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Review

New Strategies of Screening and Treatment for Sleep Apnea Syndrome

WATARU HIDA

The First Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980–8574

HIDA, W. *New Strategies of Screening and Treatment for Sleep Apnea Syndrome.* Tohoku J. Exp. Med., 1998, **186** (4), 225–241 —— The prevalence of sleep apnea syndrome (SAS) is approximately 7.5% in Japanese adults aged 18–68 years old. SAS is characterized by repeated episodes of apnea, especially obstructive apnea, during sleep. Severe SAS has life-threatening complications such as pulmonary hypertension, arrhythmias, right heart failure or brain damage, which could be caused by hypoxemia and/or hypercapnia. Upper airway relaxation is responsible for the obstruction during apnea, and an increase in the activities of the upper airway muscles dilates and stiffens the upper airway wall. Maintaining the activities of the upper airway muscles may contribute to keeping the airway patent. Submental electrical stimulation of the upper airway muscles would be a novel treatment method for obstructive apnea. ———— sleep apnea syndrome; obstructive apnea; upper airway muscles; hypoxia; electrical stimulation

Sleep apnea syndrome (SAS) is characterized by repeated episodes of apnea during sleep, resulting in hypoxemia and/or hypercapnia, and causes serious and often life-threatening complications such as pulmonary hypertension, systemic hypertension, arrhythmias, right heart failure or brain damage (Guilleminault et al. 1975, 1976; Hida et al. 1992; Iwase et al. 1992; Okabe et al. 1995b). The clinical characteristics of this syndrome include disruptive snoring, but also sleep fragmentation, excessive daytime sleepiness or morning headache. A majority of apneic episodes is the obstructive type due to upper airway obstruction during sleep.

The purpose of this report is to review screening for sleep apnea, and the role of the upper airway in the pathogenesis of obstructive sleep apnea (OSA), and to consider the possibility of a novel treatment of OSA by submental stimulation.

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Address for reprints: Wataru Hida, M.D., The First Department of Internal Medicine, Tohoku University School of Medicine, 1–1 Seiryomachi, Aoba-ku, Sendai 980–8574, Japan.
e-mail: hida@intl.med.tohoku.ac.jp

Screening for sleep apnea

Polysomnography has been used as the gold standard for the diagnosis of SAS (Rechtshaffen and Kales 1968). This technique, however, is burdensome, laborious, time consuming, costly and inconvenient as a screening test or epidemiological study, particularly outside of a hospital. A portable home sleep monitoring system is desired. Up to the present, several ambulatory sleep monitoring systems have been reported. These monitoring systems were grouped into two types. One is the portable recorder which is essentially identical to the traditional in-laboratory polysomnography (Gyulay et al. 1987; Hoeslscher et al. 1989; Acebo et al. 1991). The other is a portable recorder which monitors one or several selected parameters (Emsellem et al. 1990; Williams et al. 1991). The former system has the advantage that sleep-awake patterns can be checked, and the cost performance is also improved compared to that of laboratory polysomnography. However, it is still burdensome in terms of the administration of equipment and is relatively expensive. In contrast, the latter type is easy to operate, analysis can be performed within a short period, and it has significant cost-saving potential. The portable sleep monitoring system which we have developed is also easier to operate and can monitor apnea episodes during sleep in private homes (Hida et al. 1988). This device assesses three kinds of parameters: Oro-nasal airflow by a thermistor, tracheal sound by a microphone, and electrocardiogram (ECG), and digitally stores the time of the onset of apnea, the apnea duration and R-R intervals from ECG with a built-in microcomputer. After monitoring, the portable sleep monitor is connected to a host computer, and total apnea episodes per night, the so-called "apnea index" defined as mean apnea episodes per minute, and R-R intervals are analyzed. This system is convenient for home assessment of sleep apnea. Recently, we have improved the original system, and produced a new model of the home sleep monitor which employs oronasal airflow, tracheal sound and pulse oximeter. Using this system, we can monitor apneic episodes and desaturation episodes during sleep at home.

Prevalence of sleep apnea

It has been reported that the prevalence of SAS was less than 3% in adults (Gislason et al. 1987; Cirignotta et al. 1988). This prevalence was based on the screening questions for estimates of OSA which derived from clinical case series and center reporting of signs and symptoms associated with OSA. Recently, several investigators reported a high prevalence of SAS according to the results of measuring apnea/hypopnea using a portable sleep monitor. Young et al. (1993) found OSA, defined as an apnea/hypopnea index (AHI) greater than 5, was 9% in women and 24% in men in a community-based study. This prevalence is similar to that of other reports (Bearpark et al. 1993; Hida et al. 1993). The present authors reported that OSA, defined as an apnea index greater than 10

apnea episodes/minutes, was 7.5% (Hida et al. 1993). This prevalence was based on a study of 168 healthy workers aged 18–68 years old in one Japanese industrial company using the portable sleep monitoring system which we developed. We reported also that there were no significant correlations between the apnea index and the score estimated by sleep questionnares. These results suggest that there may be many hidden patients with SAS and also underscore the importance of direct measurement of apnea/hypopnea by the sleep monitoring system for epidemiological studies.

Upper airway activity in OSA

OSA results in rapidly progressive hypercapnia and hypoxia (Hida et al. 1987; Sasaki et al. 1989), which could initiate reopening of the upper airway and determine the postapneic ventilation together with nonchemical factors (Kimoff et al. 1994). Satoh et al. (1991) reported that the slopes of the regression line obtained from the relationship between arterial oxygen saturation (SaO_2, %) induced by apnea and the postapneic ventilation during both rapid eye movement (REM) and non-REM sleep correlated well with the hypoxic ventilatory response (HVR) during wakefulness (Rebuck and Compbell 1974) in OSA patients. These results suggest that the slopes might partly reflect hypoxic responsiveness during sleep in OSA patients and that hypoxic drive is an important factor that determines postapneic ventilation in OSA. Fig. 1 shows the slopes during non-REM sleep, during REM sleep, and the hypoxic ventilatory response during wakefulness. The awake HVR is greater than those during both sleep stages, and the HVR during REM sleep is less than that of non-REM sleep. That is, the ventilatory response to hypoxic stress is lowest during REM sleep.

It is well known that apnea and the secondary fall in SaO_2 are more severe and frequent during REM sleep than during non-REM sleep. Therefore, it is possible that REM sleep, which induces severe desaturation, suppresses the upper airway muscle activity more than non-REM. REM sleep affects the respiratory muscle activities in a different manner; upper airway muscle activities during REM sleep are lower than the diaphragm activity in healthy subjects (Sauerland and Harper 1976; Okabe et al. 1993b), as well as in animal experiments (Issa et al. 1988). The genioglossus muscle (GG) and intercostal muscle (IIM) activities in the late apneic phase during REM sleep were lower than those during non-REM sleep in OSA patients, and the relative activity of GG to IIM in the late apneic phase was also lower during REM sleep than that during non-REM sleep (Okabe et al. 1994). These results would suggest that upper airway and IIM activation in the later apneic phase during REM sleep were inhibited compared with those during non-REM sleep and that this inhibition is observed predominantly in upper airway muscles. Hypotonicity of the upper airway muscles in combination with a relatively intact diaphragm activity may cause a prolongation of the apneic period by delaying airway reopening and contribute to severe desaturation

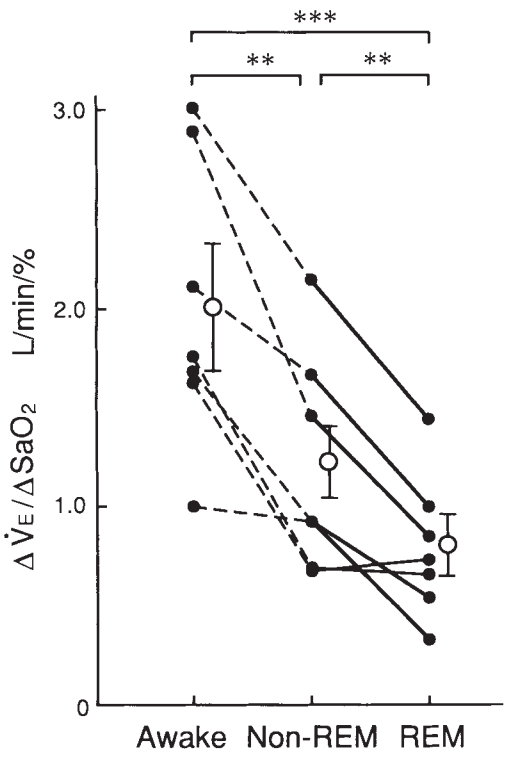

Fig. 1. Hypoxic ventilatory response ($\Delta VE/\Delta\ SaO_2$) during wakefulness, non-REM and REM sleep in OSA pateints ($n=7$). Awake ventilatory response to hypoxia was measured by the modified Rebuck-Campbell method (Rebuck and Campbell 1974). The ventilatory response during non-REM and REM sleep was obtained as the slope of the linear regression between the nadir of SaO_2 produced during each apneic phase and postapneic ventilation (Satoh et al. 1991). The hypoxic responses during non-REM and REM sleep were significantly lower than those during wakefulness. Furthermore, the response during REM sleep was smallest among the three responses. Statistical significance was determined by the by two-tailed paired t-test ($^{**}p<0.01$, $^{***}p<0.001$). ⊕, Mean±S.E.

during REM sleep.

Other mechanisms such as the depression of arousal mechanisms, lower hypoxic ventilatory response, and the decrease in lung volume during REM sleep are also considered to be causes of the severity of sleep apnea during REM sleep (Sullivan and Issa 1980; Douglas et al. 1982; Series et al. 1990; Satoh et al. 1991).

The response of the upper airway muscles to chemical drive such as hypoxia and hypercapnia (Okabe et al. 1993a; Midorikawa et al. 1994; Hida et al. 1996) is interesting for considering the pathogenesis of obstructive apnea. There are differences in the responses of upper airway muscles between progressive hypoxia and sustained hypoxia. During progressive hypoxia, upper airway muscles are activated in a fashion parallel to the diaphragm during both progressive hypoxia and hypercapnia in humans (Önal et al. 1981a, b, 1982), whereas increases in the inspiratory activity of the hypoglossal nerve and GG were relatively greater than the simultaneous increases in the respiratory activity of the phrenic nerve and diaphragm in animal experiments (Brouillette and Thach 1980; Hudgel et al.

1987).

During sustained hypoxia, ventilation is known to show a biphasic response which is comprised of an initial stimulatory phase mediated by peripheral chemoreceptors and a following depressive phase caused by central and/or peripheral mechanisms in animals and in humans (Easton et al. 1986; Neubauer et al. 1987). The responses of upper airway muscles during sustained hypoxia are also qualitatively similar to the ventilatory reponse. However, there are differences in the response patterns between upper airway muscles and respiratory muscles. Van Lunteren et al. (1989), in anesthetized cats, showed a biphasic response during sustained hypoxia and that the absolute decline from the peak value was greater in GG electromyogram (EMG) than in diaphragm EMG at the end of 10 minutes of hypoxia. Okabe et al. (1993b), in a human study, showed that responses of GG EMG and diaphragm EMG similar to those of the previous animal study could be observed in normal subjects and patients with OSA. As GG activity has an important role in upper airway patency during sleep as described in the following sections, depression of GG activity during sustained hypoxia may modulate the narrowing of the upper airway in patients with OSA.

Sustained hypoxia may also impair neuropsychological performance (Hornbein et al. 1989; Chonan et al. 1998), or reduced chemosensitivity to hypoxia could be coupled with a blunted perception of dyspnea (Kikuchi et al. 1991, 1994; Taguchi et al. 1991a, b). Therefore, the suppresion of activity in daily life in severe OSA patients may be due to the hypoxic stress during sleep.

There is a possibility that neurotransmitters or neuromodulators such as substance P, dopamine and L-glutamate, which may be released during hypoxic stress from the central nervous system, could be responsible for the differences in reponses between upper airway muscles and the diaphragm. However, it has not been clarified which neurotransmitter is released during hypoxia. Recently, in in vivo animal experiments, we reported the important role of nitric oxide (NO) in the nucleus tractus solitarii during hypoxic stress, and that this works as a retrograde messenger in an excitatory transmitter, L-glutamate, releasing a positive feedback system that contributes to the augmentation of ventilation during hypoxia (Mizusawa et al. 1994, 1995; Ogawa et al. 1995). The facilitation of the L-glutamate release system by NO might contribute to the prevention of abrupt changes in ventilation or upper airway muscle activity during hypoxia. The role of inhibitory transmitters, for example, gamma-aminobutylic acid (GABA), in the control of the upper airway during hypoxia is still unknown.

Factors of upper airway patency

Obstructive apnea is caused by an obstruction of the upper airway during sleep (Harper and Sauerland 1978; Strohl et al. 1978; Brouillette and Thach 1979; Guilleminault et al. 1980; Wilson et al. 1980; Mathew et al. 1982; Hudgel et al. 1987; Van Lunteren et al. 1989). It has been postulated that the upper airway

patency is determined by the anatomic size of the upper airway (Ikeda et al. 1998) and a balance between two counteracting forces: One is the negative intraluminal pressure generated by the contraction of the inspiratory pump muscles and the other is the upper airway dilating force developed by upper airway muscle contraction (Block et al. 1984; Shindoh et al. 1985; Sakurai et al. 1991). Furthermore, dilation of the upper airway or an increase in upper airway muscle activity occurs during bronchoconstriction (Shindoh et al. 1985), loaded breathing (Sekizawa et al. 1983, 1986), or limb muscle contraction (Sakurai et al. 1991). Among the upper airway muscles, the genioglossuss appears to be of particular importance since it is responsible for pulling the tongue forward, and a decrease in genioglossal activity has been reported to narrow or obstruct the upper airways, especially in the supine position, both in animals (Brouillette and Thach 1979) and in humans (Sauerland and Mitchell 1970, 1975; Harper and Sauerland 1978; Hudgel et al. 1987; Van Lunteren et al. 1989). An increase in the activity of the genioglossus by electrical stimulation of the genioglossus (Miki et al. 1989) or hypoglossal nerve (Miki et al. 1992) dilates the upper airway, and also opens an occluded upper airway (Miki et al. 1992). An increase in hyoid muscle activity also dilates the upper airway (Gottfried et al. 1983; Van de Graaff et al. 1984). However, there are several other factors that affect upper airway patency, such as secretions of the upper airway, mechanical stimulation of the upper airway, body and head position, and chemical drive (Hyatt and Wilcox 1961; Morikawa et al. 1961; Spann and Hyatt 1971; Bartlett et al. 1973; Proctor 1977; Miura et al. 1992). In animals, deep anesthesia depresses the respiratory controller (Chonan et al. 1984; Hida et al. 1986; Okabe et al. 1995a), inducing a decrease in the upper airway muscle tone and resulting in an increase in upper airway resistance (Gottfried et al. 1983).

Several investigators have noted that collapsed airway walls are adherent in human infant cadavers (Wilson et al. 1980; Reed et al. 1985) and in living infants (Wilson et al. 1981; Roberts et al. 1985). The stickiness of the mucosal surface of the oropharyngeal cavity could also modulate the effects of the GG tone. Strong surface adhesion occurs because of increased stickiness of the mucosal surface fluid, and a higher tone of the GG is required to open the obstructed upper airway. This adhesive characteristic may be reduced by pharyngeal lubrication with substances of low surface tension, which reduces the adhesion of mucosal surfaces and facilitates the opening of the obstructed upper airway (Hida and Hildebrandt 1984). This hypothesis was supported by the following study. We examined the effect of electrical stimulation of the hypoglossal nerve on the opening of the obstructed upper airway and the effect of pharyngeal lubrication with artificial surfactant on the opening of obstructed upper airways in the anesthetized dog. We found that the critical stimulation frequency for upper airway opening increased as the intraluminal pressure became more negative, that lubrication of the pharyngeal mucosa with artificial surfactant decreased the critical stimulation

frequency for upper airway opening at each negative pressure, and that pharyngeal lubrication with saline had no effect (Miki et al. 1992). These findings suggest that a greater upper airway tone is needed to open the upper airway as the intraluminal pressure becomes more negative and that lubrication of the pharyngeal mucosa with artificial surfactant facilitates opening of the obstructed upper airway (Miki et al. 1992). A similar phenomenon was observed by Widdicombe and Davies (1988), who found that geniphlossus activity was reflexly increased and that the upper airway resistance was reduced by surface active agents. This idea was expanded to a treatment for sleep apnea, and a topical soft tissue lubricant of the upper airway reduced the severity of OSA (Jokic et al. 1998).

Collapsibility of upper airway

The mechanical properties of the upper airway, which are influenced not only by the upper airway resistance but also by the upper airway compliance, are important for determining the pathophysiology of such conditions as OSA. This principle is based on the characteristics of the mechanical properties of the lung (Sasaki et al. 1976, 1979; Hida et al. 1979, 1981, 1982a, b, 1984a, b; Hida and Hildebrandt 1984). These two components are affected by the upper airway muscle tone. An increase in the upper airway muscle tone produced by hypoglossal nerve electrical stimulation or genioglossus stimulation reduced the upper airway resistance in animals (Miki et al. 1989b), and submental stimulation, particularly in the proximal half of the submental region, decreased the supraglottic resistance in humans (Hida et al. 1995a). Furthermore, we found that hypoglossal nerve electrical stimulation or submental stimulation increased the upper airway volume and decreased the upper airway compliance in the resting condition of the upper airway in animals (Hida et al. 1995b). We also studied the upper airway pressure changes during volume changes by inflation and deflation of air volumes, such as 5, 10, 15 and 20 ml without and with submental electrical stimulation in normal subjects and OSA patients while the upper airway was isolated with the glottis closed voluntarily at the functional residual capacity (Wu et al. 1999). Volume-pressure (V-P) properties of the upper airway obtained by this procedure were assessed by upper airway elastance (Euaw = 1/compliance). Euaw in OSA patients was greater than in normal subjects and submental stimulation increased Euaw in both OSA patients and normal subjects. These results suggest that the upper airways of OSA patients during wakefulness are less collapsible than those of normal subjects, and that, in both groups, submental stimulation may stiffen the upper airway.

There are several factors which affect the V-P properties of the upper airway. Upper airway compliance could be affected by extension or flexion of the neck (Rolfe et al. 1991; Thut et al. 1993) and by the body posture (Miura et al. 1992; Satoh et al. 1993; Pevernagie et al. 1995). Surface-active agents (Widdicombe and Davies 1988; Miki et al. 1992) or the vascular tone of the upper airway

(Wasicko et al. 1990) also could change the V-P properties of the upper airway.

The upper airway muscle tone is also an important factor that affects changes in upper airway compliance. Brouillette and Thach (1979) demonstrated that sectioning of the hypoglossal nerve reduced the suction pressure required to collapse the upper airway, and Schwarz et al. (1993) have also demonstrated that electrical stimulation of the hypoglossal nerve markedly decreased the maximal regional collapsibility at the flow-limiting site. In our recent studies, we demonstrated in anesthetized dogs that electrical stimulation of the hypoglossal nerve reduced not only the upper airway resistance but also the upper airway compliance (Miki et al. 1989b; Hida et al. 1995b). Effects similar to those of hypoglossal stimulation were found under submental electrical stimulation in anesthetized dogs (Hida et al. 1995b) and in awake human subjects (Hida et al. 1995a). This study showed additionally that submental stimulation stiffened the upper airway in normal subjects and OSA patients. Although the mechanisms involved were not clear, we speculate that submental stimulation induces an increase in upper airway muscle tone and/or a reduction in the soft tissue pressures of the upper airway (Schwarz et al. 1993), thereby keeping the upper airway patent.

The upper airway elastance in OSA patients was greater than that in normal subjects during wakefulness. This phenomenon may be explained as follows. The upper airway in OSA patients is anatomically smaller compared with that in normal subjects (Suratt et al. 1983; Brown et al. 1985; Kuna et al. 1988). As an apparent compensatory mechanism to counteract the smallness of the upper airway, patients with OSA demonstrate abnormally high levels of pharyngeal dilator muscle activity during wakefulness (Mezzanotte et al. 1992). Heightened levels of pharyngeal muscle activity are also observed during stable nonobstructed sleep in individuals with OSA (Suratt et al. 1988; Hendricks et al. 1993). Thus, the overall level of pharyngeal dilator muscle activity is substantially greater than normal in OSA patients (Petrof et al. 1996). Therefore, such increased upper airway muscle activity would induce an increase in the elastance of the upper airway and stiffen it.

An alternative explanation for the increased elastance of the upper airway in obstructive apnea is that the upper airway volume is reduced. The upper airway volume is smaller in OSA patients than in normals (Suratt et al. 1983; Brown et al. 1985; Kuna et al. 1988). This difference between OSA patients and normals may explain the difference in elastance between the two groups, since, if the upper airway volume is smaller, the pressure change would be greater when a given volume is injected into or withdrawn from a closed upper airway compared with an upper airway of greater volume. Accordingly, the slope of the V-P relationships is greater in upper airways with smaller volumes.

Kuna et al. (1988), using computed tomography during the application of positive and negative pressure, showed that the velopharynx in obese awake patients with OSA was less distensible than that in awake normals. The present

study supports their findings. On the other hand, Ryan and Love (1996) found that obese patients had a more collapsible velopharynx during wakefulness. The reason for this discrepancy is not clear. The V-P properties of the upper airway estimated by the relationships between airway area or upper airway volume and pressure in the former reports including ours could not always predict the effective compliance expressed as the ratio of the upper airway cross-sectional area by videoendoscopy in expiration to inspiration during the maximal vital capacity maneuver, because of differences in the methods of estimating the upper airway compliance.

Fig. 2 shows the relationship between Euaw and AHI. We found a significant positive correlation between the two parameters. That is, OSA patients with a greater Euaw had more frequent apnea-hypopnea episodes. OSA patients with higher elastance while awake had more frequent episodes of apnea-hypopnea during sleep. This relation would appear to be unreasonable, because increased elastance would cause an increase in stiffness, resulting in a decrease in apnea. However, if the elastance was increased during wakefulness as a result of compensatory effects, a transient loss of this compensatory hyperactivity during sleep would easily induce upper airway obstruction. Concerning the relation between the collapsibility and the activity of the upper airway muscles in OSA patients, it has been reported that these patients showed abnormally high levels of pharyngeal dilator muscle activity during wakefulness as an apparent compensatory mechanism for the smallness of the small upper airway size (Mezzanotte et al. 1992). Patients with OSA who have higher elastance during wakefulness may have a more collapsible upper airway during sleep.

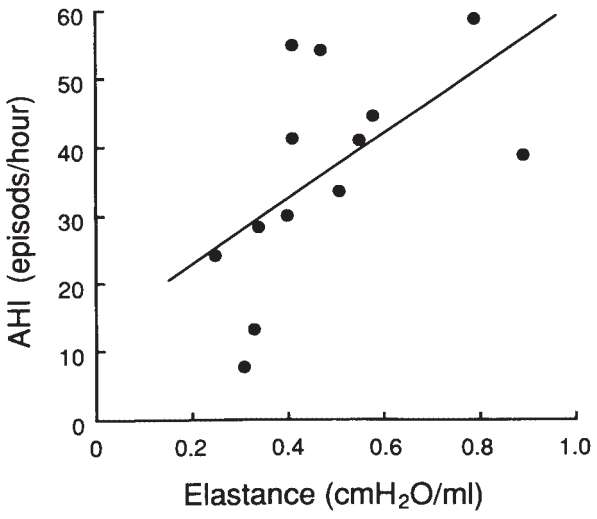

Fig. 2. The relationships between upper airway elastance (Euaw) and apnea-hypopnea index (AHI). A significant positive correlation between Euaw and the AHI was found ($r=0.69$, $p<0.05$).

Possibility of novel treatment

Electrical stimulation of the genioglossus or hypoglossal nerve induces an increase in upper airway muscle tone, thereby maintaining the patency by dilation and/or stiffening of the upper airway. Therefore, it is reasonable that genioglossus stimulation may be useful for the treatment of OSA. We tried electrical stimulation in the proximal half of the submental region instead of direct stimulation of the genioglossus in OSA patients with moderate apneic episodes during sleep. The device which we developed is an airflow demand-type portable submental stimulator (Miki et al. 1988; Hida et al. 1991). The apparatus consists of two parts: An apnea detection by oronasal flow and stimulation systems, and is operated for two nights by a rechargeable 9 volt DC battery. Electrical stimulation began when apnea lasted for 5 seconds, and was stopped after resumption of breathing or after a maximum of 20 seconds. We found a significant improvement of obstructive apnea episodes without causing significant arousal (Miki et al. 1989a; Hida et al. 1994). Submental stimulation for five consecutive nights improved the breathing disturbances during sleep, sleep quality, and daytime sleepiness. These effects remained for at least two nights following the five successive stimulation nights. However, such improvement was not complete (Hida et al. 1994).

The mechanisms by which submental stimulation reduced the frequency of apneic episodes during stimulation may be due to increased muscle tone in the genioglossus and/or geniohyoid muscles, as discussed previously, which decreases the upper airway resistance (Gottfried et al. 1983; Miki et al. 1989b; Hida et al. 1995a) or upper airway collapsibility (Remmers et al. 1978; Brouillette and Thach 1979; Hida et al. 1995b; Wu et al. 1999).

The effectiveness of submental stimulation may depend on such factors as the stimulation intensity, sleep stage, type of apnea, adhesive force in the pharynx, or anatomical abnormality of the upper airway (Hida et al. 1994). The remaining improvement for two nights following the five stimulation nights is also an interesting phenomenon. These after-effects may be because of an improvement in the ventilatory response to hypercapnia, sleep related respiration, oxygenation, sleep fragmentation, and alertness as observed in OSA patients with nasal continuous positive airway pressure (CPAP) therapy (Rajagopal et al. 1986; Berthon-Jones and Sullivan 1987; Lamphere et al. 1989). The upper airway submental edema induced before treatment may disappear during the stimulation nights and nights after stimulation, as occurs with nasal CPAP (Ryan et al. 1991).

Several other investigators have attempted to stimulate the genioglossus with transcutaneous (Schwarz et al. 1996), or intraoral electrodes (Guilleminault et al. 1995). However, the results are not consistent among these reports.

Generally, noninvasive treatment for OSA has been performed by nasal CPAP (Sullivan et al. 1981; Rajagopal et al. 1986; Berthon-Jones and Sullivan

1987; Lamphere et al. 1989; Ryan et al. 1991; Taguchi et al. 1997). However, some patients with CPAP treatment complain of air leak from the nasal mask, dry throat or mouth, the development of nasal congestion and rhinorrhea, discomfort during sleep or restriction by the mask and head gear. Therefore, further research towards new and better therapeutic approaches including submental stimulation should be undertaken.

Acknowledgments

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