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# Upper Airway Obstruction in Snoring and Upper Airway Resistance Syndrome

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## Abstract

Treatment options for snoring and upper airway resistance syndrome are hampered by either low compliance or low efficacy. Therefore, refinements in these therapeutic strategies are needed. The understanding of the pathogenic factors of upper airway obstruction and an individual's compensatory responses to defend ventilation in face of upper airway obstruction may help to develop more effective and less intrusive treatment alternatives. Undoubtedly, this may require more precise monitoring and pre- and post-treatment assessment of the factors that maintain upper airway patency and ventilation during sleep.

Snoring is a common phenomenon during sleep and associated with the obstructive sleep apnea/hypopnea syndrome (OSAHS), which has been identified as a risk factor for cardiovascular diseases [1]. Snoring is caused by upper airway obstruction, which is largely related to an increased propensity of the upper airway to collapse during sleep through a loss of neuromuscular tone in upper airway muscles. Frequently, compensatory neural responses to upper airway obstruction can adequately defend ventilation during sleep, and patients have a normal stable breathing pattern during sleep (primary snorer). Alternatively, compensatory responses to upper airway obstruction can intermittently fail, thereby reducing ventilation and inducing sleep fragmentation. These patients exhibit an unstable breathing pattern during sleep that is clinically referred to

as either upper airway resistance syndrome (UARS) or obstructive hypopneas (fig. 1). Several intrinsic and extrinsic factors can either increase the risk for upper airway obstruction or blunt neuromuscular compensatory responses to upper airway obstruction. This chapter will focus on the pathophysiology of upper airway obstruction and its implications for the management of snoring and UARS.

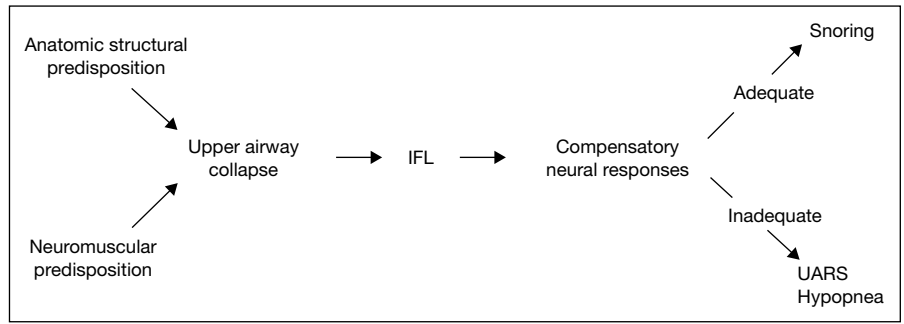
## Pathogenesis of Upper Airway Obstruction

In the last 20–30 years there has been an appreciable number of investigations of the mechanical properties of the upper airway, principally attempting to understand the pathophysiology of OSAHS. The main difficulty for the patient with OSAHS is collapse or partial obstruction of the pharyngeal airway that occurs during sleep in affected individuals [2]. To elucidate the mechanism of upper airway obstruction in obstructive sleep apnea (OSA), several approaches have been adopted to model the factors involved in the pathogenesis of pharyngeal collapse.

### *Upper Airway Function and Mechanics*

The upper airway commences at the oral and nasal openings, while at the other end it divides into the tracheal and esophageal passageways. The upper airway has a complex geometry, and is enclosed by muscles and mobile nonmuscular structures that are able to alter airway configuration. The major respiratory function of the upper

**Fig. 1.** Proposed pathogenesis of snoring and upper airway resistance syndrome (UARS). Anatomic and neuromuscular factors induce upper airway collapse and inspiratory airflow limitation (IFL). IFL induces compensatory neural responses, which may be adequate to stabilize breathing or inadequate or even absent with the subsequent development obstructed sleep disordered breathing.



airway is to permit air movement into and out of the lungs. In addition, the upper airway heats and humidifies inspired air, and is important in the regulation of both inspiratory and expiratory airflow. Under resting conditions including sleep, air flows through the nose, pharynx and larynx to the extrathoracic trachea. When airflow increases, as during heavy exercise or with nasal obstruction, breathing occurs through the mouth in addition to the nose, and hence the oral cavity is also part of the upper airway.

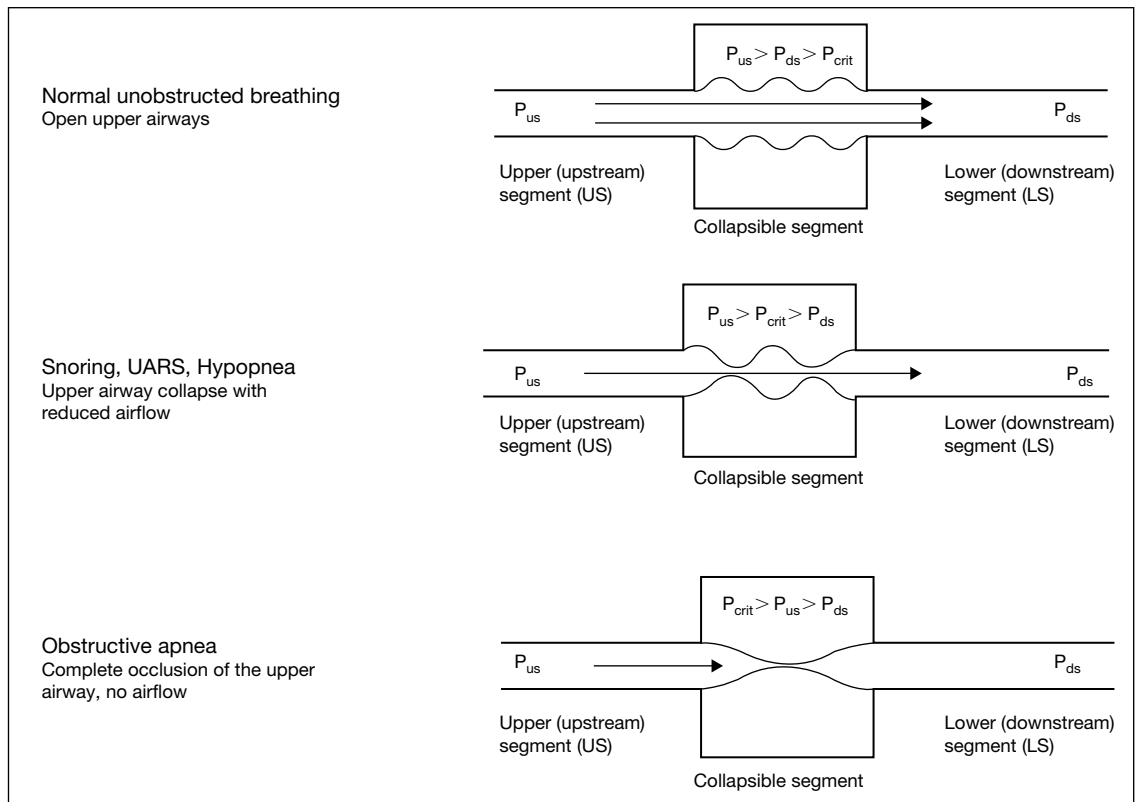
The upper airway is responsible for a major component of the total airway resistance in humans, providing 40–70% of the total pulmonary resistance during resting breathing. Nasal resistance is by far the largest component of the total upper airway resistance. Under quiet breathing during wakefulness in normal subjects, laryngeal and pharyngeal components are relatively small, but they are the most variable components of the total upper airway resistance. Upper airway size and resistance vary dynamically throughout the respiratory cycle and are also affected by the route of breathing (oral vs. nasal) [3], lung volume, level of ventilation, hypoxia and hypercapnia and behavioral state (conscious vs. unconscious and wakefulness vs. sleep). In addition, upper airway resistance can increase the work of the inspiratory muscles in producing airflow. Indeed, for patients with OSA and snorers, upper airway resistance may increase dramatically due to pharyngeal airway collapse and obstruction of inspiratory airflow [2].

#### *Starling Resistor Model for Upper Airway Obstruction*

Initial efforts for modeling upper airway obstruction focused on the interplay between extraluminal upper airway muscles that dilate and negative intraluminal pressures generated by the diaphragm that collapse the pharynx. It was originally postulated that upper airway patency was determined by the balance of pressures between the intraluminal and extraluminal space [2]. As intraluminal ‘suction’

pressures overcame the dilating forces around the pharyngeal lumen, the theory held that the pharynx would progressively collapse and ultimately occlude during sleep. Later studies, however, have minimized the role of intraluminal suction pressures in the pathogenesis of upper airway obstruction by demonstrating that upper airway occlusion could occur spontaneously, even when intraluminal pressures were positive [4]. These observations resolved a major question regarding the role of negative intraluminal pressures in the pathogenesis of OSA, and confirmed that negative pressures were not required for airway occlusion to occur. Rather, the markedly negative intraluminal pressures generated by the diaphragm during periods of upper airway obstruction were the consequence rather than the cause of upper airway occlusion.

To further elucidate the mechanism for upper airway obstruction, investigators have examined airflow dynamics during periods of obstruction, and found that pressure-flow relationships were identical to those previously described for other collapsible biologic conduits, i.e. the Starling resistor (fig. 1) [5]. This model provides a generalized approach for determining the critical pressure during inspiration, based on an analysis of pressure-flow relationships in the upper airway segment (fig. 2). A major feature of this model is that it describes the conditions leading to alterations in upper airway patency. Specifically, the model predicts that the airway would completely occlude whenever pressures both upstream ( $P_{us}$ ) and downstream ( $P_{ds}$ ) fall below a critical pressure ( $P_{crit}$ ). Under these circumstances, no flow could pass through the airway as long as  $P_{crit} > P_{us} > P_{ds}$ . As the upstream pressure is raised above the critical pressure, however, the upper airway would no longer remain occluded. Rather, the Starling resistor model predicts that a flow-limited state would ensue as long as the downstream pressure remains below critical pressure ( $P_{us} > P_{crit} > P_{ds}$ ) [6]. Inspiratory airflow limitation (IFL) is characterized by a plateauing of airflow and is associated



**Fig. 2.** The upper airway can be represented as a mechanical analogue of the Starling resistor model, consisting of a rigid tube with a collapsible segment. Upper (upstream, nasal) and lower (downstream, hypopharyngeal) segments have fixed diameters and defined resistances. Pressures in these segments are represented by  $P_{us}$  and  $P_{ds}$ , respectively. The collapsible segment has no resistance but is subject to the surrounding pressure,  $P_{crit}$ . Collapse occurs only when the surrounding pressure exceeds the downstream pressure (middle panel) and inspiratory airflow decreases compared to normal unobstructed breathing (upper panel). Complete occlusion occurs when  $P_{crit}$  exceeds both the upstream and downstream pressure (lower panel). Adapted from Gleadhill et al. [25].

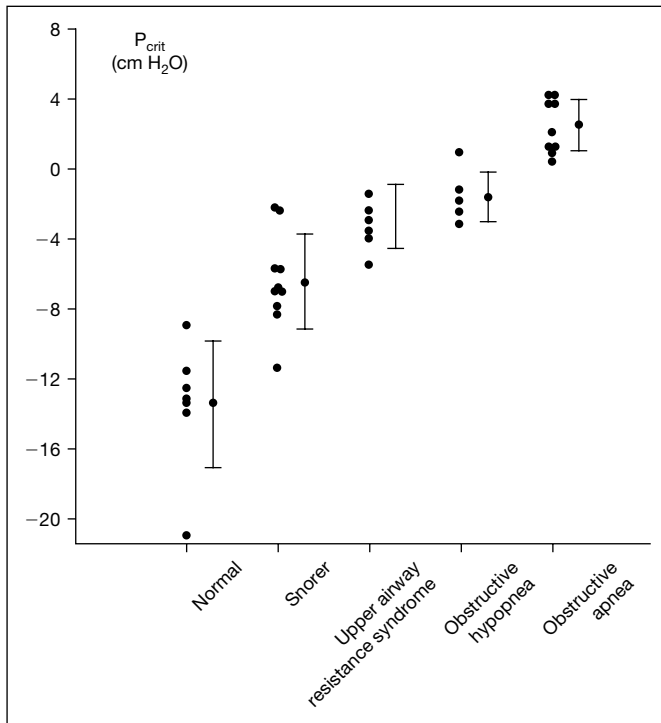
with collapse of the pharynx and audible snoring. Under conditions of flow limitation, investigators have also demonstrated that flow through the upper airway rises linearly with elevations in upstream pressure, regardless of the downstream pressure level [7]. Thus, the Starling resistor model predicts that the airway will occlude when upstream and downstream pressures remain below a critical pressure, and that flow limitation will result in linear increases in airflow as the upstream pressure is raised above the critical pressure (the conditions leading to occlusion and flow limitation in the upper airway are identical to those corresponding to zones I and II for the pulmonary vasculature, respectively).

In further studies, the upstream nasal pressure has been manipulated systematically, and critical pressures were measured in groups of individuals manifesting varying degrees of upper airway obstruction during sleep (fig. 3)

[7]. Critical pressures were markedly negative in normal individuals with evidence of airflow obstruction, whereas critical pressures were positive in apneic patients with complete upper airway occlusion. In patients with partial airflow obstruction during sleep (obstructive hypopnea, UARS, and asymptomatic snorers), critical pressures were between these two extremes (minimally to moderately negative) [7]. These observations suggested that varying degrees of upper airway obstruction during sleep were associated with quantitative differences in critical pressures, reflecting differences in upper airway collapsibility across the spectrum from health to disease.

#### *Factors Influencing Ventilation in the Face of Upper Airway Obstruction*

Inspired minute ventilation ( $V_I$ ) during sleep is determined by anatomic factors and by the neural responses that



**Fig. 3.** Upper airway collapse ( $P_{crit}$ ) and clinical expression. Critical closing pressures of the upper airway ( $P_{crit}$ ) during sleep are plotted for groups of individuals that represent the clinical spectrum of obstructive sleep apnea – non-snoring, snoring, upper airway resistance syndrome (UARS), obstructive hypopnea, and obstructive apnea.  $P_{crit}$  increases with increasing disease severity over a relatively narrow range of pressures. Note overlap between UARS and obstructive hypopneas, suggesting that the two disorders are indistinguishable in the degree of upper airway function, or in the impact of upper airway obstruction on sleep continuity. Adapted from Schwartz et al. [7] and Gleadhill et al. [25].

stabilize breathing. The factors leading to hypoventilation have traditionally been described by the basic relationship:

$$V_I = \left[ \frac{V_T}{T_I} \right] \cdot \left[ \frac{T_I}{T_{TOT}} \right] \quad (1)$$

where  $V_I$  is the inspired minute ventilation,  $V_T$  is the tidal volume,  $T_I$  is the inspiratory time,  $T_{TOT}$  is the respiratory cycle length, and  $T_I/T_{TOT}$  is the inspiratory duty cycle [8]. The conceptual framework provided by equation 1 forms the basis for our approach of characterizing the respiratory phenotypes predisposing to hypoventilation during periods of upper airway obstruction. As shown in equation 1, reductions in ventilation ( $V_I$ ) can be attributed to decreases in either the mean inspiratory flow ( $V_T/T_I$ ) or inspiratory duty cycle ( $T_I/T_{TOT}$ ). In early work, the mean inspiratory flow was found to be correlated with measurements of respiratory drive, whereas the

inspiratory duty cycle was thought to be primarily determined by the timing characteristics of the respiratory pattern generators. Thus, reductions in ventilation could be attributed to decreases in ventilatory drive or inspiratory duty cycle.

Although the mechanisms involved in stabilizing ventilation during sleep in the presence of upper airway obstruction have not been well defined, upper airway obstruction is known to increase ventilatory drive, which should increase the mean inspiratory flow (eq. 1). If the upper airway collapses, however, such increases in drive could not lead to further increase in the mean inspiratory airflow because inspiratory flow would be limited to a maximal level that could not be exceeded as effort increases. Therefore, during periods of IFL, increases in ventilatory drive can no longer prevent the individual from hypoventilating during sleep. Instead of increasing ventilatory drive and/or mean inspiratory airflow, patients can only preserve ventilation in the face of upper airway obstruction by prolonging the inspiratory duty cycle [3]. In recent work, our group has suggested that both the maximum inspiratory flow during upper airway obstruction and inspiratory duty cycle constitute distinct respiratory phenotypic traits [9], as follows: Under conditions of IFL, equation 1 becomes:

$$V_I = [V_I \max]_{IFL} \cdot \left[ \frac{T_I}{T_{TOT}} \right] \quad (2)$$

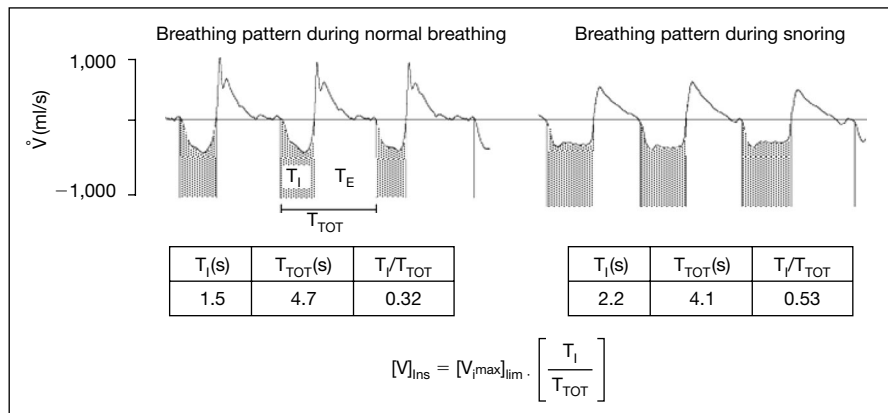
where  $(V_I \max)_{IFL}$  represents the level of maximal inspiratory airflow, which approximates the mean inspiratory airflow in the flow limited condition. From equation 2 it is evident that minute ventilation could be stabilized during periods of upper airway obstruction in one of two ways (fig. 4).

First, the level of mean inspiratory airflow could be increased. As noted above,  $(V_I \max)_{IFL}$  is determined solely by upper airway characteristics rather than the level of ventilatory drive. Any increase in the level of mean inspiratory airflow would be attributed to increases in upper airway neuromuscular responses or upper airway biochemical and physical properties.

Second, in the face of upper airway obstruction, an increase in ventilation could be accomplished by increasing the inspiratory duty cycle. As shown in figure 4, compensatory neural responses can help to maintain and stabilize ventilation during periods of upper airway obstruction by either restoring upper airway flow (inspiratory airflow) or prolonging the inspiratory duty cycle.

Taken together, the strengths of both compensatory neural responses will determine whether upper airway obstruction will be associated with stable breathing (snoring) or an unstable breathing pattern (UARS, hypopnea or apnea).

**Fig. 4.** Effect of upper airway obstruction on respiratory timing in a normal individual is illustrated in 1 subject. Upper airway obstruction was induced by lowering the nasal pressure from 5 cm H<sub>2</sub>O (left panel) to -5 cm H<sub>2</sub>O (right panel). Respiratory pattern indices (inspiratory time, T<sub>I</sub>; total respiratory cycle length, T<sub>TOT</sub>; inspiratory duty cycle, T<sub>I</sub>/T<sub>TOT</sub>) are shown for the baseline, unobstructed condition (left panel) and for the three breaths during the acute period of upper airway obstruction (right panel). The duty cycle increased substantially from the unobstructed period with the induction of upper airway obstruction. Adapted from Schneider et al. [3].



In the following section, we will discuss the factors that influence the neural compensatory drive.

### Mechanisms that Predispose to Upper Airway Obstruction

Several factors have been associated with alterations in the properties of the upper airway. These factors include anatomic or structural, neurochemical factors, and those which modify the surface tension of the upper airway.

#### Anatomic Factors

Specific anatomic alterations including tonsillar hypertrophy [10], retrognathia and variations in craniofacial structure [11] have been linked to an increased risk of OSA. Similarly, computed tomographic and magnetic resonance imaging studies have provided evidence for increased fatty tissue deposition in the lateral walls of the pharynx and submucosal edema that result in narrowing of the pharyngeal lumen during wakefulness, and are thought to predispose to airway obstruction during sleep. Isono et al. [12] have provided evidence for this hypothesis in experiments utilizing general anesthesia and complete neuromuscular blockade to eliminate neuromuscular input to the upper airway during sleep. Based on analysis of the maximal pharyngeal area (MPA) and static pressure-area curves, they demonstrated that apneic patients had significant narrowing of the upper airway (MPA:  $1.1 \pm 0.8$  vs.  $2.1 \pm 0.9$  cm<sup>2</sup>) and a more collapsible upper airway as reflected by higher closing pressures ( $2.2 \pm 3.0$  vs.  $-4.4 \pm 4.2$  cm H<sub>2</sub>O) in the velopharynx compared with control subjects [12].

Nevertheless, luminal narrowing alone may not be sufficient to produce collapse during sleep, since greater degrees of narrowing have been demonstrated in women who are resistant to upper airway collapse during sleep. Rather, such narrowing may elicit compensatory increases in upper airway neuromuscular activity that are required to maintain upper airway patency either during wakefulness or during sleep [13]. Taken together, these studies imply that snorers and apneic patients can be distinguished from normal patients on the basis of anatomic properties that predispose to upper airway obstruction when protective neuromuscular mechanisms wane at sleep onset.

#### Neural Factors

In addition to anatomic properties, it is well recognized that the upper airway is subject to neuromuscular factors that can also influence its patency. Upper airway obstruction is known to trigger various neuromuscular reflexes that activate upper airway dilator muscles and defend airway patency [14]. In animal studies of upper airway neuromuscular reflexes, these findings have led to the hypothesis that patients with OSA actually have increased levels of EMG activity that help maintain normal airway patency during wakefulness; however, when this compensating activity falls inappropriately at sleep onset airway occlusion may ensue. While these data attest to the importance of neural activation of upper airway muscles, the precise effect of EMG activity on upper airway function and ventilation during sleep has not been precisely defined.

To determine the impact of neuromuscular activity on upper airway patency, extensive studies in the isolated upper airway of animals have demonstrated that upper airway collapsibility is modulated by a complex interaction of

neuromuscular and anatomic factors that influence pharyngeal collapsibility and airflow dynamics. Among these factors are pulmonary and upper airway mechanoreceptor pathways, as well as chemoreceptors, all of which have been shown to act individually or in combination to modify upper airway dilator muscle activity [15]. In addition, it is now thought that negative pressure reflexes of the upper airway may not respond appropriately to the markedly negative intraluminal pressure generated during periods of upper airway obstruction. Moreover, Mezzanotte et al. [14] have documented elevated genioglossal EMG activity in patients with OSA compared to normals during wakefulness, suggesting that the negative pressure reflex is selectively attenuated during sleep. Finally, it appears that upper airway sensory pathways may be impaired, since temperature, two-point discrimination and vibratory thresholds are disrupted in sleep apnea patients compared with normal individuals [16]. Sensory receptor dysfunction could also attenuate the response of upper airway dilator muscles to the markedly negative airway pressures generated during periods of upper airway obstruction. Further evidence for sensorimotor dysfunction is provided by graded histopathologic and immunochemical alterations in the palatopharyngeus and musculus uvulae in sleep apnea patients, relative to asymptomatic snorers and normal individuals [17]. Findings of muscle fiber type redistribution and injury (fascicular atrophy and grouped atrophy in muscle fibers), have suggested that myopathic as well as sensory dysfunction may further compromise neuromuscular responses to upper airway obstruction.

#### *Biomechanical Characteristics of the Upper Airway Mucosal Surface*

The upper airway is lined by a liquid at the mucosal surface important to the patency of the upper airway. Many investigators have examined the role of surface tension in maintaining alveolar patency, whereas there are relatively few investigations of surface forces in upper airway patency. Wilson et al. [18] reported postmortem studies in infants which demonstrated that the intraluminal pressure required to re-open a closed upper airway was greater than the intraluminal pressure required to close the same airway. This difference between upper airway opening and closing pressure was ascribed to the force required to overcome surface tension effects between the walls of the closed airway. These findings suggest that surface forces operating in the liquid lining the upper airway exert an influence on upper airway patency. Since these first observations, there have been only a few studies that have addressed this concept. Olson and Strohl [19] demonstrated that stimulation

of upper airway secretions in rabbits made the collapsed upper airway more difficult to re-open (i.e. because of increased upper airway opening pressure). This effect was ascribed to 'stickiness' of the induced upper airway secretions. In rabbits, instillation of surfactant into the upper airway has been shown to reduce the surface tension of the mucosal lining liquid and increase upper airway patency [20–22].

It has recently been shown in humans that the surface tension of upper airway lining liquid plays an important role in the control of upper airway patency [20–22]. For example, in both awake and anesthetized [21] humans lowering the surface tension of upper airway lining liquid with exogenous surfactant decreases the intraluminal pressure required to reopen a closed pharyngeal airway. In addition a number of studies have shown that the instillation of exogenous surfactant into the upper airway of patients with OSAHS reduces the severity of the associated sleep-disordered breathing [22–24]. Thus, alteration of the surface forces of the liquid lining the upper airway may provide a mechanism for influencing the collapsibility of the upper airway; however, the clinical value of this issue is yet to be resolved.

Taken together, anatomic structural properties, neuromuscular influences and biomechanical properties of the surface liquid could account for quantitative differences in critical pressure in humans manifesting various degrees of anatomic structural predisposition for upper airway obstruction during sleep. As outlined above, normal individuals are characterized by markedly negative critical pressures, reflecting diminished upper airway collapsibility during sleep, compared to progressive elevations in critical pressure in those with partial obstruction (snoring and obstructive hypopneas) and complete occlusion (obstructive apnea) [25]. Moreover, the critical pressures in normal sleeping individuals are markedly lower than those reported in normal anesthetized subjects after abolishing neuromuscular activity with a paralytic agent. The further reduction in critical pressure in the sleeping compared to the paralyzed state suggests that neuromuscular factors prevent collapse, and play an important role in maintaining upper airway patency during sleep.

#### **Predisposing Factors for Hypoventilation in the Face of Upper Airway Obstruction**

As outlined above, it is now evident that defects in both the upper airway and neuroventilatory control are pivotal for the development of obstructed sleep disordered breathing. Although neuromuscular control of upper airway function

is crucial for the level of inspiratory airflow, the duty cycle has been identified as a distinct physiologic component for defending ventilation in response to upper airway obstruction. For example, the duty cycle contains a physiologic ceiling of approximately 0.6, at which no further increases of the duty cycle is possible [26]. If the duty cycle during unobstructed breathing is already above 0.5 as commonly seen in patients with underlying medical illnesses of the heart and lung, an individual would be able to increase the duty cycle and minute ventilation by only 20%, while a normal individual with a duty cycle of 0.3 at baseline may increase the duty cycle and ventilation by 200%.

Conversely, a hallmark of chronic obstructive pulmonary disease (COPD) and asthma is expiratory airflow limitation that leads to prolongations of the expiratory time, which in turn, shortens inspiratory time. As a consequence, these patients are also limited to increase their duty cycle, once they exhibit inspiratory upper airway obstruction, due to a ceiling effect imposed by their expiratory time requirement. However, it is currently unclear, whether this feature in patients with COPD may play a role for the increased prevalence of sleepiness and fatigue in these patients.

Gender might also affect ventilatory responses to upper airway obstruction, as testosterone, progesterone and estrogen are known to alter ventilatory control. Moreover, gender differences exist in lung function and metabolic demand, both of which may affect the ventilatory compensatory responses to upper airway obstruction.

Similarly, it has been shown that normal individuals exhibit substantial variation in the magnitude of duty cycle response, even when the baseline duty cycles are similar between subjects [3]. The response in inspiratory duty cycle in the setting of upper airway obstruction varied between 0.02 and 0.18, indicating that the duty cycle in response to upper airway obstruction may serve as an intermediate physiologic trait that may provide a link to specific genetic factors relevant to the expression of obstructive sleep disordered breathing [3].

Taken together, the duty cycle during unobstructed breathing may determine an individual's ability to respond adequately to upper airway obstruction. However, it is not clear whether such abnormalities exacerbate sleep related hypoventilation and UARS in normal patients with milder degrees of upper airway obstruction.

## Upper Airway Resistance Syndrome

### *Definition*

While primary snoring is by definition associated with a stable sleep and breathing pattern, UARS, similar to

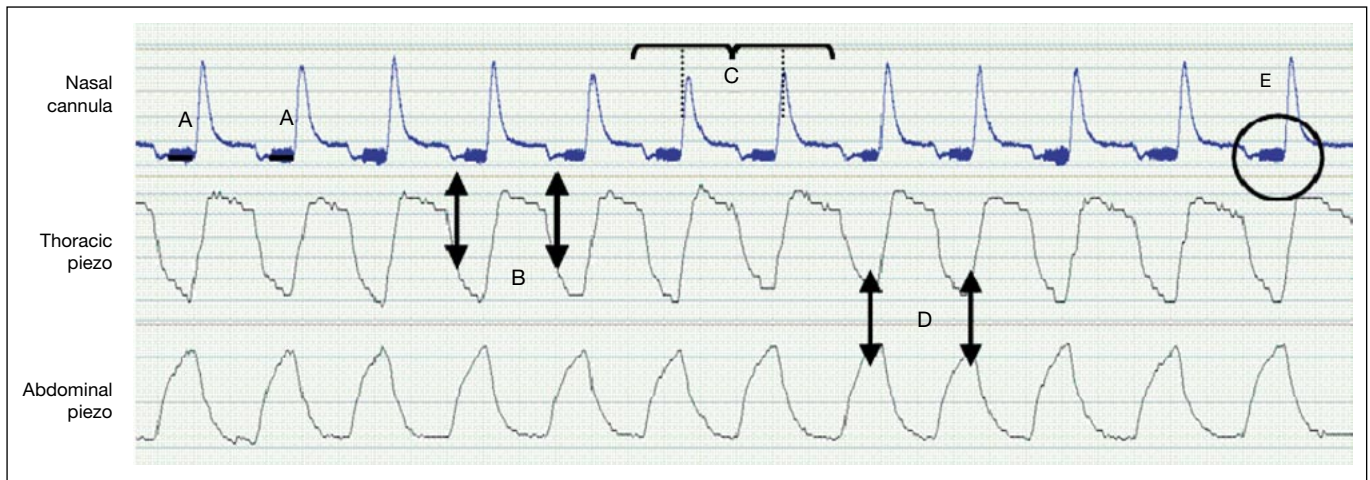
OSA, is defined by repetitive upper airway collapse resulting in IFL and subsequent arousals from sleep. Upper airway collapsibility, as reflected in the critical closing pressure ( $P_{crit}$ ), of patients with UARS is intermediate between normal patients without sleep disordered breathing and patients with OSA [7, 25] establishing UARS on the spectrum of obstructive sleep disordered breathing. While OSA is associated with intermittent oxyhemoglobin desaturations and significant reductions in airflow, UARS does not share these features.

### *History of UARS*

The term 'upper airway resistance syndrome' was first coined by Guilleminault and his colleagues in 1993. Over a decade earlier, they had published results of the first study of this clinical entity in children. In a retrospective study of 25 children with snoring, excessive daytime sleepiness, and behavioral disturbances, compared to 25 control children, they found that while subjects did not have overt OSA, the case subjects had more frequent episodes of IFL with significant intrathoracic pressure swings and subsequent arousals, compared to the control group. Treatment of case subjects with tonsillectomy and adenoidectomy resolved all daytime symptoms, implicating increased upper airway resistance in the pathophysiology of this clinical entity. Subsequent research in adults identified UARS as a significant cause of daytime hypersomnia.

UARS describes the constellation of daytime hypersomnolence due to respiratory arousals related to IFL, without overt apneas or hypopneas. Although controversy remains regarding the establishment of UARS as a distinct clinical entity. UARS is generally recognized as a subset of OSA syndrome, due to similarities in pathophysiology and treatment. Silent UARS, defined as UARS without clinically evident snoring, is present in 1% of patients evaluated for hypersomnolence in sleep laboratories [27]. Because of unique features in clinical presentation and diagnostic strategies, UARS continues to be an under-recognized and untreated form of sleep-disordered breathing.

IFL results in the generation of significant negative intrathoracic pressure with each breath. Gleeson and colleagues demonstrated a correlation between brief arousals and the magnitude of esophageal pressure swings, with a consistent arousal response when intrathoracic pressure reached a level of approximately  $-15$  cm  $H_2O$ . Thus, frequent respiratory arousals associated with IFL can predictably result in sleep disruption and subsequent daytime hypersomnolence. While IFL is the hallmark of UARS and other obstructive sleep disorders, variation in clinical expression of IFL may also be determined by other patient



**Fig. 5.** Snapshot of polysomnography from a patient with inspiratory flow limitation. Signals of interest include airflow (via nasal cannula) and respiratory effort (via thoracic and abdominal piezo belts). Inspiratory flow limitation is characterized by constant or reduced inspiratory airflow (A) in the setting of continued or greater respiratory effort (B); prolongation of the inspiratory duty cycle (C); desynchrony of thoracic and abdominal movements with inspiratory (D), and snoring (E).

factors, such as comorbidity, gender and heritable alterations in ventilatory control as discussed above. This is also highlighted by the significant overlap of  $P_{crit}$  observed in patients with simple snoring, UARS, and obstructive sleep hypopneas [7, 25] suggesting that the clinical expression of IFL is determined by factors such as ventilatory protective mechanisms, degree of oxyhemoglobin desaturation with respiratory events, degree of hypercapnia, time since previous awakening or arousal, total sleep time, and temporal proximity to REM sleep [28].

### Diagnosis

Diagnosis of UARS requires a heightened clinical suspicion of obstructive sleep disordered breathing along with sensitive diagnostic airflow measurements. Clinical history alone does not discriminate between types of obstructive sleep disordered breathing. Patients presenting with UARS often complain of excessive daytime sleepiness, snoring, fatigue, and morning headaches, similar to OSA. Physical examination may reveal an overcrowded pharynx, retrognathia, macroglossia, and other such features which would predispose to upper airway obstruction. Obesity can be a feature of patients with UARS, but is not necessary.

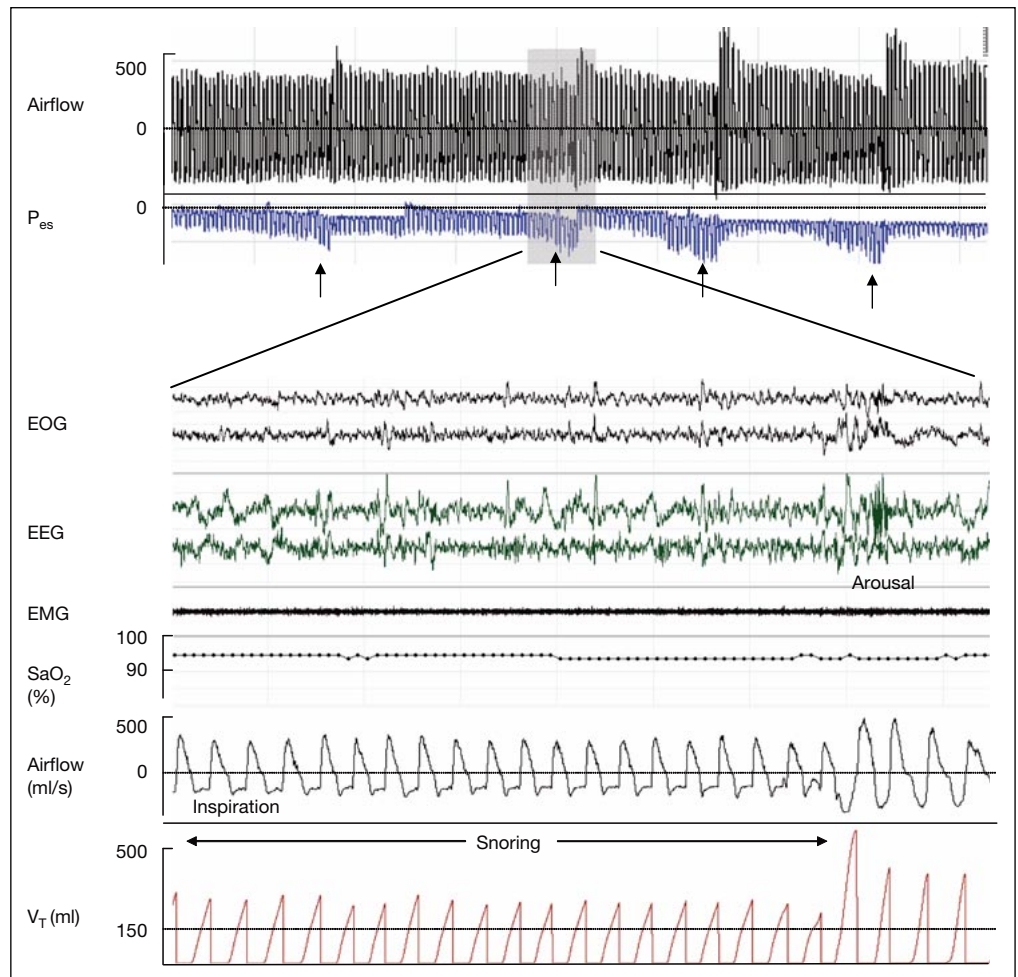
Nocturnal polysomnography is necessary to diagnose UARS. Esophageal balloon manometry, as a measure of intrathoracic pressure, and pneumotachography, a quantitative airflow measurement, have been the gold standard measurements for UARS. Although alternative measurements of respiratory effort (piezo belts, plethysmography)

and airflow (nasal cannula, thermistors, thermocouples) are sufficient enough to detect IFL (fig. 5), they are often not sensitive or specific to detect UARS particularly due to the lack of either quantifying airflow or inspiratory effort. Reductions in airflow and progressively more negative intrathoracic pressure prior to an arousal was identified to be the hallmark of UARS (fig. 6). Frequent leg movements in the setting of IFL are often misclassified as periodic limb movements [29], when esophageal pressures and quantitative airflow measurements are not available.

### Therapeutic Implications

Continuous positive airway pressure (CPAP) has been designed to overcome upper airway obstruction (positive critical pressure) by elevating upstream pressures at the nose or mouth [30]. CPAP has been a mainstay of therapy for OSA for nearly 20 years, and is effective in relieving obstruction in patients with OSAHS syndrome. However, snoring subjects and patients with UARS exhibit a very low compliance on CPAP due to (1) the inconvenience of wearing the cumbersome nasal masks, and (2) potentially sub-therapeutic CPAP settings due to the difficulty in assessing an optimal therapeutic nasal pressure, and therefore often seek alternative less-intrusive treatment options.

There are several alternative approaches for relieving snoring, all of which can be subdivided into two basic principles. The first approach is to improve the structural

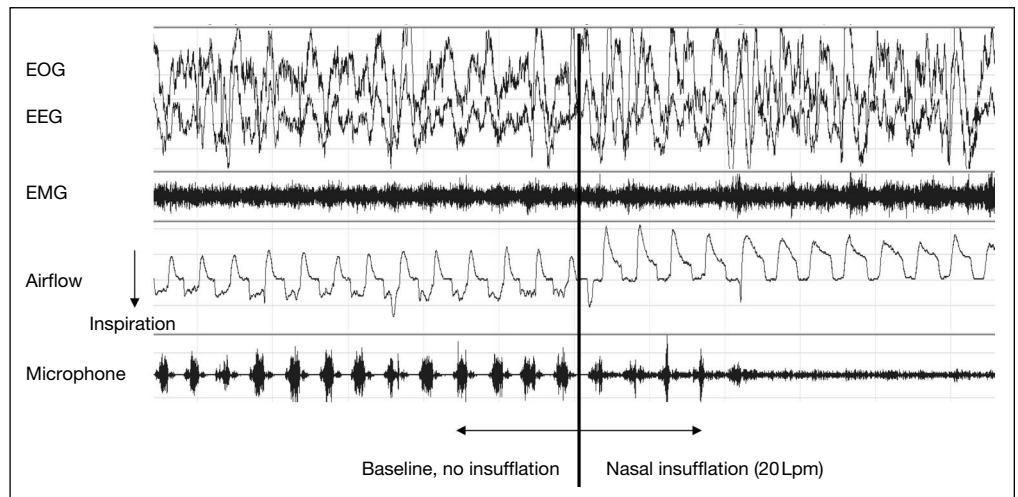


**Fig. 6.** Snapshot of polysomnography from a patient with upper airway resistance syndrome. In the upper panel a compressed (10 min) view of the airflow and esophageal pressure ( $P_{es}$ ) signal. As can be seen, while minimal fluctuations occur in the airflow signals, there are intermittent progressive increases in  $P_{es}$  (upward arrows), indicating increases in upper airway resistance. As amplified in the panel below, periods of increased  $P_{es}$  were due to snoring with inspiratory flow limitation and reductions in tidal volume that led to an arousal from sleep. EOG = Electrooculogram; EEG = electroencephalogram; EMG = electromyogram;  $SaO_2$  = oxygen saturation,  $V_T$  = tidal inspiratory volumes.

and neuromuscular properties of the upper airway, thereby lowering the critical closing pressure during sleep, the other is to protect neural compensatory responses to upper airway obstruction, thereby increasing ventilation and reducing the frequency of arousal from snoring.

The first alternative therapeutic approaches target to lower the critical pressure by either augmenting the structural or neuromuscular mechanisms required for the maintenance of airway patency. Current approaches to correcting alterations in upper airway mechanics include weight loss [31] and postural maneuvers [32]. Upper airway reconstructive

surgery (uvulopalatopharyngoplasty, transpalatal resection, adenotonsillar resection), and a variety of procedures designed to move the hyoid, mandible and maxillary bones anteriorly [33] are also designed to lower critical closing pressure. These methods have been shown particularly effective in patients with milder degrees of upper airway obstruction but are limited by their intrusiveness and low efficacy in obese and older subjects. Surgical interventions are therefore not being recommended as first line treatment of snoring and UARS. Oral appliances, either mandibular advancement devices or tongue repositioning devices, function by



**Fig. 7.** Effect of nasal insufflation on inspiratory airflow limitation. The inspiratory flow contour indicates snoring (as highlighted in the recording of the sound signal by a microphone in the bottom tracing). With initiation of nasal insufflation, inspiratory flow contour normalizes and snoring abolishes (right panel). EOG = Electrooculogram; EEG = electroencephalogram; SaO<sub>2</sub> = oxygen saturation. From McGinley et al. [36].

mechanically increasing the posterior pharyngeal airspace, and can adequately treat partial upper airway collapse.

Pharmacologic strategies that either lower the surface tension or stimulate upper airway motor neuron pools with tricyclic antidepressants and serotonergic agents may offer partial relief of upper airway obstruction [34]. However, these methods also are limited by either a low efficacy or systemic side effects that inhibit its use in normal individuals who snore or patients with UARS.

The second alternative set of approaches are targeted at the improvement of ventilation during sleep. CNS depressants such as alcohol, benzodiazepines and opioids block compensatory neural responses in several ways, and should therefore be avoided in patients with snoring and UARS. First, although alcohol ingestion has been shown to decrease genioglossal muscle activity, thereby blunting reflex recruitment of the upper airway musculature and predisposing to worsening obstruction, these agents are also known to reduce arousal responses and ventilation during sleep. For example, the arousal responses to airway occlusion are known to be prolonged in normal sleeping subjects after alcohol ingestion, thereby increasing the risk of hypoventilation in face of upper airway obstruction. Finally, the combined effects of CNS depressants on the upper airway musculature and arousal responses could account for observed increases in the frequency and duration of sleep disordered breathing episodes, and

worsening oxyhemoglobin desaturations after alcohol ingestion [35].

A new less-intrusive treatment for abolishing IFL by insufflating air through an open nasal cannula system was recently introduced [36]. Although this treatment seems to be effective in abolishing snoring (fig. 7), the precise mechanism and clinical efficacy remain to be resolved before recommending nasal insufflation for general use.

In summary, treatment options for snoring and UARS are hampered by either a low compliance or low efficacy. Therefore, refinements in these therapeutic strategies are needed. The understanding of the pathogenic factors of upper airway obstruction and an individual's compensatory responses to defend ventilation in face of upper airway obstruction may help to develop more effective and less intrusive treatment alternatives. Undoubtedly, this may require more precise monitoring and pre- and post-treatment assessment of the factors that maintain upper airway patency and ventilation during sleep.

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