SLEEP and SLEEP DISORDERS

Neuromuscular Mechanisms of Upper Airway Patency

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The pathophysiology of obstructive sleep apnoea (OSAS) is principally based on an imbalance of the collapsing forces of the upper airway (UA) during inspiration and the counteracting dilating forces of the UA dilating muscles. A narrowed UA is very common among OSAS patients, which is usually due in an adult to non-specific factors such as fat deposition in the neck, or abnormal bony morphology of the UA. Functional impairment of the UA dilating muscles is particularly important in the development of OSA, and patients have a reduction in both tonic and phasic contraction of these muscles during sleep when compared to normals. A variety of defective respiratory control mechanisms are found in OSA, including impaired chemical drive, defective inspiratory load responses, and abnormal UA protective reflexes. These defects may play an important role in the abnormal UA muscle responses found among patients with OSA. Local UA reflexes mediated by surface receptors sensitive to intrapharyngeal pressure changes appear to be important in this respect. A better understanding of the integrated pathophysiology of OSAS should help both in the choice of optimum therapy for each individual patient, and also in the development of new therapeutic techniques. (Sleep and Hypnosis 2000;5:241-247)

Key words: sleep apnoea, upper airway, neuromuscular, reflexes, respiratory control

INTRODUCTION

The pathophysiological mechanisms involved in obstructive sleep apnoea (OSA) are complex and not fully understood. Critical upper airway (UA) narrowing/collapse usually occurs in the oropharynx, between the nasal choanae and epiglottis, an area lacking rigid support. Patency of this vulnerable segment is dependent on the action of pharyngeal dilator and abductor muscles that are normally activated in a rhythmic fashion during each inspiration (1). Collapse of the UA occurs if the negative UA pressure generated by inspiratory pump muscles exceeds the dilating force of these UA muscles (1,2). This review will focus on various factors influencing the neuromuscular mechanisms that operate to maintain UA patency, particularly during sleep.

UPPER AIRWAY DILATOR MUSCLE ACTIVITY

The role of UA dilator muscles in stiffening or distending the collapsible pharyngeal airway during inspiration (1,3) is suggested by the presence of EMG activity in these muscles co-ordinated with respiration (4). Effective function of these muscles is generally considered to be paramount in maintaining UA patency.

Activity of these UA muscles is modulated by chemical stimuli, vagal input, changes in UA pressure, and baroreceptor activity (5,6). Breathing through a narrowed UA generates a greater suction pressure and thus greater collapsing force, and pharyngeal dilator muscles must therefore contract more forcefully to prevent UA collapse. Progressive hypercapnia, hypoxia, asphyxia and the application of negative pressure all augment drive to UA dilator muscles (6-10). Furthermore, phasic inspiratory activity of these muscles reaches its nadir at the beginning of an apnoea, when the UA collapses, and increases to above pre-apnoeic levels at the resolu-

tion of the apnoea when patency is restored (11). Ineffective UA muscle responses, or incoordination of UA and diaphragm activity, have each been proposed as factors predisposing to OSA (12-14). However, it is difficult to study these responses since the complexity of the UA makes it unlikely that dysfunction of a single muscle group is responsible for OSA (3). Thus, assessment of activity of any single muscle may not be a reliable index of UA obstruction. Nevertheless, a number of UA muscles have been studied and, grouped anatomically, include the following:

(a) Nose: The alae nasi (AN) dilate the anterior nares during inspiration, and the degree of preactivation of the AN EMG ahead of the DIA EMG may be used as an index of ventilatory drive to the UA (15). During non-REM sleep, AN preactivation increases from the beginning to the end of an apnoea, implying that ventilatory drive to the AN increases with apnoea duration (16). This increase in preactivation, which is also seen in other UA muscles (15), can be viewed as a compensatory attempt to open or stiffen the UA before airway pressure is lowered by contraction of the DIA and ribcage (RC) muscles.

(b) Tongue: The genioglossus (GG) is a major pharyngeal dilator, pulling the tongue forward and opposing pharyngeal collapse due to inspiratory negative pressure (1,4,17,18), as shown by earlier peaking of GG EMG activity ahead of DIA EMG activity during inspiration (6). Both phasic inspiratory and tonic expiratory GG EMG activity increase from the upright to the supine position (19). Phasic inspiratory GG activity decreases with sleep in normal subjects (4,20), and almost ceases during REM sleep (17,21), while it increases significantly from wakefulness to non-REM sleep, between apnoeas in OSA patients and in older obese control subjects (22). Thus normal subjects have less EMG activity than patients with OSA, yet do not have occlusive apnoeas, and the augmented activation of GG in OSA subjects could represent a protective mechanism that occurs when patency of the pharyngeal airway is compromised (23), as suggested by the long axis of the UA being orientated in the AP dimension (24) in patients with OSA.

Any factor that interferes with this increase in GG activity, such as onset of phasic REM sleep or periodicity of central drive, can predispose to UA collapse. Indeed, GG EMG activity is reduced or abolished at apnoea onset, and increased at the termination of the obstruction (1,11,22). In addition awake patients with OSA have marked reductions in GG EMG activity when exposed to sustained hypoxia, unlike normals where it is relatively well maintained. This difference could result from sleep fragmentation or may possibly be a primary factor in the pathogenesis of OSA.

(c) Hyoid: Muscles that cause forward movement of the hyoid bone (geniohyoid [GH], sternohyoid [SH], thyrohyoid [TH]) are thought to enlarge and stabilise the pharyngeal airway (25-27). Pharyngeal volume displays an inverse relation with hyoid muscle (GH, SH) length (26), while forward movement of the hyoid bone occurs on adoption of the supine posture (28). These muscles show phasic inspiratory activity, and greater mechanical activity with significant hypercapnia (25). Both the GH and TH show augmented and prolonged activity after occlusion at end-expiration. Phasic inspiratory activity of the GH is seen in normal awake subjects, with a sleep-related fall in tonic activity in all stages of sleep (27,29), and there is a negative correlation with UA resistance.

(d) Soft palate: Reduced activity of the tensor palatini (TP) muscle, which retracts the palate from the posterior pharyngeal wall during nasal breathing, may also play an important role in maintaining UA patency (23,30,31). Both tonic and phasic activity of the TP decreases during sleep and correlates with increased UA resistance during sleep (23,30,32). Other velopharyngeal muscles, such as the levator veli palatini, palatoglossus and palatopharyngeus are also thought to play a role in modulating UA patency during sleep (11,33).

Structural abnormalities of the UA can put these muscles at a mechanical disadvantage, such as the reduced effectiveness of the GG in retro/micrognathia. The degree of UA narrowing may therefore exceed the ability of UA dilator muscles to compensate fully for the reduced UA calibre, with a fall in EMG activity with sleep onset. The main mechanical forces acting on the UA are summarised in Figure 1.

Furthermore, these UA muscles may undergo structural changes as a consequence of recurrent apnoeas. It has been shown that UA dilator muscles such as GG and musculus uvulae, demonstrate metabolic and physiologic characteristics commonly found in resistive exercise-trained muscles, with significant differences from controls (34). These changes most likely occur as a direct consequence of increased activity during wakefulness to maintain UA patency and of periodic bursts of pharyngeal dilator muscle activity at the termination of an apnoea. In addition, such changes may also be accompanied by evidence of muscle damage, with muscle fibre injury and replacement by fibrous tissue (35). These myopathic changes could result in a substantial degree of pharyngeal dilator muscle dysfunction in the setting of OSA, and changes observed in individual dilators could be additive in their detrimental effects. These changes could set up a cycle of effects with wors-

ening OSA promoting further changes in the muscles and so on. It is not known whether such processes are reversible with treatment of OSA.

UPPER AIRWAY REFLEXES

Upper airway dilator muscles are thought to be involved in reflex mechanisms that serve to maintain UA patency (10,36,37). Evidence suggests that these reflex mechanisms are pressure sensitive, and a reduction in their effectiveness could lead to an imbalance between intrapharyngeal pressure and the contraction of UA dilating muscles, resulting in obstructive apnoeas (1). The importance of these reflexes is supported by the finding of fatal pharyngeal airway closure in rabbits in which UA reflexes are abolished by topical anaesthesia (38).

Topical oropharyngeal anaesthesia (TOPA) in normal human subjects results in increased pharyngeal resistance during sleep (39) and increased frequency of obstructive apnoeas, independent of any direct effect of lignocaine on the UA muscles themselves. A significant increase in obstructive events has also been demonstrated after TOPA in a group of otherwise asymptomatic snorers (40). In contrast, TOPA did not produce any significant increase in AHI among patients with OSA (41,42).

The differing AHI responses to TOPA in the above studies would favour a primary abnormality in UA reflexes among OSA patients, since subjects with loud snoring would also be expected to have a mechanical vibration in the UA similar to that among patients with OSA. Indeed, temperature sensitivity in the oropharynx in OSA patients is significantly impaired compared to age-matched nonsnoring control subjects (43). However, TOPA has been noted to reduce the amount of phasic activity of the GG EMG for a given level of inspiratory effort during the terminal portion of an obstructive apnoea (42). This observation would argue that UA mechanoreceptors still contribute to UA reflexes in OSA patients. In addition, studies examining the role of UA mechanoreceptors in arousal have strongly suggested that there is a secondary impairment of these receptors, resulting from the reversible effects of repeated apnoeas across the night (44,45). Thus, UA collapse and occluded inspiratory efforts may be more potent in blunting mechaoreceptor activity than vibration due to snoring. Additional insight into these reflexes can be gained by studying the application of negative or positive pressure to the UA.

(a) Responses to negative UA pressure:

Upper airway muscle EMG activity increases when negative pressure is applied to the isolated UA of tra-

Figure 1. Diagrammatic representation of the main mechanical forces acting on the upper airway (UA) at tongue level in the supine position, and the factors influencing their relative contribution. The tendency for gravity to cause dorsal movement of the tongue is counteracted by the genioglossus (GG), which pulls the tongue forwards. Encroachment on the lateral walls of the UA (horizontal arrows) can result from bony abnormalities and/or an increase in soft tissue.
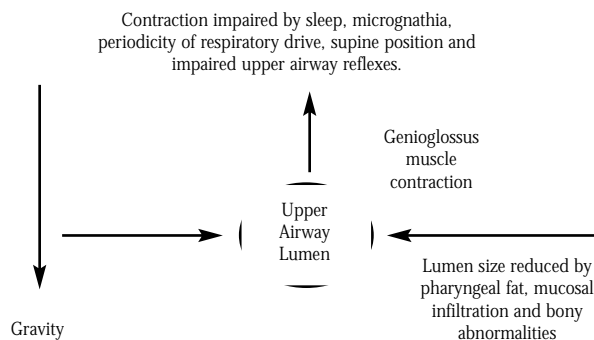
cheotomised rabbits (36), most likely through reflexes involving mechanoreceptors located above the trachea, and via several afferent pathways. Small but consistent changes in respiratory frequency are also seen suggesting some involvement of the respiratory centre in these changes (36). Negative pressure applied to the UA in dogs causes a predominant increase in phasic activity of AN and posterior cricoarytenoid muscles, and also in tonic activity of the GG, while preactivation of these muscles with respect to the DIA is increased (46). A decrease in the rate of rise of DIA EMG with a prolongation of inspiratory time also occurs, and topical anaesthesia eliminates these responses.

In awake humans, the sudden administration of negative airway pressure to the UA produces a pronounced and repeatable reflex increase in GG activity (10). Contributions from both supraglottic and subglottic receptors appear to be involved, and topical anaesthesia blocks the response when the glottis is closed. This response is reduced during non-REM sleep (47). When continuous negative airway pressure (CNAP) is applied to supine awake normal subjects there are both immediate and sustained increases in UA and DIA muscle activity to preserve tidal volume (48). However, when CNAP is applied during NREM sleep no immediate muscle or timing responses are seen, and apnoeas/hypopnoeas result. Re-establishment of UA patency is dependent on arousal and increased muscle activity. These findings suggest that protective reflexes, which act to maintain UA patency in the presence of negative airway pressure during wakefulness are compromised by the sleep state.

(b) Responses to positive UA pressure:

Continuous positive airway pressure, applied through the nares (nCPAP), is an effective therapy for OSA, and yet reduces UA dilator EMG activity during wakefulness and sleep (49,50). Studies in normal subjects have shown this reduction to be mediated by UA receptors, since UA anaesthesia abolishes the fall in EMG activity during wakefulness (50).

Many of the parameters discussed above are significantly influenced by changes in head position and body posture. Such effects are important since most individuals adopt a supine posture during sleep.

(a) Head position: The relative positions of the head and neck are important determinants of pharyngeal patency, with neck flexion able to considerably increase pharyngeal resistance during wakefulness and anaesthesia, particularly in obese subjects (51). Varying head position between flexion and extension can cause significant variations in size of the retroglossal space and hyoid position on lateral cephalometry. Neck flexion makes the UA more susceptible to collapse, while neck extension makes the UA more resistant to collapse (12), irrespective of changes in general body posture. Mouth opening can cause increased UA resistance, since this results in dorsal movement of the ventral attachments of UA dilator muscles, with resultant shortening in muscle length and reduction in efficiency (52).

(b) Posture: Pharyngeal CSA is reduced from the upright to the supine position in normal subjects (53), and in both apnoeic and non-apnoeic snorers (54). This reduction in UA patency with the supine posture does not result from decreased UA dilator muscle activity, since these muscles increase their electromyographic (EMG) activity with the transition from the upright to the supine posture, in both OSA and normal subjects (19,51,53). Moreover, patients with OSA have smaller percentage changes in CSA at the oro-pharyngeal junction than snorers or controls, thought to be due to increased activity of UA dilator muscles to prevent the UA from collapsing (54). Some patients with OSA can vary their AHI significantly between positions, while others do not (55). This discrepancy could be related to how the lateral pharyngeal walls behave in response to change in posture.

Supraglottic resistance is also greater, and maximum inspiratory airflow reduced, in the supine than the sitting position, for both normal subjects and patients with OSA (56,57). In obese patients with severe OSA the UA is less collapsible at 30… elevation compared to the lateral and supine positions (58). Maintaining FRC constant in normal subjects from the upright to the supine position does not prevent the fall in CSA, sug-gesting that the decrease in lung volume observed in the supine posture is not a significant contributor to UA narrowing in the normal subject and that the supine posture effect appears to be due to gravitational forces acting to narrow the UA (53). However, patients with OSA often have a reduced FRC when upright and a further fall in FRC, when assuming the supine position, may be associated with a significant fall in UA calibre (59).

RELATIONSHIP OF THE UPPER AIRWAY TO INSP RATORY PUMP MUSCLES AND CENTRAL FACTORS

Relationship of UA Muscle and Inspiratory Pump Muscles

The role of UA dilating muscles in counterbalancing the negative UA pressure generated by inspiratory pump muscles has already been mentioned above. The EMG activities of these UA muscles and of the diaphragm respond in a qualitatively similar manner to hypercapnia, hypoxia, and airway occlusion (6,7,9,60). This association suggests that central control mechanisms of UA and respiratory pump muscles in humans are intimately related. The UA stabilising properties of UA dilator muscles is aided by inspiratory activation of these muscles occurring earlier than activation of the DIA (3,15,46). Any reduction or delay in UA inspiratory muscle contraction, relative to DIA and RC muscle activity, will predispose to UA narrowing or collapse during sleep.

Despite qualitative similarities in the phasic inspiratory activity of the GG and DIA in response to chemical stimuli, important quantitative differences can occur. Activity of the hypoglossal nerve at lower levels of chemical (hypoxic and hypercapnic) drive is less than, and at higher levels of chemical drive greater than, phrenic nerve activity in anaesthetised dogs (7), although allowance must be made for the fact that anaesthesia selectively inhibits neural output to the UA. Oxygen breathing in rabbits decreases GG more than DIA EMG, while hypercapnia and prolonged occlusions preferentially activate GG compared to DIA (6), and these responses are abolished by carotid body denervation. Non-specific respiratory stimuli (light, sound, touch) preferentially increase phasic inspiratory GG activity (6), similar to that seen with EEG arousals at the termination of obstructive apnoeas (1). Some reports have suggested that respiratory motor drive to the pharyngeal musculature decreases during sleep, with an unchanged output to the diaphragm (61). However, other reports have suggested that a preferential decrease in UA muscle activity is not necessary for the development of occlusive apnoeas (14,20).

It has also been hypothesised that patients with OSA have instability of ventilatory control similar to periodic breathing, with fluctuations in the relative timing of inspiratory EMG activity of the UA to inspiratory pump muscle (DIA and RC) activity during sleep (20,62). During the hypopnoeic portion of the periodic breathing cycle, when ventilatory drive is low, both the relative amplitude and the relative timing of the inspiratory activity of the UA and chest wall muscles favour UA occlusion, since there is a greater fall in amplitude of UA muscle EMG than diaphragmatic EMG, and the normal preactivation of UA EMG is not apparent (62). Thus occlusive apnoeas occur when DIA and GG inspiratory activity both near the nadir of their cycle, which is lower than awake or sleep onset values (20). After apnoea onset, these EMG activities tend to decrease further for the first 1-3 inspiratory efforts (20) and activity of the UA muscles remain behind the RC muscles (62). As the apnoea proceeds there is a progressive increase in EMG activities until resolution of the apnoea. At apnoea resolution GG EMG increases to a greater degree than DIA EMG, and also for the first 1-2 post-apnoeic breaths, and activity of UA muscles precedes activity of the pump muscles when the UA opens. After several post-apnoeic hyperventilation breaths, both EMGs will decrease in activity again, which predisposes to further occlusive apnoeas (20).

This pattern could represent periodicity of the respiratory controller (62), with reduced damping and increased gain. Some support for this concept is provided by the observation that as ventilation falls around the onset of apnoea, oesophageal pressure swings associated with respiration remain unchanged (64). It would be anticipated that increased pressure swings would be seen, as the UA starts to collapse and become reduced in calibre. The lack of such an increase in amplitude of the pressure swings further suggests a decrease in central respiratory drive at the onset of apnoea, with failure of appropriate arousal and respiratory responses during the first several occluded respiratory efforts. In addition, it has been noted that, with progressive asphyxia in sleeping OSA subjects, there is no augmentation of drive to UA muscles despite an apparent increase in drive to the DIA (65).

Periodic breathing may also be influenced by changes in CO_2 and O_2. A $PaCO_2$ threshold well above the eupnoeic level is observed for GG muscle stimulation during all stages of sleep and wakefulness, while the DIA shows increased activity at even minor degrees of hypercapnia (21). This imbalance of activity, which favours UA collapse, seems to be greatest during phasic REM sleep. In the setting of respiratory instability, such as in periodic breathing, $PaCO_2$ may oscillate around the GG EMG threshold, to set up a cycle of recurrent airway occlusion and recovery. In sleeping OSA patients, the induction of hypercapnia during sleep preferentially stimulates inspiratory tonic activity in UA muscles relative to inspiratory activity, of chest wall muscles, and this reduces periodic breathing and apnoea duration (66). A clinical model of a disturbed timing relationship between UA and diaphragmatic contraction predisposing to OSA is seen in patients with diaphragmatic palsy treated with an electrophrenic pacemaker. About 50% of such patients develop OSA after insertion of this pacemaker (67) since the pacemaker results in DIA contraction at times other than when UA muscles contract.

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