephalograph was recorded with electrodes attached at C3-A2 and C4-A1 according to the criteria by Rechtschaffen and Kales (Ruehland et al., 2011). Electromyographic activity was recorded from the genioglossus, anterior tibial, and diaphragm muscles. Apnea was defined as the cessation of airflow at the nose (two thermistors) and mouth (one thermistor) for more than 10 s. Hypopnea was defined as a 50% reduction in airflow for 10 s associated with a > 4% decrease in oxygen saturation and/or arousal. Apnea and hypopnea were considered obstructive when thoracoabdominal movements were observed. A single electrocardiogram lead (modified V_2) was monitored to detect cardiac arrhythmias. The polysomnograms were scored by a clinical neurophysiology specialist.

MRI

The patients were examined at the Second Hospital Affiliated to Wenzhou Medical University under continuous supervision by a radiologist and an orthodontist. The patients were deprived of sleep for 20 h prior to the MRI and denied alcohol and sedatives the day before the procedure. The MRI was performed using a 1.5 superconducting magnet (Geroscan Intera type; Philips Co.; Amsterdam, The Netherlands) in a posterior and anterior neck coil. The sequence used to perform the UMRI was a fast gradient echo plus sequence. The techni-

cal parameters were as follows: echo time, 12 ms; repetition time, 2.3 ms; flap angle, 25°; matrix, 192 x 512; and section thickness, 7 mm. The imaging time per slice for this sequence was 0.96 s. A total of 120 consecutive images were obtained as a single section, with a total imaging time of 115.2 s. Respiratory motion was monitored with a magnetic resonance (MR)-linked cuff placed around the ribcage. The respiratory cycle was monitored on the operator screen using a respiratory gating system, which cannot be recorded on paper and video. The crest and trough of the wave corresponded to inspiration and expiration, respectively. Oxygen saturation was measured using a pulse oximeter, and snoring was monitored using the microphones in the MRI cylinder. The subjects were placed in supine position. The orbitoauricular plane was oriented 95° to the horizontal plane. A sponge pillow was placed under the cranial base and on both sides of the head. A quick setting silicone rubber (Optosil Xantopren Comfort; Heraeus; Hanau, Germany) was applied to the forehead and on the superficial coils (Li et al., 2003). The head was fixed in the interior of the neck coil after the silicone rubber had coagulated for 3 min. Airtight earplugs were inserted into the external auditory canal to minimize machine noise. The patient was instructed to squeeze a small rubber ball once every 2 to 3 min. The sound of the rubber ball was transmitted to the radiologist examination room to indicate that the subject was awake. MRI was first conducted when the subject was asleep and then awake after 20 min of quiet respiration. All images were input to a Picture Archiving and Communication Systems (PACS) workstation. Wakefulness was documented based on the patient's response to questions by the radiologist or the sound created by the small rubber ball when the patient squeezed it. The subject was verbally stimulated whenever it did not interfere with image acquisition, usually every minute and at least every 3 min. Sleepiness was documented (Trudo et al., 1998; Ciscar et al., 2001; Ikeda et al., 2001) when irregular snoring was heard through the microphones of the cylinder, when the oxygen saturation decreased by $\geq 4\%$, and when the rubber ball was not heard. Slowing and disorder of the respiratory rhythm were synchronously monitored with an MR-linked cuff placed around the rib cage. Snoring and decreased oxygen saturation occur only when patients are asleep (Ciscar et al., 2001).

Image analysis

A dynamic film was produced from the images obtained. A fixed window level of 650 H and a window width of 1200 were used to standardize all scans. Sagittal images were played back in a closed loop movie format so that the real-time changes in sagittal area could be displayed. Up to 120 consecutive images were measured for each patient. The mean minimum and maximum values were obtained from 5 minimum values and 5 maximum values, respectively. All measured values were completed consecutively by 1 author. The distances were measured on 2 occasions, yielding a mean percentage variation of 4.2%. The reference frame was established using the PACS system (Figure 1).

Statistical analysis

Statistical comparisons between pairs of means were performed using paired *t*-tests with the SAS 6.10 software. A probability level of $P < 0.05$ was considered to be statistically significant.

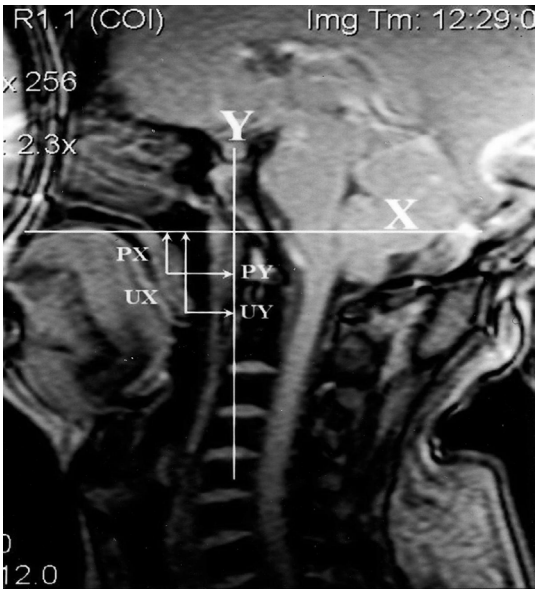

Figure 1. Reference frame of the measurement of the soft palate and uvula x-axis, an extended line from the anterior nasal spine to the posterior nasal spine; y-axis, a perpendicular line from the mid-point of the pituitary to x-axis. The following lengths were measured: the longest distance and the shortest distances were from the uvular tip to the x-axis and the y-axis (UX, UY) during wakefulness and sleep, respectively. The value of the differences between the longest and shortest distances; the maximum and minimum distances from the mid-point of the soft palate to x-axis and the y-axis (PX, PY) during wakefulness and sleep, respectively; the value of differences between the maximum and minimum distances.

RESULTS

During wakefulness, the soft palate and uvula showed no obvious changes. During sleep, the upper airway is continuously obstructed and opened. The soft palate and uvula are pushed downward and elongated during obstruction. By contrast, the soft palate and the uvular tip were pushed forward and upward and/or backward during opening. The soft palate and uvula passively and continuously moved forward and backward, and then upward and downward to form an elastic piston in the upper airway. The maximum and minimum distances from the soft palate and uvular tip to the x- and y-axes during wakefulness and sleep, as well as their differences, are shown in Tables 1 and 2. The dynamic changes in the upper airway during sleep are shown in Figures 2 to 5. The positions of the uvula and soft palate among OSAH patients during wakefulness are shown in Figure 6.

Table 1. PX, PY value and its change of the mid-point of the soft palate during wakefulness and sleep in the 15 sleep apnea hypopnea patients.

		While awake	In sleep	*t*
PX	Maximum value	1.86 ± 0.20	2.48 ± 0.24	18.19*
	Minimum value	1.69 ± 0.17	2.05 ± 0.21	8.70*
	Difference between maxi- and mini-value	0.17 ± 0.05	0.41 ± 0.17	5.82*
PY	Maximum value	1.63 ± 0.13	2.04 ± 0.15	17.82*
	Minimum value	1.36 ± 0.09	1.05 ± 0.16	7.60*
	Difference between maxi- and mini-value	0.27 ± 0.09	1.00 ± 0.23	13.16*

*P < 0.01.

Table 2. UX, UY value and its change of the uvular tip during wakefulness and sleep in the 15 sleep apnoea hypopnea patients.

		While awake	In sleep	*t*
UX	Maximum value	3.70 ± 0.40	4.95 ± 0.48	23.78*
	Minimum value	3.37 ± 0.38	2.04 ± 0.29	17.54*
	Difference between maxi - and mini - value	0.33 ± 0.09	2.83 ± 0.38	25.89*
UY	Maximum value	1.55 ± 0.13	2.02 ± 0.23	8.79*
	Minimum value	1.23 ± 0.10	1.03 ± 0.17	4.28*
	Difference between maxi - and mini - value	0.32 ± 0.09	0.99 ± 0.30	8.95*

*P < 0.01.

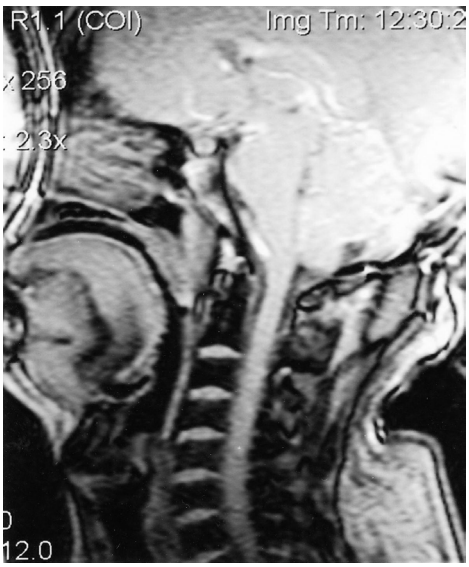

Figure 2. Typical position of soft palate and uvula posterior while contact of uvular tip with pharyngeal.

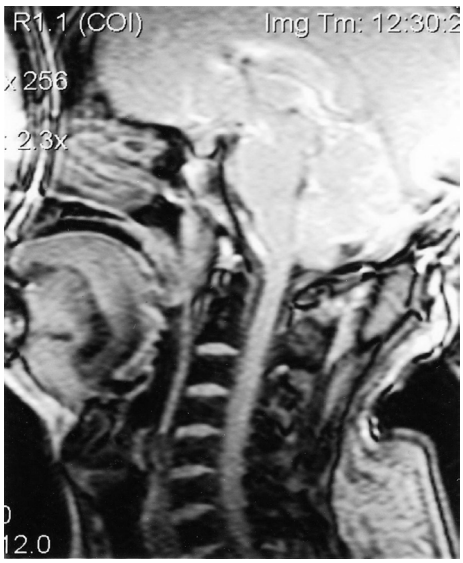

Figure 3. Typical position of soft palate and uvula posterior while velopalatine obstructed during sleep.

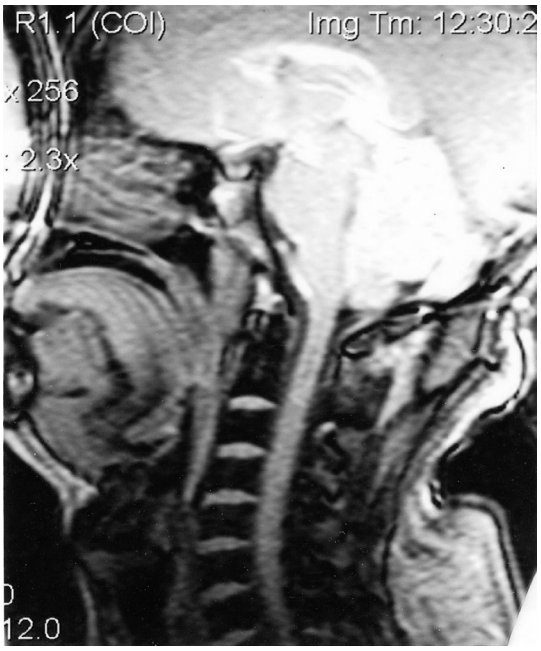

Figure 4. Soft palate and uvula were elongated while velopalatine and glossopharynx were obstructed during sleep in the typical case.

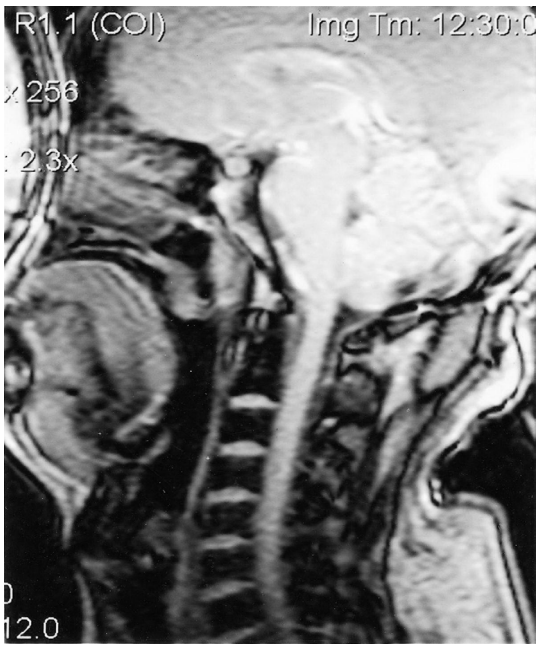

Figure 5. Soft palate and uvula were blown to the posterosuperior direction during sleep while airway opened during sleep in the typical case.

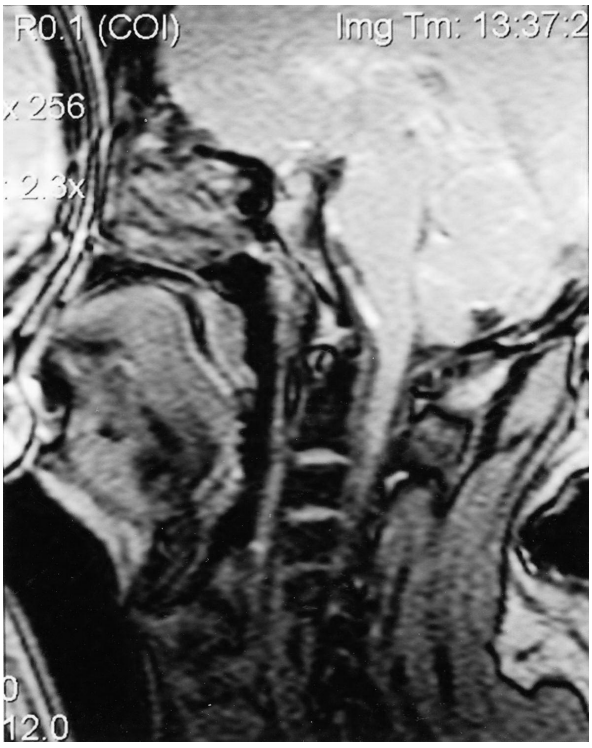

Figure 6. Position of the uvula and soft palate during wakefulness in sleep apnea-hypopnea.

DISCUSSION

Abnormal movement of the soft palate and uvula were observed during sleep in OSAH patients. The orientations of the soft palate and uvula are critical for respiration because they are located at the entrance of the palatopharynx. A variety of methods (Lowe et al., 1995; Trudo et al., 1998; Liu et al., 1999), including physical examination (Liu et al., 1999), cephalometric analysis, CT (Lowe et al., 1995), and routine MRI (Trudo et al., 1998) indicated that the soft palate and uvula of OSAHS patients are longer than those of normal subjects without snoring issues, and that they are correlated with the severity of sleep apnea. However, these measurements were conducted while the OSAH patients were awake, and only the size and morphology of the soft palate and uvula under a static state were measured. Wakefulness and sleep are physiologically different states. The majority of OSAH patients have no obvious obstruction in the upper airway while awake. Apnea occurs during sleep; thus, only the changes in the size and movement of the soft palate and the uvula during sleep truly reflect the morphological and functional status when apnea occurs (Ciscar et al., 2001; Ikeda et al., 2001; Rama et al., 2002). In the present study, consecutive instantaneous imaging (one image per 0.92 s) of the soft palate and uvula was performed on OSAH patients during wakefulness and sleep using UMRI (Ciscar et al., 2001; Ikeda et

al., 2001). The dynamic changes in the soft palate and uvula were observed as videos. The distance from the center of the soft palate to the x-axis (the hard palate level) (PX), from the center of the soft palate to the y-axis (PY), from the uvular tip to the X-axis (UX), and from the uvular tip to the y-axis (UY) were measured. Comparison of the sleep and wakefulness of OSAHS patients revealed that the dynamic changes in the soft palate and uvula were obviously abnormal. The minima of PX, PY, UX, and UY during sleep were lower than those during wakefulness ($P < 0.01$), whereas the maxima of PX, PY, UX, and UY during sleep were higher than those during wakefulness ($P < 0.01$). The differences between the maxima and minima of PX, PY, UX, and UY during sleep were higher than those during wakefulness ($P < 0.01$; Tables 1 and 2). This result indicates that the anterior-posterior and superior-inferior ranges of movement of the soft palate and the uvula during sleep were larger. Images showing the time-distance changes in the soft palate and the uvula of typical patients indicated similar results. The ranges of the movement from the mid-point of the soft palate and the uvular tip to the X-axis and the Y-axis during sleep were larger than those during wakefulness, and they followed an irregular movement pattern (Figures 2, 3, 7, and 8).

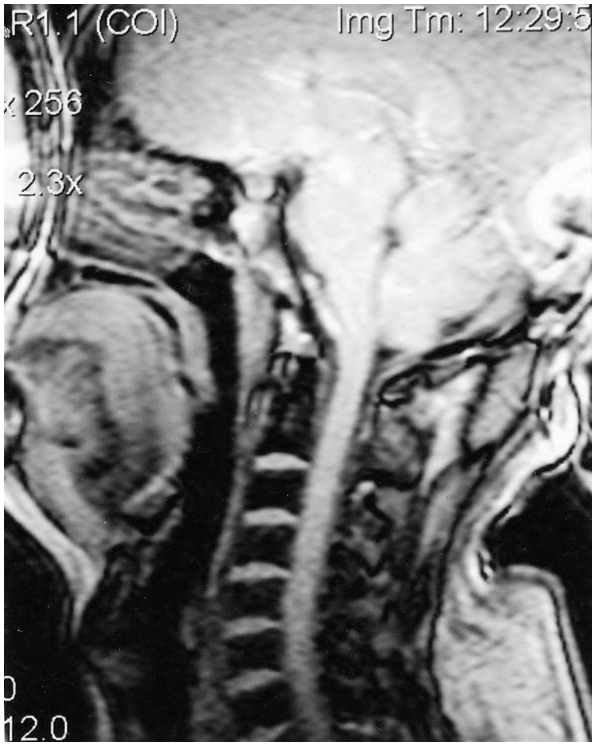

Figure 7. A, b, c typical position of uvula and soft palate while airway opens during sleep.

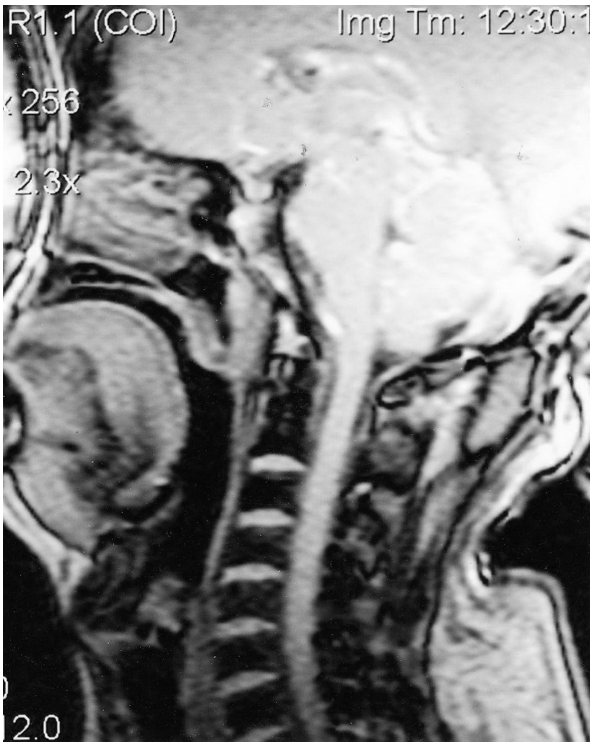

Figure 8. Typical contact of uvular tip with pharyngeal posterior wall during sleep.

Dynamic MRI images of sleeping OSAH patients showed that the obstruction of the upper airway is caused by the contact of the uvular tip with the posterior wall of the pharynx (Figures 2-5). The velopalatine is then obstructed, and the uvula and soft palate are pushed downward and elongated. When the airway reopens after obstruction, the uvular tip is irregularly blown upward and forward or upward and backward. The position of the uvula and soft palate then gradually reverts to their normal position. Afterward, the second occlusive event begins (Figures 2-5 and Figures 7-8). The soft palate and uvula function as an elastic piston at the entrance of the airway, which occludes the upper airway when the cycle repeats. The position of the uvula and soft palate during wakefulness in OSAH patients was normal (Figure 6).

The mechanism and significance of the movement abnormality of the soft palate and the uvula in sleeping OSAH patients.

The muscles that dominate the soft palate and uvula are the tensor veli palatine, levator veli palatine, and uvulae. These muscles maintain a relatively constant level of activity throughout the respiratory cycle (De Chazal et al., 2011). The relevant tongue muscle is the genioglossus, which is referred to as an inspiratory phasic upper airway muscle because its activity is substantially reduced (although not eliminated) during expiration when the pressure inside the airway becomes positive. Its activity is increased during inspiration, which stiffens and dilates the upper airway to counteract the collapsing influence of negative airway pressure (van Lunteren, 1993). During wakefulness, these pharyngeal dilator muscles are tightly controlled to maintain pharyngeal patency. Several variables carefully control the activity of pha-

ryngeal dilator muscles, including motor nuclei control, standard respiratory stimuli (increased PCO_2 and decreased PO_2), 'wakefulness' drive, and the reflex of the negative intrapharyngeal pressure, which is the most important variable (Fogel et al., 2004; Pierce et al., 2007).

The sleep-wake state is important in the pathogenesis of OSAH because disordered breathing events only occur during sleep, even in patients with severe apnea. Muscle tone decreases when the patient falls asleep (Eckert et al., 2007). The activity of the tensor veli palatine is only 20 to 30% of the normal value while awake. Mathur et al. (1995) (Tangel et al., 1991; Wheatley et al., 1993) reported that the decrease in the muscular tone is correlated with the delay in the timing of the negative pressure on the upper airway neuroreceptor and the decrease in response capacity. Horner et al. (1994) indicated that the reflex activity of the sphincter in the upper airway increases with increasing internal pressure of the upper airway but decreases during sleep. The delay of the beginning of the reflex during wakefulness was 40 ms, whereas that during sleep was 110 ms. In addition, the upper airway resistance was high because of an anatomical narrowing of the pharyngeal airway in OSAHS patients. To overcome this resistance, the activity of the upper airway sphincter shows a compensatory increase to ensure airway patency during wakefulness (Mezzanotte et al., 1992; Fogel et al., 2001). During sleep, this compensatory ability is abolished and soft tissue compliance increases; thus, opposing the traction force of the inspiratory negative pressure produced by the inspirational muscle is difficult (Mezzanotte et al., 1992; Huang and Williams, 1999), resulting in the obstruction of the airway. When the upper airway is obstructed, the internal pressure in the upper airway decreases, and the negative pressure on the pharyngeal airway leads to the robust activation of these muscles. The increase in PCO_2 and decrease in PO_2 also stimulate activity and ultimately reopens the upper airway. The caliber of the upper airway and consequent airflow are uninterrupted when the cycle repeats. The effects of the changes in upper airway caliber and airflow on the soft palate and uvula are different between wakefulness and sleep. When an OSAH patient is awake, the caliber of the upper airway is still enlarged because of the compensatory increase in the excitability of the upper airway sphincter (Horner et al., 1994; Fogel et al., 2001). At the same time, the excitability of the veli palatine and uvulae also remain high. The airflow turbulence caused by the changes in intrapulmonary pressure is minimal and does not induce larger movements in the soft palate and uvula tip during quiet respiration. When an OSAH patient falls asleep, the excitability of the musculus veli palatine and musculus uvulae decreases, and the lumen of the upper airway narrows and collapses because the airflow dynamics in the upper airway are disturbed. These factors significantly increase the movement range of the soft palate and uvula tip. During inspiration, the soft palate and uvula are influenced by airflow, resulting in the initial obstruction and narrowing of the palatopharyngeal area. The soft palate and uvula are elongated and inhaled into the inferior pharyngeal cavity, resulting in combined obstruction at numerous points in the upper airway when the intrapulmonary pressure further decreases. The uvula is irregularly blown forward and upward or backward and upward when the upper airway reopens because the intrapulmonary pressure abruptly increases. The obstruction of the upper airway during sleep in OSAH patients (Mezzanotte et al., 1992; Huang and Williams, 1999; Schellenberg et al., 2000; Fogel et al., 2001) is ascribed to structural abnormality, as well as the increased compliance of the upper airway. This study indicated that the specificity of the site of the soft palate and uvula induces this obstructive event, and the palatinopharynx is the most likely site.

The progression of sleep apnea/hypopnea has attracted the interest of many researchers (Petrof et al., 1994; Kimoff et al., 2001; Fogel et al., 2004). The Wisconsin Sleep Study

indicated that the mean AHI increases from 2.6 to 5.1 events per h within 8 years (Fogel et al., 2004). The reason for this increase in the severity of apnea over time is still unclear. However, several factors may contribute to this development. First, snoring and repeated upper airway occlusion lead to edema and swelling of the upper airway soft tissue structures. These conditions contribute to further narrowing of the upper airway, rendering it more susceptible to collapse. Second, the repeated vibratory trauma that occurs during snoring injures or remodels the upper airway muscles and nerves. This concept is supported by the impaired ability of patients with OSAH to detect sensory stimuli in the upper airway. This condition can be partially reversed with continuous positive nasal airway pressure (Kimoff et al., 2001). In cats, repeated contraction of the upper airway dilator muscles during experimental occlusion results in eccentric muscle contractions (contraction during active muscle lengthening), which causes muscle injury. Petrof et al. (1994, 1996) identified several changes in the upper airway musculature using the English bulldog model for OSAH, including a change in fiber type (increased fast twitch fibers) and signs of muscle injury and fibrosis. Considering their specific position and structure in vertical form, the soft palate and uvula have large dynamic vertical and horizontal ranges of motion among OSAH patients during sleep. This study demonstrates that the soft palate and uvula may be subjected to vibratory trauma, edema, and swelling, which increases the severity of apnea.

In conclusion, when OSAH patients fall asleep, the range of movement of the soft palate and the uvular tip, measured in the upward, downward, forward, and backward directions during sleep, were larger than those during wakefulness. These increases in compliance may trigger the airway obstruction.

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