Oral Maxillofacial Surg Clin N Am 14 (2002) 285–292

ORAL AND MAXILLOFACIAL SURGERY CLINICS

Pathophysiology of obstructive sleep apnea

M. Safwan Badr, MD

Medical Service, Detroit Veterans Affairs Medical Center, Detroit, MI, USA
Division of Pulmonary Critical Care and Sleep Medicine, Department of Medicine, Wayne State University School of Medicine, 3990 John R, Detroit, MI 48201, USA

Obstructive sleep apnea (OSA) is a fairly common disorder with significant adverse health consequences; however, the pathogenetic mechanisms remain incompletely understood. Upper airway (UA) patency is determined by several neuromuscular and non-neuromuscular factors including the following: (1) UA-dilating muscle activity, (2) the collapsing transmural pressure generated during inspiration, (3) changes in caudal traction, (4) vasomotor tone, and (5) mucosal adhesive forces. This article addresses the effect of sleep on UA function and how these factors conspire to cause UA obstruction.

The occurrence of UA obstruction during sleep and not wakefulness implicates the removal of the wakefulness stimulus to breathe as a key factor underlying UA obstruction during sleep. Most of the data on sleep effect are derived from studies during nonrapid eye movement (NREM) sleep, given the difficulty in achieving REM during invasive studies in the laboratory environment.

Physiology of sleep

The sleep state is classified into two distinct broad states: NREM sleep and REM sleep.

Nonrapid eye movement sleep

NREM sleep is classified into four stages by increasing depth from 1 through 4. Stage 1 is light sleep, slightly beyond drowsiness; stage 4 represents deep sleep. The electroencephalogram (EEG) shows decreased frequency and increased amplitude as sleep progresses from stages 1 through 4.

Rapid eye movement sleep

REM sleep is the stage when most dreaming occurs. While all antigravity muscles are paralyzed; there is increased activity of the central nervous system (CNS), and the EEG is fast with low amplitude waves (resembling an "awake" EEG). Thus, REM sleep is described as "paradoxical" sleep, showing an active CNS and paralyzed periphery. REM sleep occurs in cycles every 90 to 110 minutes. Its duration is often reduced in the laboratory environment, especially if complex instrumentation is used.

Effect of sleep on ventilation

Although sleep is viewed as a quiet resting period, judging by the "passive" appearance of a sleeping subject, this is far from true. The sleep state represents a challenge rather than rest period for the ventilatory system. The effects of sleep on ventilation set the stage for the development of sleep apnea and may provide the mechanistic link in susceptible individuals. Loss of the wakefulness stimulus to breathe is the key factor driving changes in breathing during sleep. Thus, ventilation becomes dependent on chemoreceptor and mechanoreceptor stimuli. Consequences of loss of wakefulness include reduced tidal volume, reduced activity and UA dilators, reduced UA caliber and loss of load compensation [1,2] (Fig. 1).

E-mail address: sbadr@intmed.wayne.edu (M.S. Badr).

PII: S1042-3699(02)00036-5

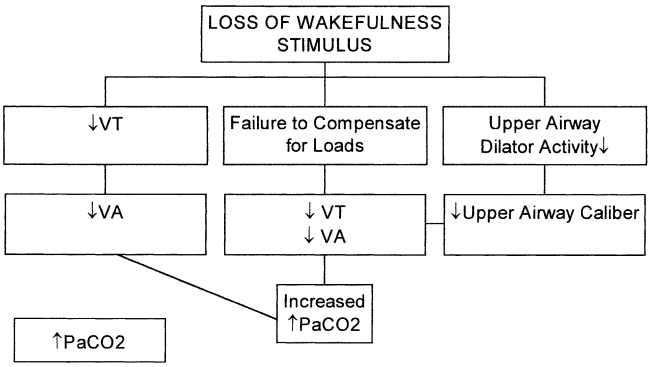

Fig. 1. Effects of sleep on ventilation and upper airway mechanics during sleep. VT, tidal volume; VA, alveolar ventilation; $PaCO_2$, arterial CO_2 partial pressure.

Reduced tidal volume

Reduced ventilatory motor output during sleep is associated with reduced tidal volume, reduced alveolar ventilation, and elevated $PaCO_2$. Increased arterial PCO_2 is also caused by increased UA resistance and impaired load compensation (see later).

Reduced activity of upper airway dilators

UA-dilating muscle activity is reduced during NREM sleep, especially in muscles with tonic activity (independent of the phase of respiration), such as the tensor palatinii muscle, which is reduced at sleep onset [3].

Reduced upper airway caliber

UA caliber is reduced during sleep, likely because of decreased UA-dilating muscle activity [4,5]. The mechanical corollary of reduced caliber is increased UA resistance [6,7]. If UA caliber is reduced sufficiently, inspiratory flow limitation develops, manifesting by a plateau in flow despite continued development of negative pressure [8]. Fig. 2 illustrates increased UA resistance and flow limitation during sleep in a normal subject.

Loss of load compensation

The ability of the ventilatory control system to compensate for changes in resistance is essential for the preservation of alveolar ventilation. Breathing through a resistor during wakefulness (load) leads to increased ventilatory effort to maintain ventilation and $PaCO_2$. In contrast, loads are not perceived during sleep and immediate compensation to added loads is compromised. Therefore, resistive loading results in decreased tidal volume and minute ventilation, and thus alveolar hypoventilation. The ensuing elevation of arterial $PaCO_2$ restores ventilation toward normal levels [9,10]. Teleologically, failure to perceive and immediately respond to loads allows for sleep to continue unperturbed. The main consequence of undisturbed sleep is a mild increase in $PaCO_2$. In fact, elevated $PaCO_2$ during sleep is common and is one of few physiologic situations where hypercapnia is tolerated.

Snoring, a marker of pharyngeal narrowing

Increased UA resistance during sleep is physiologic; however, a substantial increase in resistance may cause "fluttering" of the soft palate because of turbulent flow. This fluttering is responsible for the acoustic phenomenon known as snoring. In addition, individuals who snore demonstrate increased pharyngeal wall compliance during sleep, resulting in inspiratory flow limitation when flow plateaus during inspiration, despite continuous generation of subatmospheric intraluminal pressure(see Fig. 2). If increased resistance and inspiratory flow limitation are severe, increased work of breathing and hypoventilation can lead to frequent arousals from sleep and ensuing excessive daytime sleepiness. Fig. 3 depicts decreased tidal volume, reduced flow with flattening of the flow profile, and increased PCO_2 during sleep relative to wakefulness. This has been recently described as a distinct clinical entity called the *upper airway resistance syndrome* [11].

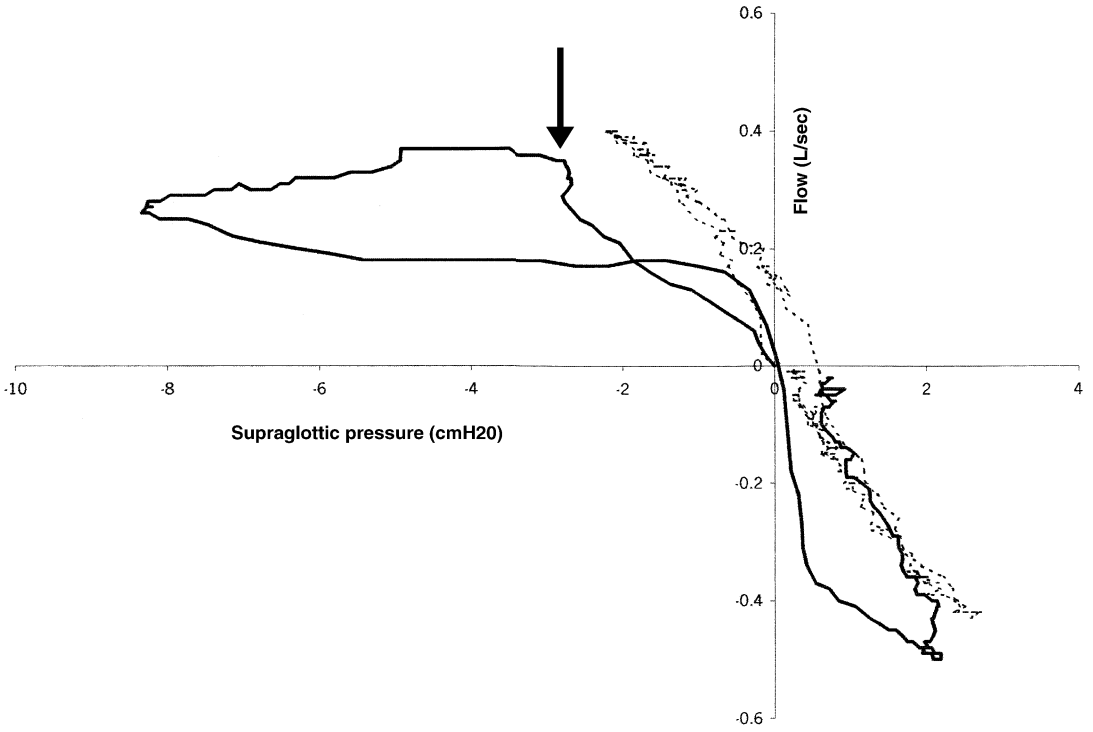

Fig. 2. Pressure-flow loops during wakefulness and sleep. Note that flow is less during sleep for a given pressure. Also, note the development of inspiratory flow limitation during sleep evidenced by a plateau in flow despite decreased (more negative) subatmospheric pressure. The arrow indicates the onset of flow limitation.

Chemoresponsiveness and the hypocapnic apneic threshold

The loss of the wakefulness stimulus to breathe renders ventilation during NREM sleep critically dependent on chemoreceptor stimuli (PaO_2 and $PaCO_2$). Reduced $PaCO_2$ is a powerful inhibitory factor of ventilation. Therefore, central apnea develops when $PaCO_2$ is reduced below a highly reproducible hypocapnic apneic threshold, unmasked by NREM sleep [12] (Fig. 4). Hypocapnia is probably the most important inhibitory factor during NREM sleep. Many cases of central sleep apnea are due to breathing instability leading to hypocapnia.

REM sleep: a special case

Most of the studies on sleep effect were in NREM sleep because REM is difficult to achieve under instrumented conditions.REM sleep is associated with muscle atonia affecting many UA dilators and intercostals; the diaphragm is spared.Despite the muscle atonia, pharyngeal compliance is not increased during REM sleep [4,5]. In fact, the retropalatal airway is less compliant during REM sleep relative to NREM [4]. This finding indicates the significance of non-neuromuscular factors in maintaining UA patency during sleep.

REM sleep is a special case because peripheral atonia is accompanied by augmented inspiratory medullary neuronal activity, and the REM sleep EEG shares many features of the awake EEG. Whether hypocapnia inhibits ventilation during REM sleep has not been proved.

Determinants of upper airway patency during sleep

Upper airway size and shape

There is evidence that the pharyngeal airway is smaller during wakefulness in patients with OSA

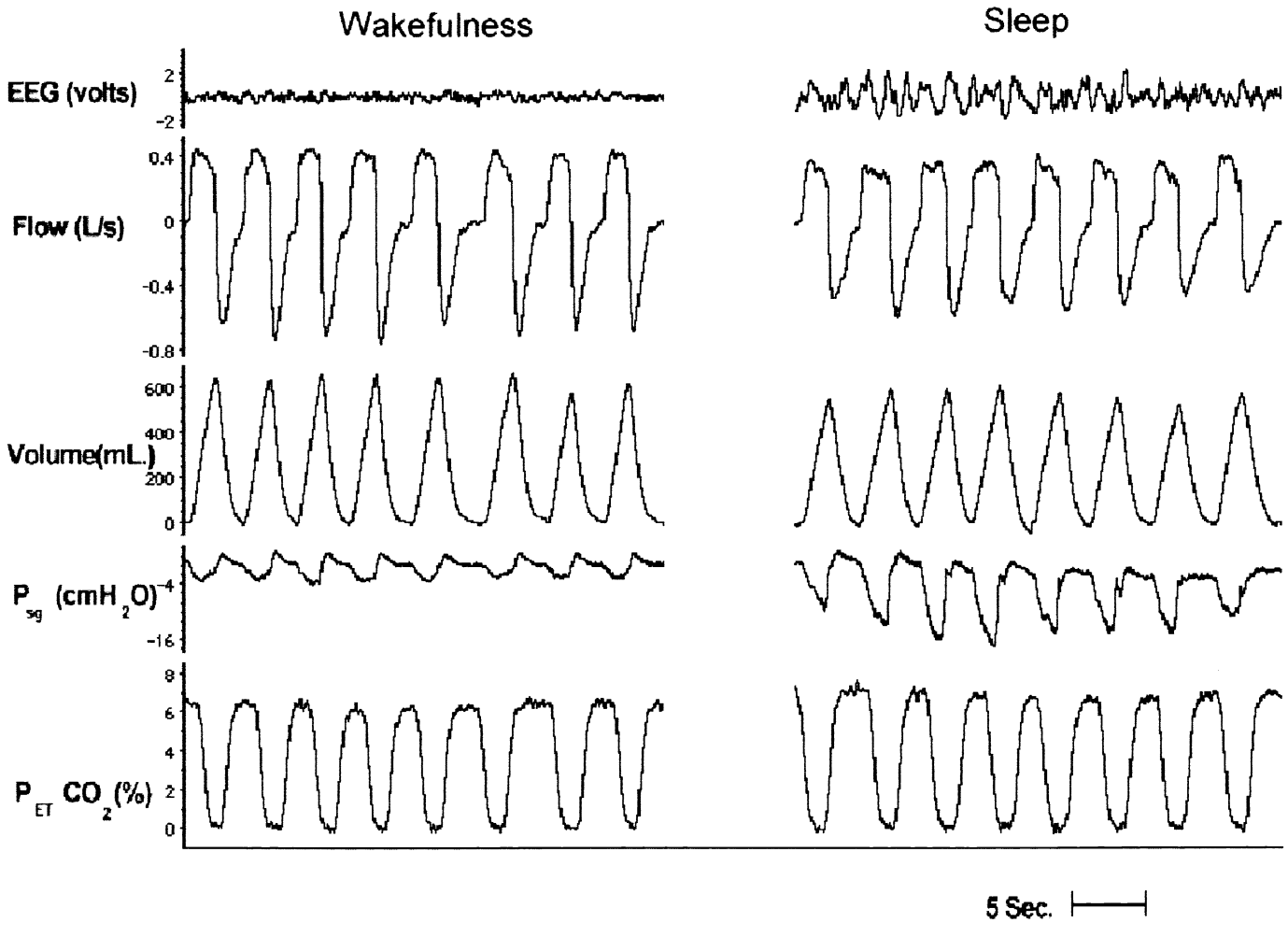

Fig. 3. A polygraph segment depicting changes in breathing from wakefulness to nonrapid eye movement sleep. Note the augmentation of supraglottic negative pressure (P_{sg}), decreased tidal volume (volume), and increased P_{ET} CO_2, partial pressure of end-tidal CO_2. EEG, electroencephalogram.

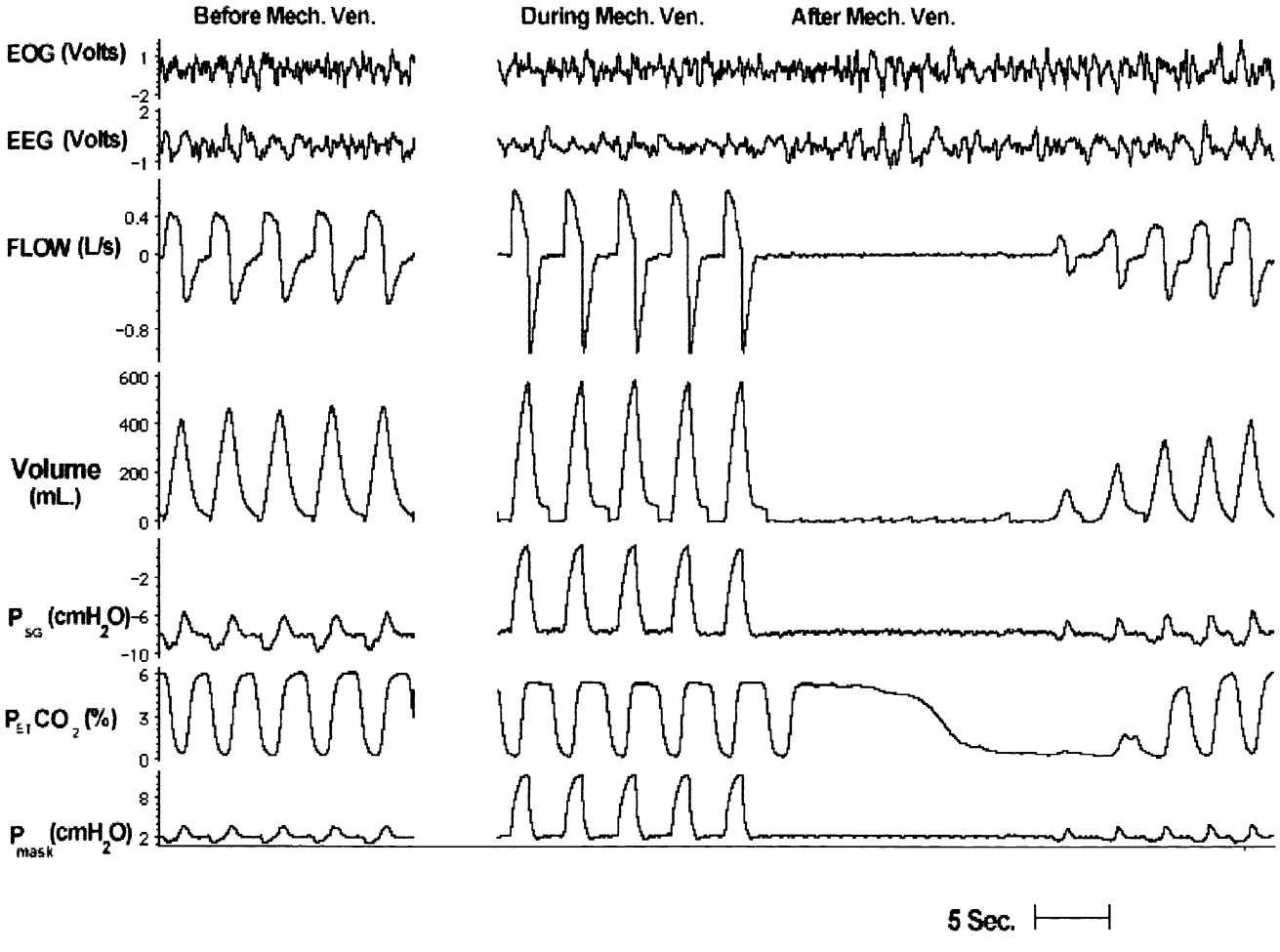

Fig. 4. Induced hypocapnic central apnea. Nasal mechanical ventilation (mech. vent.) was used to decrease P_{ET} CO_2 below apneic threshold. Termination of mechanical ventilation resulted in a prolonged central apnea. EOG, electro-oculogram; EEG, electroencephalogram; P_{SG}, supraglottic negative pressure; $P_{ET}CO_2$, partial pressure of end-tidal CO_2; P_{mask} pressure in the nasal mask.

compared with that of normal individuals [13,14]. In addition, the pharyngeal airway in patients with sleep apnea has an anterior/posterior configuration unlike the horizontal configuration in normal individuals [13]. The implications of the observed lateral narrowing to the pathogenesis of UA obstruction during sleep are yet to be determined.

Transmural pressure

A collapsing transmural pressure can be generated either by a negative intraluminal pressure or a collapsing surrounding pressure. The role of negative intraluminal pressure in the pathogenesis of UA obstruction is widely presumed [15]. Accordingly, a subatmospheric intraluminal pressure generated by the thoracic pump muscles causes UA obstruction by "sucking" the hypotonic UA. There are no data showing that subatmospheric intraluminal pressure causes UA obstruction in sleeping humans. In addition, Badr et al [16] have demonstrated that pharyngeal obstruction does not require negative pressure. Using fiberoptic nasopharyngoscopy, they have shown complete UA collapse during central apnea in patients with sleep apnea [16]. The occurrence of complete UA obstruction in the absence of negative intraluminal pressure supports the hypothesis that the UA collapsed by extrinsic pressure. Similarly, Isono et al [17] compared the mechanics of the pharynx in anesthetized, paralyzed normal subjects and patients with obstructive steep apnea. The pharynx was patent at atmospheric intraluminal pressure in normal subjects and required negative intraluminal pressure for closure. In contrast, patients with obstructive sleep apnea had positive closing pressure (ie, the pharynx was closed at atmospheric intraluminal pressure). Thus, the surrounding extraluminal pressure is an important contributor to the collapsing transmural pressure during sleep [18,19].

Pharyngeal compliance

The compliance of the pharyngeal wall is an important modulator of the effect of collapsing transmural pressure; a stiff tube is more likely than a compliant tube to remain open, even in the face of a collapsing transmural pressure. The intrinsic stiffness of the pharyngeal wall is caused by neuromuscular and non-neuromuscular factors; however, studies on the effect of UA muscle activity on pharyngeal compliance are inconclusive. For example, patients with OSA demonstrate increased pharyngeal compliance and increased activity of the genioglossus muscle during wakefulness [20] and sleep [21], perhaps to compensate for anatomically reduced caliber. Other studies have shown a dissociation between compliance and reported muscle activity. Rowley et a1 [4,5] showed using nasopharyngoscopy that pharyngeal compliance at the retroglossal level is not increased during REM sleep, relative to NREM sleep (ie, stiffness is unaltered) despite the known inhibitory effects of phasic UA dilators. This finding clearly shows that non-neuromuscular factors play a major role in pharyngeal compliance.

Thoracic caudal traction

The UA is connected to the thoracic cage and the mediastinum by several structures. Increased lung volume during inspiration is associated with increased UA caliber in awake individuals, likely because of thoracic inspiratory activity providing caudal traction on the UA, independent of UA-dilating muscle activity [22]. Caudal traction may transmit subatmospheric pressure through the trachea and ventrolateral cervical structures to the soft tissues surrounding the UA, increasing transmural pressure, and hence dilating the pharyngeal airway. This mechanism has been shown in sleeping subjects who experienced reduced UA resistance and increased retropalatal airway size when end-expiratory lung volume was increased by passive inflation [23]. Caudal traction may either dilate or stiffen the pharyngeal airway. It is likely that patients with OSA are more dependent on the effects of increased lung volume because dilatation and/or stiffening may be more prominent in a highly compliant UA.

Vascular and muscular factors

Vasoconstriction and vasodilatation cause a decrease and increase in UA resistance, respectively [24]. The effect of changes in vascular blood volume in the neck on UA patency in sleeping individuals remains unknown.

Once UA closure occurs, surface mucosal forces—stickiness—may impede subsequent UA opening and promote further narrowing/occlusion. Mucosal-lining forces may be particularly important in patients with OSA caused by mucosal inflammation from repeated trauma [25]. Data on sleep are limited. A recent study showed that pharyngeal mucosal surface tension is associated with decreased apnea/hypopnea index in sleeping persons [26]. The

relative contribution of reducing mucosal surface tension to the treatment of sleep apnea has not been determined.

Upper airway obstruction: putting the pieces together

Although many of the determinants of UA patency are known, the pathogenesis of pharyngeal obstruction remains elusive; however, common features can be assembled in plausible proposed mechanisms. The underlying defect is a small pharynx susceptible to collapse. Morrell et al [27] proposed that central breathing instability leading to reduced ventilatory motor output to UA dilators is the critical trigger setting in motion a cascade of events leading to pharyngeal obstruction during sleep. In fact, UA obstruction often occurs during experimentally induced periodic breathing at the nadir of ventilatory motor output [28]. A central breathing instability was found when periodic breathing persisted after tracheostomy in patients with OSA [29]. Accordingly, central ventilatory control instability may be a key mechanism of UA obstruction.

The reduction in ventilatory drive leads to reduced pharyngeal stiffness via reduction of neural output to UA-dilating muscles. The ensuing pharyngeal narrowing occurs because of the collapsing transmural pressure, which is caused by collapsing intraluminal and extraluminal forces.

The narrowing of the pharyngeal airway leads to increased velocity of flow and subsequently to a further reduction in intraluminal pressure (the Bernoulli principle) and further pharyngeal narrowing. Eventually, complete pharyngeal obstruction occurs. Mucosal adhesive forces and gravity lead to prolonged apnea, asphyxia, and arousal from sleep. The ensuing ventilatory overshooy leads to hyperpnea, hypocapnia, and subsequent reduction of ventilatory motor output when sleep is resumed.This sequence does not explain how the cycle is initiated. In patients with severe sleep apnea, removal of the wakefulness stimulus to breathe may produce a sufficient reduction of ventilatory motor output to cause UA obstruction. Sleep-state instability at sleep onset may be the trigger in others.

In conclusion, UA occlusion is a result of an interaction between multiple anatomic and physiologic abnormalities, the common features of which are the development of a collapsing transmural pressure and a small, compliant pharynx. Although subatmospheric intraluminal pressure contributes to the generation of a collapsing transmural pressure, it is unlikely to be the sole mechanism of UA obstruction during sleep.

References

[1] Henke KG, Badr MS, Skatrud JB, et al. Load compensation and respiratory muscle function during sleep. J Appl Physiol 1992;72:1221–34.
[2] Skatrud JB, Badr MS, Morgan BJ. Control of breathing during sleep and sleep disordered breathing. In: Altose MD, Kawakami Y, editors. Control of breathing in health and disease. New York: Marcel Dekker; 1999. p. 379–422.
[3] Tangel DJ, Mezzanotte WS, White DID. Influence of sleep on tensor palatini EMG and upper airway resistance in normal men. J Appl Physiol 1991;70: 2574–81.
[4] Rowley JA, Zahn BR, Babcock MA, et al. The effect of rapid-eye movement (REM) sleep on upper airway mechanics in normal subjects. J Physiol (Lond) 1998;510:963–76.
[5] Rowley JA, Zhou X, Vergine I, et al. Influence of gender on upper airway mechanics: upper airway resistance and Pcrit. J Appl Physiol 2001;91:2248–54.
[6] Hudgel DW, Martin RJ, Johnson B, et al. Mechanics of the respiratory system and breathing pattern during sleep in normal humans. J Appl Physiol 1984;56: 133–7.
[7] Skatrud JB, Dempsey JA. Airway resistance and respiratory muscle function in snorers during NREM sleep. J Appl Physiol 1985;59:328–35.
[8] Henke KG, Dempsey JA, Badr MS, et al. Effect of sleep-induced increased in upper airway resistance on respiratory muscle activity. J Appl Physiol 1991;70: 158–68.
[9] Badr MS, Skatrud JB, Dempsey A, et al. Effect of mechanical loading on expiratory and inspiratory muscle activity during NREM sleep. J Appl Physiol 1990;68:1195–202.
[10] Wiegand L, Zwillich C, White D. Sleep and the ventilatory response to resistive loading in normal man. J Appl Physiol 1988;64:1186–95.
[11] Guilleminault C, Stoohs R, Clerk M, et al. A cause of excessive daytime sleepiness: the upper airway resistance syndrome. Chest 1993;104:781–7.
[12] Skatrud J, Dempsey J. Interaction of sleep state and chemical stimuli in sustaining rhythmic ventilation. J Appl Physiol 1983;55:813–22.
[13] Schwab RJ, Gefter WB, Hoffman EA, et al. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing. Am Rev Respir Dis 1993;148:1358–400.
[14] Morrell MJ, Badr MS. Effects of NREM sleep on dynamic within breath changes in upper airway patency in humans. J Appl Physiol 1998;84:190–9.
[15] Remmers JE, de Groot WJ, Sauerland EK, et al. Patho-

genesis of upper airway occlusion during sleep. J Appl Physiol 1978;44:931–8.
[16] Badr MS, Tbiber F, Skatrud JB, et al. Pharyngeal narrowing/occlusion during central sleep apnea. J Appl Physiol 1995;78:1806–15.
[17] Isono S, Remmers J, Tanaka A, et al. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. J Appl Physiol 1997;82: 1319–26.
[18] Wolin AD, Strohl KP, Acree BN, et al. Responses to negative pressure surrounding the neck in anesthetized animals. J Appl Physiol 1990;68:154–60.
[19] Shelton KE, Woodson H, Gay S, et al. Pharyngeal fat in obstructive sleep apnea. Am Rev Respir Dis 1993; 148:462–6.
[20] Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyograrn in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). J Clin Invest 1992;89:1571–9.
[21] Suraft PM, McTier RF, Wilhoit SC. Upper airway muscle activation is augmented in patients with obstructive sleep apnea compared with that in normal subjects. Am Rev Respir Dis 1988;137:889–94.
[22] Van de Graaf WB. Thoracic influence on upper airway patency. J Appl Physiol 1988;65:2124–33.
[23] Begle RL, Badr MS, Skatrud JB, et al. Effect of lung inflation on pulmonary resistance during NREM sleep. Am Rev Respir Dis 1991;141:854–60.
[24] Wasicko JJ, Hutt DA, Parisi RA, et al. The role of vascular tone in the control of upper airway collapsibility. Am Rev Respir Dis 1990;141:1569–77.
[25] Olson LG, Strohl KP. Airway secretions influence upper airway patency in the rabbit. Am Rev Respir Dis 1988;137:1379–81.
[26] Jokic R, Kilmaszewski A, Mink J, et al. Surface tension forces in sleep apnea: the role of a soft tissue lubricant. Am J Respir Crit Care Med 1998;157:1522–5.
[27] Morrell M, Arabi Y, Zahn B, et al. Progressive retropalatal narrowing preceding obstructive apnea. Am J Respir Crit Care Med 1998;158:1974–81.
[28] Önal E, Burrows DL, Hart RH, et al. Induction of periodic breathing during sleep causes upper airway obstruction in humans. J Appl Physiol 1986;61:1438–43.
[29] Önal E, Lopata M. Periodic breathing and the pathogenesis of occlusive sleep apneas. Am Rev Respir Dis 1982;126:676–80.