The Upper Airway Resistance Syndrome*

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The upper airway resistance syndrome (UARS) is a recently described form of sleep-disordered breathing in which repetitive increases in resistance to airflow within the upper airway lead to brief arousals and daytime somnolence. This review will first describe the chronological progression of our understanding of UARS within the broader context of sleep-disordered breathing. The primary symptom, daytime somnolence, appears to result directly from repetitive EEG arousals. The level of negative intrathoracic pressure is the most likely stimulus for arousal, possibly mediated by mechanoreceptors in the upper airway. A general consensus regarding the exact clinical definitions and the physiologic measurement techniques leading to a diagnosis does not exist, although esophageal manometry and pneumotachographic airflow measurements taken during polysomnography are the “gold standard.” Less invasive diagnostic modalities have been proposed, but none of them have been well-validated. Aside from daytime somnolence, hypertension is an important sequela of this disorder, likely resulting from autonomic and cardiovascular changes induced by increased negative intrathoracic pressure. Nasal continuous positive airway pressure is the most efficacious form of therapy, although low patient compliance may limit its practical application. The safety and efficacy of surgical treatments are poorly documented in the literature. Palatal tissue reduction by radiofrequency ablation and the use of oral appliances hold promise as safe and effective modalities, but these treatments require further study.

Key words: arousals; continuous positive airway pressure; esophageal pressure; excessive daytime somnolence; laser-assisted uvulopalatoplasty; snoring; somnoplasty; upper airway resistance syndrome; UPPP

Abbreviations: AHI = apnea/hypopnea index; ASDA = American Sleep Disorders Association; BMI = body mass index; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; EMG = electromyogram; ESS = Epworth sleepiness scale; IUAR = increased upper airway resistance; LAUP = laser-assisted uvulopalatoplasty; MSLT = multiple sleep latency test; nCPAP = nasal continuous positive airway pressure; OSAS = obstructive sleep apnea syndrome; Pes = esophageal pressure; PSG = polysomnogram; RDI = respiratory disturbance index; REM = rapid eye movement; SWS = slow-wave sleep; TST = total sleep time; UARS = upper airway resistance syndrome; UPPP = uvulopalatopharyngoplasty; Vt = tidal volume

Abnormal airflow through the upper airway during sleep and chronic daytime sleepiness were first recognized as important and related clinical entities in 1965.1 Over the past 33 years, our ability to recognize, treat, and identify the morbidity associated with sleep-related breathing disorders has vastly improved. The boundaries of what is considered to be abnormal respiration during sleep have likewise grown because of more sensitive polysomnographic airflow and driving pressure measurements and a renewed understanding of what constitutes clinically significant EEG arousal. The evolution of our understanding of the upper airway resistance syndrome (UARS) is a prime example of this growth. In this review, we will consider this evolution, as well as our current understanding of the pathophysiology, clinical recognition, and treatment of UARS.

In 1993, the term “upper airway resistance syndrome” was first used by Guilleminault and colleagues2 to describe a subgroup of patients with conditions that were formerly diagnosed as idiopathic hypersomnia or CNS hypersomnia. These terms were used to describe excessive daytime sleepiness (EDS) without a cause that was clearly defined by a nocturnal polysomnogram (PSG) or the multiple sleep latency test (MSLT).3 The patients with UARS displayed repetitive increased upper airway resistance (IUAR) that was defined by increasingly negative inspiratory esophageal pressure (Pes) that occurred concomitant with decreased oronasal airflow.

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in the absence of frank apnea or oxygen desaturation. These periods of IUAR were brief, typically lasting one to three breaths, and resulted in brief EEG arousals (from 2 to 14 s), followed immediately by decreased upper airway resistance.

**Historical Perspective**

UARS may be better understood by reviewing its historical development from the initial inclusion of these sleep-disordered patients as idiopathic hypersomniacs, to their subsequent description as sleepy snorers, and to their current description as UARS patients. In 1982, Guilleminault and colleagues published the results of invasive polysomnography (including Pes measurements in 80% of those tested) on 25 pediatric patients who had been referred for snoring, EDS, and behavioral disturbances and 25 control subjects. Although the two groups did not differ during quiet wakefulness, the PSGs of the patient group showed significantly larger swings in Pes nadirs during sleep when compared with the control patient group showed significantly larger swings in differences during quiet wakefulness, the PSGs of the control subjects. Although the two groups did not differ during quiet wakefulness, the PSGs of the patient group showed significantly larger swings in Pes nadirs during sleep when compared with the control group, respectively: inspiratory Pes nadirs of $-30$ to $-53$ cm H$_2$O vs $-11$ to $-20$ cm H$_2$O. The patient group also demonstrated intermittent tachypnea, arrhythmias, and snoring, although none had significant oxyhemoglobin desaturation or met the criteria for obstructive sleep apnea syndrome (OSAS). These parameters, as well as the MSLT and Wilkinson addition test score results, improved both clinically and statistically in all 25 symptomatic patients following tonsillectomy and/or adenoidectomy. Of note, the oronasal airflow was measured by nasal and buccal thermistors, and these data were only used to calculate the respiratory rate in the analysis.

The following year, Lugaresi et al suggested a continuum of sleep-disordered breathing that ranged from snoring, to OSAS, to severe daytime somnolence and hypopventilation, which was based on polysomnographic measurements that included snoring severity, Pes swings, oxyhemoglobin desaturations, and daytime sleepiness. Snoring was an essential component of each stage along this continuum. The authors provided a case history representing the mildest end of this spectrum (stage 0 or the preclinical stage). The longest period with the lowest Pes nadirs ($-25$ to $-35$ cm H$_2$O) from the PSG of this hypersomnolent patient showed no significant oxyhemoglobin desaturation, suggesting that the patient may have had UARS. Curiously, the authors mention “trivial snoring” in their introductory discussion of this continuum, but even the mildest case reported had heavy snoring and EDS. In a 1990 review article, Stroob and Guilleminault suggested a continuum of severity focusing on partial to complete upper airway obstruction as opposed to snoring. Their data included postpalatopharyngoplasty patients who no longer snored but, despite their diminished palate size, continued to manifest OSAS most likely attributed to retrolingual obstruction. The authors hypothesized that a partial upper airway obstruction may have varying effects depending on age, with patients at the extremes of age having the least ability to compensate. They stated that middle-aged patients may partially compensate by increased work of breathing during sleep, the so-called “athletic snorers.” Unpublished data on chronic heavy snorers with intermittently increased negative Pes leading to arousals and mild sleep disruption were also quoted. The authors postulated that if early treatment were not instituted in these individuals, upper airway obstruction would likely worsen, eventually leading to decompensation with apneas and oxyhemoglobin desaturation.

In 1991 Hoffstein and colleagues examined the relationship of snoring intensity and frequency with sleep architecture. All 15 of their subjects snored, but only 2 had an apnea/hypopnea index (AHI) of $>10$, and their average body mass index (BMI) was only about 25 kg/m$^2$. The researchers found a correlation between the snoring index (the number of snores per hour) and both sleep efficiency and wakefulness time after sleep onset, but they found no significant effect of snoring on sleep architecture. Although their analysis and discussion focused primarily on snoring itself, the tabular data showed that most of the subjects had a significant number of arousals per night (mean, 57; range, 14 to 178), less than half of which were associated with identifiable respiratory events. Therefore, it is possible that many of these subjects had UARS, although no assessment of daytime somnolence was included. That same year, Guilleminault et al published data on 15 heavy snorers without sleep apnea, most of whom had mild daytime somnolence. Most of these subjects had many brief arousals ranging from 2 to 10 s that were likely related to IUAR, as demonstrated by Pes measurements and pneumotachography. Furthermore, the subjects showed a significant improvement in MSLT scores after treatment with nasal continuous positive airway pressure (nCPAP), despite relatively minor pretreatment complaints of daytime sleepiness that were revealed, typically, only after direct questioning. Interestingly, three of the subjects had low arousal indexes (one to three arousals/h) and had no improvement in MSLT scores after nCPAP therapy, implying that not all regular heavy snorers have this syndrome. Conversely, Guilleminault and colleagues in 1992 proposed that not all of the patients with this clinical syndrome snored.

Guilleminault and colleagues presented data that
proved the latter assertion in a 1993 publication. They prospectively evaluated all of the patients referred for EDS to their sleep disorders clinic over a 6-month period, and they found 15 patients who met the strict criteria for UARS based on brief arousals, esophageal manometry, and pneumotachography. Two of the 15 qualifying patients never snored, and 3 of the 15 had only light, intermittent snoring. The researchers concluded that snoring was neither sufficient nor necessary for the diagnosis of UARS. It is interesting that in all 15 patients, cephalometry showed a narrow posterior pharynx at the base of the tongue.

In 1994, Braver and Block9 showed that positional therapy and nasal decongestants had no effect on snoring, but they did find a significant decrease in the AHI of asymptomatic snorers. Woodson10 published a case report of a patient who developed UARS 3 years after uvulopalatopharyngoplasty (UPPP) for OSAS. The author substantiated the diagnosis of UARS with esophageal manometry, showing 89 arousals/h associated with increased negative Pes nadirs. Although anecdotal, this report supports the contiguity of UARS and OSAS on a continuum of severity because it is likely that UPPP only partially ameliorated the patient’s upper airway pathology.

Despite these data, the notion that snoring occupies the mildest end of the pathophysiologic spectrum of sleep-disordered breathing has persisted in the literature. In 1998, for example, Friberg et al11 studied the histologic specimens of palatopharyngeal muscles from 10 asymptomatic nonsnorers, from 10 OSAS patients who snored, and from 11 snorers who did not meet the criteria for OSAS. All 21 of the snorers had various degrees of EDS. The biopsies showed findings that were consistent with a primary neurogenic lesion (including muscle fiber hypertrophy, atrophy, and type grouping), the severity of which varied with the percent of periodic obstructive breathing. The researchers postulated that a progressive, local neurogenic lesion resulting from the trauma of snoring was the cause of these findings. However, they failed to define the extent of the upper airway pathophysiology present in the snoring patients who did not have OSAS. Because EDS was present in this entire group, it is possible that a substantial proportion of these patients had UARS rather than simple snoring; therefore, the speculation that snoring, per se, produces neurogenic lesions is poorly substantiated.

Therefore, given the existing data on the absence of snoring in some patients with UARS and OSAS, the paucity of data supporting a direct association or progression from snoring to UARS or OSAS, and the improvement in snoring but not in OSAS in many cases following palatal surgery, it is reasonable to conclude that snoring is not simply the mild end of a pathophysiologic continuum, but rather a separate entity that frequently coexists with other forms of sleep-disordered breathing.

Pathophysiology of Daytime Symptoms

The key feature used to identify episodes of IUAR in the seminal studies of UARS was the brief arousal that occurred in the absence of oxyhemoglobin desaturation.2,8 Therefore, brief arousals were a logical focus for studying the etiology of associated symptoms. In 1993, Strollo and Sanders12 questioned the relationship between nonapneic snoring and adverse health effects including EDS, but they concluded that there was insufficient evidence to arrive at an answer through epidemiologic means. Previous work had shown a correlation between daytime sleepiness and nocturnal sleep disruption, commonly from arousals or awakenings longer than those typically seen in UARS. Using the MSLT, Philip et al13 were able to demonstrate a significant decrease in mean sleep latency in eight healthy young adults following a night with repetitive brief arousals (averaging 11 s) provoked by auditory stimulation. The mean (± SD) MSLT scores decreased from a baseline of 15 ± 4 to 8.8 ± 5 s (p = 0.009). Additionally, the researchers found higher arousal thresholds during slow-wave sleep (SWS), during rapid eye movement (REM) sleep, and later in the night. Martin and colleagues14 reported similar results using auditory stimulation during sleep. They observed brief arousals following auditory stimuli that were defined as at least a 3-s shift to alpha or theta in the EEG frequency. The investigators were able to demonstrate changes in mood (energetic arousal and hedonic tone mood dimension scores) and cognitive function (Trailmaking B and paced auditory serial addition task 4-s tests) after just one night of brief arousals.

Conversely, Berg et al15 were unable to find a difference in the frequency of brief arousals between symptomatic snorers and asymptomatic nonsnoring control subjects. Significantly more respiratory events were found in the snoring group, mostly in the form of IUAR, although the same percentage of respiratory events resulted in arousals in both groups. The authors questioned whether differences in the arousal duration between the two groups accounted for the difference in symptoms, although this parameter was not examined. They also postulated a possible qualitative difference between respiratory and nonrespiratory arousals. These are provocative and, as yet, unanswered questions.
Regardless, the majority of the available data favors brief arousals as the cause of daytime symptoms in UARS, especially given the lack of oxyhemoglobin desaturation in this syndrome.

The next logical step in understanding the pathogenesis of symptoms in this disorder is to elucidate the mechanisms(s) leading to arousal. Stoohs and Guilleminault,\(^1\) hypothized in 1991 that the arousals in UARS were, at least partly, due to flow limitation and the mechanical changes reflected by increased negative Pes. In fact, Gleeson et al\(^2\) had previously demonstrated a close correlation between arousal (defined as increased electromyogram [EMG] activity and a shift to alpha in the EEG) and the magnitude of Pes nadir just prior to arousal in a group of normal male subjects. There was no lower limit imposed on the duration of these arousals; therefore, brief arousals similar to those seen in UARS were included in the analysis. The researchers demonstrated that arousal occurred at approximately the same Pes nadir (about \(-15\) cm H\(_2\)O), regardless of the primary stimulus used to induce the arousal, including increased external resistive load, hypoxia, and hypercapnea. Furthermore, the level of hypoxia or hypercapnea correlated poorly between different arousals resulting from the manipulation of the other stimuli.

Berry and Light\(^3\) reported similar findings after occluding the inspiratory limb of a tight-fitting face mask in six young normal male subjects during sleep; arousal occurred at similar Pes nadirs in all subjects under both normoxic and hyperoxic conditions. Hyperoxic airway occlusions resulted in a longer time to arousal after occlusion without a significant change in the respiratory rate, implying a slower change in the Pes nadir with each inspiration. An increased rate of negative inspiratory pressure generation in the breaths just preceding arousal was also found. The authors concluded that the Pes nadir threshold for arousal was constant, despite alterations in its rate of change induced by hyperoxia.

These investigations support the belief that the level of negative intrathoracic pressure generated (as reflected by the Pes nadir) is the primary physiologic change inducing arousal. Other factors (including changes in oxygenation, hypercapnea, time since the previous awakening, total sleep time [TST], and temporal proximity to REM) probably modify this response secondarily.\(^4\) Therefore, these secondary factors may account for the variations in the arousal threshold seen between different individuals, and for changes in the arousal threshold seen in the same individual at different times during sleep. The mechanism of arousal would be further illuminated by the precise identification of the origin and afferent pathways involved in the detection of this threshold.

The mechanoreceptors in the respiratory muscles, chest wall, and lower and upper airways have been suggested as potential loci for the generation of afferent CNS input leading to arousal. The data in this area, much of it from animal studies, have been conflicting and inconclusive.\(^5\) The results from two recent investigations deserve mention, however. Basner and colleagues\(^6\) noted an increased time to arousal following external airway occlusion in subjects wearing full face masks after their nasal and oropharyngeal mucosa had been anesthetized with 4% lidocaine. Similarly, Berry et al\(^7\) found decreased genioglossus activity during obstructive apneas, increased apnea duration, and greater Pes nadirs prior to apnea termination after anesthesia of the upper airway with 4% lidocaine.

Given the currently available information, the most plausible explanation for daytime somnolence in UARS is that sleep disruption from multiple brief arousals occurs as a result of increasingly negative intrathoracic and airway pressure, with the response most likely mediated by mechanoreceptors in the upper airway. Obviously, much more work is needed in this area before any definite conclusions can be reached.

**Diagnosis**

UARS research and even the clinical diagnosis of this syndrome are plagued by the lack of standardization in nomenclature, criteria, and measurement techniques, as is the entire field of sleep-disordered breathing. It can be said, however, that most of the published studies do involve patients who do not meet the standard criteria for OSAS, who do not show significant oxyhemoglobin desaturation during sleep, and who do have EDS, even if mild.

**Clinical Definitions**

In 1991, Guilleminault et al\(^8\) used Pes measurements and pneumotachographic airflow assessment to identify repetitive IUAR leading to brief arousals (a 2- to 10-s shift to alpha or fast theta in EEG frequency) in regular heavy snorers with mild daytime sleepiness. The scoring of an event began with the identification of an arousal. If the Pes nadir of one of the two breaths preceding the arousal had the greatest magnitude since the last arousal (the snoring period) and was accompanied by a simultaneous decrease in pneumotachographic airflow, an IUAR event was scored (Fig 1). Additional requirements included a less negative Pes nadir and increased airflow during and after two breaths after the arousal, and the absence of another identifiable cause of arousal. Pes nadirs ranging from \(-29\) to \(-68\) cm H\(_2\)O were
seen during these events. Permutations on this basic method have appeared since that time.

One year later, for example, the Stanford group published the results of a study\(^3\) in which patients were selected who did not meet criteria for OSAS and who demonstrated snoring during \(>10\%\) of the TST. These patients displayed Pes nadirs that were 1 SD more negative than the mean Pes nadir measured during 30 min of quiet supine wakefulness. The most negative baseline Pes value was \(-7\text{ cm H}_2\text{O}\). An arousal (a 3- to 5-s shift to alpha in EEG frequency) was scored as related to IUAR if the Pes nadir preceding it was more negative than what was seen during baseline wakefulness, and if it was the most negative Pes nadir of the snoring period. A lesser Pes nadir with the breath following the arousal was also required. Of note, oronasal thermistors were used to detect airflow during this study; airflow was not used in the definition of IUAR events. The Stanford group used an amalgam of these previous criteria in their 1993 study.\(^2\) The patients had to demonstrate more than 10 transient EEG arousals/h of sleep (a 3- to 15-s shift to alpha in EEG frequency). As before, the breath preceding the arousal had to be associated with a Pes nadir more negative than 1 SD below the mean Pes nadir measured during quiet supine wakefulness. The Pes nadir had to be the most negative of the snoring period, and it had to decrease in magnitude with the breath immediately following the arousal. Polysomnography with a face mask and pneumotachography was performed on the following night. Segments of the tracings were screened randomly to ensure a decreased calculated tidal volume (\(\text{VT}\)) in the breath just preceding the arousal. The authors reported a mean (\(\pm\) SD) \(\text{VT}\) reduction of \(22 \pm 6\%\) during that breath. In addition, a declining \(\text{VT}\) was noted for only one to three breaths preceding the arousal, rather than a prolonged gradual decline. Based on the results seen in previous sleep-fragmentation subjects following nCPAP therapy, a cutoff of \(>10\) brief arousals/h was used to define the presence of the syndrome. The patients with improved daytime symptoms all had arousal indexes of \(<10\)/h during nCPAP treatment.

In 1997, Berg et al\(^{15}\) defined the syndrome in a very different manner. IUAR events were scored

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**Figure 1.** Two consecutive epochs from a PSG of a patient with UARS. An esophageal pressure transducer was used to measure the Pes, and a full-face mask connected to a pneumotachograph and differential pressure transducer was used to measure the inspiratory airflow. Three IUAR events are defined as progressively negative Pes with concomitantly decreasing airflow until Pes nadirs are reached, followed directly by EEG arousals, less negative Pes, and increased airflow. Note that oxyhemoglobin saturation (\(\text{O}_2\) Sat, bottom tracing) does not change significantly. The arrowheads indicate EEG arousals, the closed circles indicate an abrupt increase in airflow, and the arrows indicate the Pes nadirs. Chin = submental EMG; LOC = left oculomyogram; ROC = right oculomyogram; SCM = sternocleidomastoid; INT = intercostal muscle EMG; mic = microphone; Abd = abdominal plethysmography.
when the negative Pes amplitude increased by 20% compared to baseline values for at least 15 s, accompanied by a decrease in airflow of ≤ 50% as measured by a face mask/pneumotachograph. The mean Pes nadir was −15 cm H2O. Most of these events were not accompanied by an oxyhemoglobin desaturation. If the airflow decreased by > 50% for ≥ 10 s accompanied by an oxyhemoglobin desaturation of > 4%, the event was scored as a hypopnea. Arousals were not used to locate or define IUAR events because they were the primary variable being examined. More recently, Lofaso et al22 looked at the BP response to transient EEG arousals in nonapneic/nonhypopneic snorers. The subjects had an AHI of < 5, but had > 10 brief arousals/h of sleep by American Sleep Disorders Association (ASDA) criteria.23 The subjects had Epworth sleepiness scale (ESS) scores of > 10 and had > 10 respiratory events/h. A respiratory event was defined as a flow-limited (flattened) airflow tracing with a concomitant increased Pes nadir, both of which normalized after the event. Essentially, these subjects had UARS, although this term was never specifically used. In a study of the surgical management of UARS, more simplistic criteria were used that consisted of a respiratory disturbance index (RDI) of > 5 and Pes nadirs of < 10 cm H2O during PSG in patients with EDS.24 Although such criteria seem intuitively reasonable and do not contradict data from earlier, more rigorous studies defining this syndrome, it is not clear that these patient populations are equivalent.

**Measurement Techniques**

In their 1991 research on adult somnolent snorers, Guilleminault and colleagues8 used a balloon (5-mm long and 3.2 cm in circumference) that was attached to a polyethylene catheter connected to a differential pressure transducer to measure Pes. The balloon was positioned in the midesophagus by first advancing it into the stomach, as indicated by positive pressure during inspiration, and then withdrawing it about 10 cm. The result was a catheter insertion distance of 36 to 40 cm, measured at the nares. That same year, Chartrand et al25 used a 5F catheter-tip pressure transducer for Pes measurement. In 1997, Berg and colleagues15 used a microchip sensor catheter in a study including UARS patients. A tight-fitting full-face continuous positive airway pressure (CPAP) mask attached to a pneumotachograph was used to measure airflow. The airway resistance was calculated by computer software after these data were digitized.

Chervin and Aldrich26 used a water-filled 6F pediatric nasogastric tube connected to a pressure transducer in the largest study to examine the effect of esophageal manometry on sleep quality and architecture. They retrospectively found small but statistically significant decreases in total recording time, TST, sleep efficiency, and increased REM latency in 155 patients with Pes monitoring, compared with 155 control subjects matched for age, gender, AHI, and minimum oxyhemoglobin saturation. A decrease in stage 2 and REM sleep and an increase in SWS were also reported in Pes patients. The authors26 concluded that these small changes, though statistically significant, were unlikely to be clinically important and should not deter the use of this potentially important device. Basner and colleagues20 found that upper airway anesthesia with 4% lidocaine, commonly applied before the insertion of Pes-monitoring devices, increased the time to arousal following the occlusion of the face mask, as previously mentioned. This suggests that the placement of such devices may alter the threshold for arousal during flow-limited breathing, resulting in a higher threshold for the initial 1 to 2 h of polysomnography until the upper airway anesthesia abates.

Montserrat and colleagues27 showed that the square root of the signal from a standard nasal cannula attached to a sensitive differential pressure transducer was comparable to the tracing from a pneumotachograph, obviating the need for an obstructive, tight-fitting face mask. Hosselet et al28 showed similar results. An earlier publication29 described the increased sensitivity of this device when compared to a nasal thermistor in 11 OSAS and 9 UARS patients; even liberal thermistor criteria, defined as any change in the appearance of the tracing, detected only 75% of the events in the OSAS patients and 38.6% of the events in the UARS patients that had been detected using a nasal cannula. A flow-limited (flattened) pattern was included in the scoring of events by nasal cannula. This particular investigation, however, did not include an assessment of accuracy by comparison with a face mask/pneumotachograph. The authors reported that pressure swings of 0.5 cm H2O were detected by nasal cannula during quiet breathing. The pressure transducer used in this type of system should be able to detect differential pressures in the range of ±5 cm H2O, and a direct current or an alternating current amplifier with a time constant of > 5 s is necessary to correctly identify the flow limitation.

Hosselet and colleagues28 also reported the use of the nasal cannula system in a more advanced clinical application. They studied 10 symptomatic and 4 asymptomatic subjects with an esophageal or supraglottic pressure catheter and a nasal cannula/differential pressure transducer. The symptomatic subjects included one snorer, five OSAS patients, and
four UARS patients. A statistically significant correlation existed between the calculated upper airway resistance and the shape of the inspiratory flow tracing; high resistance correlated with the flattening of the inspiratory flow tracing, interpreted as flow limitation. The symptomatic group showed a significantly greater percentage of flow-limited breaths. The investigators did not use the square root of the inspiratory flow tracing, interpreted as flow limitation. The symptomatic group showed a significant correlation with the calculated upper airway resistance and the shape of the inspiratory flow tracing; high resistance correlated with the flattening of the inspiratory flow tracing, interpreted as flow limitation. The symptomatic group showed a significantly greater percentage of flow-limited breaths.

Therefore, caution must be used in interpreting either quantitative flow data or driving pressure Pes data alone. Because they rely on changes in temperature as a surrogate of airflow, thermistors or thermocouples correlate poorly with quantitative flow measurements, resulting in an erroneous assessment of IUAR.

CLINICAL FEATURES

Signs and Symptoms

By definition, UARS patients have daytime sleepiness or fatigue. The original 1982 description concerned children and reported frequent snoring, restlessness during sleep, and sweating. Other characteristics more specific to children included a change in appetite, poor performance in school, and problems with behavior. Initial studies in adults included only men; it was later recognized that the syndrome was also present in women, with a roughly equal gender distribution. Contrary to what is seen in OSAS patients, UARS patients are typically nonobese, with a mean BMI of \( \leq 25 \) kg/m\(^2\). They are also frequently younger than OSAS patients; the 1993 study showed a mean age of 37.5 years. Additionally, all 15 subjects in this investigation had mildly abnormal upper airway anatomy (most commonly retrolingual narrowing) as determined by cephalometry. In the same study, it was also recognized that not all UARS patients snored, as was previously thought; only 10 of 15 patients were regular snorers, and 2 of 15 patients never snored. Furthermore, snoring may be absent after palatal surgery, even though UARS may be present. Low soft palates, long uvulas, increased overbites, and high, narrow hard palates have also been described in this syndrome; these features in combination with EDS, hypertension, and snoring may render these patients clinically indistinguishable from OSAS patients in the absence of PSG.

POLYSOMNOGRAPHY

Multiple brief EEG arousals occur during polysomnography because of respiratory events that may be undetectable by standard oronasal thermistors or abdominal and thoracic strain gauges. Therefore, an increased arousal index in a patient with idiopathic hypersomnia should raise suspicion of UARS. The patients typically demonstrate significantly decreased SWS, 1.2 ± 2% of TST in one study; REM sleep time seems to be less affected. The presence of these features only suggests UARS if IUAR is not clearly demonstrated.

SURROGATE POLYSOMNOGRAPHIC MARKERS

The hallmark of IUAR in UARS is an increase in the driving pressure across a partially obstructed upper airway with a constant or decreased airflow. Direct confirmation of this condition requires invasive monitoring, as discussed. Therefore, since the initial discovery of UARS, investigators have tried to identify noninvasive, surrogate polysomnographic markers of IUAR events (Fig 2). Guilleminault and colleagues mentioned brief EEG arousals occurring without identifiable cause (eg, a change in position or other large body movement), a change in the snoring pattern, or a change in breathing pattern (the amplitude or breath duration by impedance plethysmography as compared to a previously established pattern). In a later publication, they cited > 10 alpha EEG arousals/h without another cause as a marker of this syndrome, but warned that the “patient friendly” approach of identifying increasing snoring intensity followed by EEG arousals would produce a significant number of false-negatives. Furthermore, only moderate interobserver agreement was found in a recent study of variability in scoring arousals (\( k = 0.47 \)). The 14 scorers who participated in this study demonstrated the best agreement for arousals during SWS, the stage most severely curtailed in patients with untreated UARS. Therefore, the scoring criteria that rely heavily on arousals without other concomitant markers may lack reproducibility. In addition, a significant number of brief arousals were demonstrated in a “nor-
mal” population by Mathur and Douglas34 in 1995. They studied 55 patients from a family practice list having a single overnight PSG and they found a mean arousal index of 21 (95% confidence interval 7.0, 56.0) by ASDA criteria.23 Excluding patients with snoring, occasional daytime sleepiness, or witnessed apneas did not change the mean frequency and increased the 95% confidence intervals. Woodson10 also reported a pattern of crescendo snoring followed by transient EEG arousals in the absence of oxyhemoglobin desaturation as highly suggestive of UARS. He listed other criteria though, including nonobesity and a small retroglottal posterior airspace in somnolent patients. Improved daytime somnolence as well as increased SWS following treatment with nCPAP has also been cited in multiple publications.2,8,10,24

More recently, Lofaso and colleagues22 proposed beat-to-beat BP evaluation by infrared plethysmography as a more sensitive marker of IUAR than brief arousals. They studied six men with ESS scores of > 10, AHIs of < 5, and brief arousal indexes of > 10/h of sleep. The subjects were studied with Pes monitoring as well as with airflow measurement with a tight-fitting face mask and pneumotachograph to assess IUAR. The subjects demonstrated elevations in BP following respiratory events that correlated in magnitude with the intensity and duration of EEG arousal. However, the researchers also observed small BP elevations after IUAR events that elicited no detectable cortical arousal, and they postulated that increased subcortical brainstem activity was a cause of autonomic activation leading to these small hemodynamic changes. Of note, EEG monitoring during polysomnography included only two central derivations. Carley et al35 reported similar results when they found increases in respiratory rate and VT after acoustic stimulation, regardless of whether detectable EEG arousals were seen in the central and occipital derivations. The authors concluded that a generalized arousal response is not a necessary precedent to a respiratory response. They hypothesized that regional or localized cortical responses or even subcortical responses may have gone undetected during these events. Therefore, evidence exists that standard polysomnographic EEG leads may miss subtle arousals and that criteria based on these devices may not attain the highest possible sensitivity.

Ruhle and colleagues36 suggested in a recent review that upper airway impedance measurements using the forced oscillation technique may be useful as a surrogate of Pes in the diagnosis of UARS. With this technique, an airflow of 2 L/min is applied to a conventional nCPAP mask at an oscillatory frequency of 20 Hz. The researchers studied 25 nonobese patients with EDS and a mean RDI of 3.4. Although the majority of arousals could not be explained on the basis of standard polysomnographic measurements, this technique showed IUAR in over
half of these unexplained events.\textsuperscript{37} These authors also suggested that the pulse transit time (the time between the ECG R wave and the fingertip pulse shock wave) correlated with subtle changes in both the Pes and the arousals. They also discussed changes in BP as a marker of IUAR because more negative intrathoracic pressure would decrease BP and arousal would increase BP.\textsuperscript{36}

With the inclusion of frontal leads, O'Malley and colleagues\textsuperscript{38} demonstrated an improved detection of EEG arousals in five UARS patients and five CPAP-treated OSAS patients. Using 1992 ASDA criteria,\textsuperscript{23} brief arousals in the central and occipital leads were noted to accompany 73% of the respiratory events defined as an airflow reduction of $> 50\%$ for $> 10$ s or a flattening of the inspiratory flow tracing (suggesting flow limitation). Of the remaining respiratory events, 22% were associated with arousal seen only in the frontal leads, suggesting that unexplained daytime symptoms in UARS or treated OSAS may be accounted for by the detection of previously unexplained arousals.

Although patterns of snoring, arousals, airflow by thermistry, and abdominal/thoracic plethysmography from conventional polysomnography may, at times, suggest the diagnosis of UARS, they are by no means definitive or confirmatory measurements. Some of the newer, more technically advanced measurement techniques reviewed hold promise as reliable, non-invasive modalities for UARS diagnosis, but testing in larger populations is required to compare these advancements with standard diagnostic methods.

**Sequelae and Associated Disorders**

**Daytime Somnolence**

By definition, daytime somnolence is a component of UARS and may be as severe as that found in OSAS.\textsuperscript{39} Guilleminault et al\textsuperscript{4} first demonstrated significant daytime somnolence by the MSLT and Wilkinson addition test scores, as well as behavioral abnormalities from UARS in a population of nonapneic/nonhypopneic snorers (an AHI of $< 5$) with ESS scores of $> 10$ and multiple episodes of IUAR. These subjects, in essence, had UARS. Elevations in systolic and diastolic BP were found following arousals with IUAR. When the events were stratified by the length of arousal, the authors found a correlation between the arousal length and the magnitude of BP elevation. Even IUAR events with no detectable arousal showed a smaller but significant rise in BP. The authors concluded that undetectable arousals were likely occurring during these events and that it was the autonomic response to arousal that led to BP increases, rather than changes in intrathoracic pressure or ventricular interdependence.

Guilleminault et al\textsuperscript{41} reported similar results in 110 patients known to have UARS. In these patients, systolic and diastolic BP increased during the breaths associated with the arousal when compared to the BP measures that directly preceded the arousal. The systolic and diastolic BP also increased significantly during segments of labored breathing without the arousal Pes nadir (more negative than $- 30$ cm H$_2$O) in a subset of seven patients. Echocardiography demonstrated a leftward shift of the interventricular septum during segments with the most negative Pes nadirs (more negative than $- 35$ cm H$_2$O). Pulsus paradoxus was also demonstrated during these segments. Also shown were significant decreases in the average systolic and diastolic daytime BP as well as the average nocturnal diastolic BP in six patients with borderline hypertension who were treated with
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Silverberg and Oksenberg concluded, in an extensive review of the literature regarding hypertension and sleep-disordered breathing, that most cases of “essential hypertension” are caused by IUAR during sleep from either OSAS or UARS. They quoted a 30% to 40% incidence of OSAS and a 30% to 75% incidence of nonapneic snoring in hypertensive patients, gleaned from data published within the previous 5 to 6 years. They also hypothesized that the epidemiologic, physiologic, hereditary, clinical, and laboratory similarities between the populations with essential hypertension and the populations with sleep-disordered breathing were the result of a causal relationship, and that treatment of sleep-disordered breathing may be central to the management of essential hypertension. This is an interesting, but not well-substantiated, proposal.

TREATMENT

CPAP, surgery, oral appliances, and weight loss are all viable treatment modalities for UARS, and they have received more recent attention in the literature. Unfortunately, the data regarding compliance, efficacy, safety, or a combination of these factors are lacking in many cases.

CPAP

In 1991, Guilleminault et al. showed that in a group of 15 regular heavy snorers with UARS the institution of nCPAP resulted in significantly fewer arousals and improved MSLT scores. The CPAP values ranged from 3 to 8 cm H2O with a mean of 5.8 cm H2O. Interestingly, none of these patients wanted to continue nCPAP beyond the study protocol, although daytime somnolence was not their primary complaint (the mean initial MSLT score was 11.29 min); therefore, these patients likely represented the mild end of the UARS clinical spectrum. In 1993, the same group of researchers studied more somnolent UARS patients. Fifteen patients with a mean MSLT score of 5.3 min were restudied after 1 month of nCPAP therapy, at which time none of them reported EDS. The mean MSLT score increased to 13.5 min, the mean percent of SWS increased from 1.2 to 9.7, and the mean transient EEG arousals/h decreased from 31 to 7. Strollo and Sanders concluded in a 1993 review that the efficacy of CPAP in UARS was not so much the question as was compliance, because of a lack of sufficient data. They recommended offering titration of nCPAP or bilevel ventilation after PSG with Pes if necessary, and to continue its use if sleep fragmentation and daytime performance improved. Furthermore, Guilleminault and colleagues demonstrated the efficacy of nCPAP in treating hypertension, as discussed. The titration of nCPAP was performed in the supine position so that the peak end-inspiratory Pes was never more negative than −7 cm H2O.

Two more recent studies have examined nCPAP compliance in nonapneic snorers. Krieger and colleagues reported an initial acceptance rate of only 34% in 98 patients with an AHI of ≤ 15 (the so-called “nonapneic snorers”), but the compliance in acceptors was > 60% at 3 years. Furthermore, the mean (± SD) rate of use was 5.6 ± 1.4 h/day. Although the initial acceptance was much lower than that seen in patients with an AHI of > 15, the nonapneic snorers were offered nCPAP as only one of several therapeutic modalities. Unfortunately, this group was not well characterized and likely included patients with mild OSA, UARS, and simple snoring; no Pes or quantitative airflow data appear to have been collected. Rauscher and colleagues also studied nCPAP in nonapneic snorers, defined as patients with EDS and an AHI of < 5. These patients had a mean (± SD) 3- to 15-s EEG arousal index of 20 ± 10/h. Therefore, this was a more homogeneous population, and many of them likely had UARS, although, again, no invasive monitoring was used. Only 19% of the patients (n = 11) accepted nCPAP therapy, with a mean (± SD) daily use time at 6 months of 2.8 ± 1.5 h. Surprisingly, 73% of the acceptors reported decreased sleepiness with therapy. Again, the patients were offered the option of surgical therapy, and 11 chose UPPP. Although the acceptors had slightly more apneas and hypopneas than the refusers, they did not differ in arousal index, initial EDS, BMI, age, or percent of SWS. Thus, the authors were unable to determine any reliable criteria that could predict CPAP acceptance or compliance.

The available data support nCPAP as an efficacious form of therapy in UARS, although compliance is much less certain. Further research is needed to resolve the issue of compliance in patients having cases of this syndrome that are clearly and unquestionably documented.

Surgery

In 1996, Pepin and colleagues reviewed surgical therapy for snoring, UARS, and OSAS. They noted, in general, that the studies included small patient...
numbers and were of a descriptive rather than a comparative nature. They found no randomized studies involving UARS patients. They also identified poorly defined entry criteria and population characteristics, as well as a lack of clearly defined procedures for surgery, anesthesia, perioperative management, and endpoints. For example, they described a study of UPPP in nonapneic snorers wherein questionnaires and nocturnal oximetry were the only assessments performed. They cited two studies of the severe complications of UPPP; one study demonstrated an approximate 10% incidence of upper airway obstruction, and another study showed a 15% incidence of significant hemorrhage.

Krespi et al published data on the efficacy of laser-assisted uvulopalatoplasty (LAUP) in snoring, OSAS, and UARS. Forty-two of the 423 patients who underwent the procedure were reported to have UARS, although no specific diagnostic criteria were cited. In a collective group of UARS and mild OSAS patients, significant improvements were reported in sleep quality (28%) and daytime somnolence (24%); slight improvements were reported in sleep quality (46%) and daytime somnolence (49%). These factors were assessed by questionnaire. Statistically significant improvements in sleep maintenance, fatigueability, daytime alertness, irritability, restlessness, sleep-time nasal obstruction, and nocturnal choking and gasping were also reported in UARS and OSAS. Unfortunately, no comparable pre- and postoperative polysomnographic data were presented for the UARS group and the mild OSAS group, nor were any data on UARS patients alone presented.

Newman and colleagues published a prospective evaluation of surgical intervention in patients presenting over a 1-year period with snoring and EDS; only patients with Pes nadirs < -10 cm H2O and RDIs of < 5 were included. All nine patients reported for surgical interventions, including septoplasty with turbinate reduction, LAUP, UPPP, mandibular osteotomy with tongue advancement, and hyoid myotomy with suspension. The mean (± SD) pretreatment Pes nadir was -36.7 ± 16.2 cm H2O, but only two patients underwent postoperative PSG with Pes measurements. After treatment, their respective Pes nadirs had changed from -52 to -40 cm H2O and from -30 to -17 cm H2O, which are still in ranges that are lower than the generally accepted normal range of -10 cm H2O. The authors also reported an impressive change in the mean (± SD) ESS score from 12 ± 6.6 to 3.4 ± 1.9, although three of the nine patients had initial scores within the normal range of < 7. These authors did use more appropriate and specific inclusion criteria for UARS, but they studied a small number of patients and restudied only a small proportion postoperatively. This same group of researchers later published a retrospective review of the efficacy of surgical intervention in sleep-disordered breathing. Ninety-five of 299 patients in an outpatient population referred to a surgical clinic were considered to be surgical candidates, including 11 patients with UARS who underwent LAUP. The initial evaluations showed Pes nadirs that were more negative than -20 mm Hg, along with RDIs of < 10 and ESS scores of ≥ 7. Of the UARS patients, 81.8% reported improved EDS, with the mean (± SD) ESS score changing from 13.5 ± 4.4 to 8 ± 2.5. The authors provided a thorough description of their clinical evaluation and criteria as well as the surgical procedures, but they did not include any postoperative PSG data. Again, their patient numbers were small.

Most recently, Powell et al reported the results of palatal tissue reduction by radiofrequency ablation (somnoplasty). A 22-gauge radiofrequency needle electrode was used to apply low- to mid-level energy to the submucosa of the upper airway under local anesthesia. The 22 study subjects had snoring and mild sleep-disordered breathing. Fourteen were UARS patients, as documented by the Pes measurements. Two to three days after the procedure, the patients reported minimal pain, problems with speech and swallowing, and a mild worsening of oxyhemoglobin saturation and RDI, all of which resolved at 10 to 12 weeks. For the entire group, there was an improvement in the sleep efficiency index, the ESS score, the Pes nadir, and subjective snoring. Changes in these variables, however, were not reported for patients with UARS or in this subgroup as a whole, except for two patients with respective Pes nadirs of -19 cm H2O and -13 cm H2O, both of whom had Pes nadirs of -5 cm H2O postoperatively. Therefore, specific conclusions about the efficacy of this procedure in UARS are difficult to draw, although it does appear relatively safe. More detailed data from larger populations with UARS are needed before this procedure can be recommended as a primary therapy for this condition.

Oral Appliances

Oral appliances that advance the mandible and tongue are already used to treat OSAS. These devices hold promise for treating UARS because of good patient acceptance and low morbidity, but, unfortunately, there are almost no data available to support their use. Loube et al reported a well-documented case of a 40-year-old man with UARS who was successfully treated using an oral appliance. The patient had declined CPAP at 9 cm H2O after a 2-month trial because of subjective increased sleep.
fragmentation. A repeat PSG following 2 weeks of therapy with a mandibular advancement device showed a decreased arousal index from 53 to 10/h, a decreased IUAR index from 44 to 2 events/h, an improved mean (± SD) Pes nadir from −5 ± 2 to −5 ± 3 cm H2O, and improved sleep efficiency. The patient’s ESS score decreased from 17 to 6, and he denied any side effects or complications. If an extensive series or a similarly well-documented prospective trial can show a reasonable percentage of patients with this type of result, this may become a very important treatment modality for UARS.

Other Therapies

Levy et al. were unable to find any data on the efficacy of weight loss for UARS in their 1996 review of the management of snoring, UARS, and moderate OSAS. Braver and Block studied the efficacy of oxymetazoline nasal spray and positional therapy in asymptomatic snorers. Although they found no effect on snoring, they did find a decrease in the AHI with combined therapy, especially in patients with lower pretreatment AHIs. The similarity of these patients to the patients studied by Guilleminault and colleagues in 1991 suggests the possibility of this type of conservative therapy for UARS patients who are not amenable to other therapies.

Future Directions

Given the growing interest in UARS, it is clear that much more work is needed to further our understanding of several aspects of this disorder. Epidemiologic investigation is needed to first understand the magnitude of this problem. Standardized criteria for the diagnosis of UARS are still lacking, hampering the epidemiologic investigation. The wide adoption of standardized criteria likely awaits the validation of a reliable, noninvasive means of making this diagnosis that will be practical and acceptable for both clinicians and patients. Finally, the treatment of this condition seems to be the area most in need of further study (using clearly defined criteria and endpoints), so that a rational comparative evaluation of available modalities will be possible.

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