REVIEW ARTICLE

Upper Airway Resistance Syndrome (UARS)

Rayleigh Ping-Ying Chiang, Christian Guilleminault
Stanford University Sleep Disorders Program

Indian J Sleep Med 2006; 1.4, 175-182

Introduction

The field of sleep medicine has undergone an evolution since the first description of obstructive sleep apnea in the Pickwikian syndrome in the recent two decades [1, 2]. After better establishment of the clinical pictures of obstructive sleep apnea-hypopnea syndrome (OSAHS), there is still a group of patients left undiagnosed and untreated even if severely impaired. The term ***upper airway resistance syndrome (UARS)*** was utilized to describe such group of patients who didn't meet the diagnostic criteria of OSAHS. In the original literature which identified UARS, this group of patients presented daytime sleepiness subjectively and objectively in Multiple Sleep Latency Test (MSLT). Fragmented sleep was revealed without an apnea-hypopnea index (AHI, counts of events of apnea and hypopnea per hour of sleep) > 5 when using thermal devices for airflow measurement in polysomnographic study [3]. However, there have been some controversies about UARS. Some authors think UARS as one of the entities in the spectrum of sleep-disordered breathing (SDB) which includes simple snoring, UARS, obstructive hypopnea, obstructive sleep apnea (OSA), and hypoventilation syndrome. An investigation of upper airway collapsibility during sleep showed that changes in pharyngeal properties of UARS subjects are between those of OSA patients and normal controls [4]. Even more, some arguments about the existence of UARS was mentioned [5, 6]. In the latest edition of "International Classification of Sleep Disorders", UARS is subsumed under the entity of "obstructive sleep apnea, adult" because the pathophysiology of both terms do not differ significantly[7]. But this may not be correct: clinical presentation is different and the fact that SaO2 drops are not present means that autonomic nervous system will be stimulated differently, with more vagal stimulation in UARS and more sympathetic stimulation in OSAS, with very different secondary consequences.

As we have learned, OSAHS is defined as patients with symptoms of daytime sleepiness and obstructive apneas on polysomnography (PSG).[8]. Obesity is common in OSAHS patients. In recent researches, however, the clinical presentations of UARS are similar to functional somatic syndrome, with many somatic, psychosomatic, or psychiatric conditions, including fibromyalgia, chronic pain, headaches, parasomnias, attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD), bruxism, as well as chronic insomnia. And most patients with UARS are slim or normal in body habitus, with some orthostatic symptoms like cold hands and/or feet, fainting, dizziness [9-11] . This could explain the reason why many of the patients with UARS were seen by general practioneers and psychiatrists[12]. We have also learned that OSAHS is associated with local sensory impairment which is responsible for the occurrence of the hypopnea and/or apneas. But in UARS, there is intact local neurological system with the ability to respond to the changes in upper airway dimensions and resistance to airflow[13, 14]. By measuring esophageal pressure with esophageal catheter[15] and the use of nasal cannula/pressure transducer[16], we could identify subtle changes in physiology during sleep. Nowadays, we have a better understanding about the UARS both in clinical presentations and pathophysiology that are quite different from those of OSAHS and will be focused on in this chapter.

Address for correspondence:

Christian Guilleminault, MD, Biol.D
Stanford University Sleep Disorders Clinic
401 Quarry Road, #3301, Stanford, CA 94305
Telephone: 650-723-6601, Fax: 650-725-8910
E-mail: cguil@stanford.edu

Pathophysiology – Comparison between OSAS and UARS

Based on pathologic, neurophysiologic, and clinical researches, the concept of presence of local neuropathies in pharynges of OSAS patients was proposed by Swedish investigators. The histological changes associated with OSAHS was first described by Edstrom et. al.[17]. In this study, biopsies of palatopharyngeal muscle from 8 patients of OSAHS showed muscular changes suggesting a neurogenic alteration which might be either a primary phenomenon or secondary to the repetitive trauma and prolonged stretching of the pharyngeal structures during apneac episodes. Their data are in accordance with those shown by Woodson et. al.[18] and Series et. al. [19]. Friberg et. al. carried out histological and electron microscopic investigations of the palatopharyngeal muscles in OSAHS patients [20]. In this study, progressive lesions consistent with a polyneuropathy was shown. The degree of the abnormal changes correlated with the severity of obstructive events. Further more, the same group used immunohistochemical staining techniques to demonstrate an increase of sensory nerve terminals density in the mucosa of soft palate, indicating afferent nerve lesions [21]. In another research, Friberg [22] compared the neurophysiologic and histologic findings of OSAS patients with those of the subjects with "vibration-induced white finger syndrome". Long-term application of low frequency handheld vibrating tools resulted in decreased sensitivity to vibration and temperature stimuli, hypertrophy of myocytes, and obvious loss of nerve fibers and myelin sheaths indicating a demyelinating neuropathy in the peripheral nerves. Heavy snoring produces similar low frequency vibration on the soft palate. The author hypothesized that vibration trauma may contribute to the development of similar lesions in oropharynges and possibly larynges.

A recent investigation of the upper airways sensory threshold in OSAS patients was conducted by Nguyen et. al. [23]. Endoscopic sensory testing technique with an air-pulse stimulator was used in OSA and control groups. The results showed no difference in sensory thresholds between OSA patients and matched controls when air-pulse was applied on the lips; however, there was a significant impairment in sensory detection threshold for OSA versus control subjects in oropharynges, velopharynges and larynges. The threshold stimulus intensity for the laryngeal adductor reflex was also significantly higher for OSA subjects. In addition, for OSA patients with abnormal laryngeal sensation, there were significant correlations between laryngeal sensory values and the severity of apnea. They concluded that mucosal sensory dysfunction is located over multiple sites of upper airway in OSA patients.

By measuring the 2-point-dicrimination responses in the soft palate, one study compared the responses between age and gender matched OSAS, UARS and normal controls with 20 subjects per group. The results showed similar responses between UARS and controls groups, while OSAS group had abnormal responses [14]. The second study followed 47 OSAS patients with nasal CPAP for 5 years and showed that 2-point discrimination response was still impaired at the end of adequate treatment [24]. It is recognized that interruption of the causative processes of such lesions does not lead the upper airway neuropathies to return to normal, therefore undesired sequelae are presented. The well-documented local neurologic impairments in upper airway can explain the development of hypopneas and apneas of OSAS patients.

In terms of the afferent processing pathway, differences between OSAS and normal subjects were hypothesized. Evoked responses studies were performed in OSAS patients. Davenport et. al. showed respiratory related evoked potentials (RREP) could be reliably elicited by stimuli relating to increased inspiratory effort [25]. Afifi et. al. performed a simultaneous investigation of auditory evoked responses and RREP in OSAS and controls during wakefulness and sleep. They demonstrated abnormal evoked responses to inspiratory occlusion stimuli during NREM sleep in OSAS patients only, but not in matched normal controls. However, with auditory stimuli, the same OSAS subjects showed normal responses of evoked potential. These findings confirm a blunted cortical response to inspiratory occlusions that is specific to sleep. The absence of significant group differences in the responses to auditory stimuli highlighted that the sleep-related differences seen in OSAS patients are specific to the processing of inspiratory effort related stimuli [26]. The above studies suggest that specific abnormal cortical responses of sensory input from the pharyngeal and the laryngeal regions are present in OSAS patients.

On the other hand, studies about local neurogenic lesion in UARS are more limited. Dematteis et. al. showed that impairment of pharyngeal sensitivity and the number of patients with impaired sensitivity are

correlated with the severity of SDB [27]. It is hypothesized that in UARS, persistence of sensory input would lead to a better response to change in upper airway size and faster arousal if needed [3, 9]. However, neurogenic lesions as seen in the upper airway of OSA patients would not allow an appropriate adjustment of upper airway muscle tone to many challenges. When the upper airway is too narrow at the beginning of inspiration, it would lead to airway collapse. Because of the impairment of local sensory pathway, the coordination between intrathoracic efforts and upper airway muscle contractions would become abnormal. Apneas and hypopneas would occur if the modulation of airway patency is slow. The presence or absence of these neurogenic lesions would be the basis for the distinction of UARS and OSAS.

The anatomic collapsibility in UARS has been investigated. One study showed that breathing impairments in nasal airway passage could lead to UARS, such as in patients with collapse of the nasal valves, enlargement of inferior nasal turbinates, and a deviated nasal septum or any combination of them [28]. Due to abnormal_inspiratory airflow dynamics [29] or increased collapsibility of the upper airway during expiration [30], the airway in UARS patients might be more easily collapsed. However, perception of the change in airway size is much faster in UARS and the triggering of its response is also much faster as in comparison with that in OSAS patients. The fast response may be a reflex leading to a subcortical activation, presenting as phase A1 of the cyclic alternating patterns (CAPs) on EEG. Furthermore, a phase A2 and A3 of CAPs occur with stronger and broader activation, [31], CAP phase A3 correlates with what is called an "alpha EEG arousal" according to the Atlas Task Force of the American Sleep Disorders Association [32].

Study of UARS subjects with hypotension [11], bradycardia [33] and heart rate variability using Fast Fourier Transformation[34], have all shown that UARS patients present an active vagal tone. In contrast, a hyperactivity of the sympathetic tone has been postulated in OSAS patients due to the correlation with cardiovascular diseases [35-39]. The sympathetic activity could be reduced in OSAS patients after CPAP treatment [40]. In UARS, absence of decrease in oxygen saturation (SaO2) of UARS also eliminates one of the important stimuli of the sympathetic activity during sleep. Liberation of vagal tone during sleep would contribute to mild orthostatic symptoms seen in UARS patients.

In summary, the "upper airway reflexes" in UARS are intact, whereas they are impaired in OSAS with the repetition of decrease in SaO2 during sleep, leading to resetting and progressive hyperactivity of sympathetic tone, which is not seen in UARS.

Clinical Symptoms

In terms of clinical presentations, UARS shares many similarities with OSAS in some parts. However, there are indeed many distinct differences between these two syndromes noted in recent studies [41]. UARS patients present with chronic insomnia more often then patients with OSAS. Many of them complain of sleep onset insomnia and/or sleep maintenance insomnia. The former have difficulties in falling asleep after going to bed, the latter tend to wake up during sleep, then become difficult to fall asleep again from the awakenings [42]. The daytime symptom of sleepiness as seen in OSAS is much less complained of by adult patients with UARS. They tend to have more complaint about fatigue and myalgia. Therefore, it is prone to categorize this group of patients as "chronic fatigue syndrome". It is more difficult for them to get up in the morning and is likely for them to develop the "delayed sleep phase disorder, (DSPD)" which was first described by Czeisler et. al. [43]. Gold and colleagues (2003) emphasized that the complaints of UARS patients were more related to functional somatic syndromes, such as headaches, sleep-onset insomnia, and irritable bowel syndrome [10]. Other presentations include confusional parasomnias with sleepwalking and sleep terrors [44], anxiety and depression. In addition to chronic fatigue syndrome mentioned above, UARS is easily misinterpreted as psychiatric disorders, such as attention deficit disorders (ADD)/ attention deficit hyperactivity disorders (ADHD) [45] or depressive disorders. In terms of the symptoms of the airway, one clinical case report of UARS presented symptoms similar to nocturnal asthma [46]. Some symptoms of nasal allergy are often seen, with occasional chronic sinus infection.

Between one-fifth and a quarter of UARS subjects present cold hands and/or cold feet with sometimes other signs associated with dominant vagal tone. In addition, around one quarter of them have symptoms of orthostatism, such as lightheadedness with abrupt positional changes, sometimes more pronounced when awakenings, and subjects may have learned early to avoid "jumping out of bed". History of fainting, mostly seen in teenagers and young adult, may be noted. This

symptom may be explained by the finding that hypotension (SBP <100 mm Hg) is more commonly associated with UARS [47, 48] in contrast to hypertension with OSAHS patients [35]. Craniofacial anomalies [9] such as small jaws are other reported manifestations which may related to the cause of UARS – narrow orophayngeal and hypopharyngeal airway. Because of small maxilla and/or mandible, history of impaction of wisdom teeth with requirement for removal between 15 and 25 years, orthodontic treatment with usage of dental retainer or other dental device during childhood, or symptom of bruxism are often noted [49].

To sum up, the clinical presentations of UARS are as the following:

1. Presentations of atypical symptoms for OSAHS, especially the functional somatic complaints.
2. Low blood pressure in about a quarter of the subjects, often associated with moderate worsening with orthostatic maneuvers.
3. Craniofacial anomalies associated with anatomic narrowing of the upper airway. These may remind physicians of UARS when making the diagnosis of OSAS - Nose: asymmetric nostrils, collapse of nasal alar/alars at inspiration, narrow and long nose, hypertrophic inferior nasal turbinates, deviated nasal septum. Maxilla: maxillary deficiency, high and narrow hard palate, overlapping of teeth, short inter-molar distance. Mandible: retro-position of mandible indicated as "overjet" (>2.2 mm), presence of indentation of teeth on lateral border of tongue, presence of scars on buccal mucosa due to lateral biting. Evaluation of face would facilitate understanding of narrowing of upper airway, as with elongation of anterior lower third of face, steep mandibular plane, and narrow elongated chin. Soft tissues should be evaluated with determination of the size of tonsils using standard scales and the placement of the tongue in relation to the uvula using the Mallampatti scale [50].

Although the clinical evaluations allow one to suspect UARS with its potential relationship to anatomical impact on the upper airway, it is sometimes difficult to dissociate patients with UARS from those with mild OSAHS based on the clinical symptoms and signs alone. Moreover, patients could be left ignored or mislabeled with a different diagnosis [51]. The diagnosis of UARS can only be confirmed by polysomnography (PSG).

Diagnosis: Polysomnography-Based

In addition to the clinical features described above, cephalometric image study could help in clarifying the anatomic relationships of the upper airway. However, PSG is the only definite diagnostic tool. With the development of technology, PSG could detect more subtle physiological change during sleep. The introduction of nasal cannula/pressure transducer offers a more sensitive tool to quantify the respiratory changes [52, 53] has been used to detect respiratory effort-related arousals (RERAs). The assessment of respiratory efforts by measuring esophageal pressure (Pes) remains the gold standard for detection of respiratory abnormalities. In addition to the above, nasal cannula/pressure transducer system and Pes, other respiratory channels, such as mouth thermistor (mandatory to recognize mouth breathing when nasal obstruction occurs), thoracic and abdominal piezo-electrical bands or inductive respiratory plethysmography, pulse-oximetry and neck microphone are important to allow proper diagnosis. The EEG channels have to be all present in these cases, not only C3-A2 and C4-A1, but also frontal and occipital leads, that will help detecting the presence of arousals with the duration of 3 seconds or more [54] and calculation of cyclic alternating patterns (CAPs) during NREM sleep. It is necessary to calibrate all different channels, particularly the Pes, before the beginning and at the end of PSG monitoring.

The diagnostic findings of UARS on PSG include AHI < 5, the SaO_2 > 92% throughout the night [9, 55, 56], predominance of respiratory effort-related arousals (RERAs), frequent cyclic alternating patterns (CAPs), an increase in alpha rhythm, and a relative increase in delta sleep, which persists in the latter cycles of sleep. Other events such as long sleep onset latency could be noted.

In addition to apnea and hypopnea as classically defined, "flow limitation" is another important respiratory event which is based on the analysis of the nasal cannula curve. Flow limitation will appear as the "flattening" of the bell shape curve of the normal breath with a decrease in the amplitude of the curve by 2 to 29% compared with the immediately preceding normal breaths. The nasal cannula/pressure transducer, however, has not been demonstrated to have sensitivity comparable with Pes measurement. By reviewing articles on Pes analyses, three abnormal types of Pes tracings have been described [55, 57]. The first type is "Pes crescendo" showing progressively increased negative peak inspiratory

pressure in each breath. The crescendo terminates with an alpha-wave EEG arousal or a burst of delta wave and is not associated with a drop in SaO_2 of 3% as used for definition of hypopnea. In the second type, the Pes tracing shows a relatively stable and persistent negative peak inspiratory pressure, which is more negative than the baseline and non-obstructed breaths. This is called "sustained continuous respiratory effort" and the duration is longer than 4 breaths. The third type is "Pes reversal". There is an abrupt drop in respiratory effort indicated by a less negative peak inspiratory pressure after a sequence of increased respiratory efforts not related to EEG change. This indicates the end of an abnormal breathing period, which is independent of the EEG pattern.

Although indispensable for the diagnosis of UARS, the necessity of inserting a catheter into the nostril all the way down to esophagus of the examinee make Pes measurement relatively more invasive. The use of a pediatric feeding catheter instead of the esophageal balloon has made the procedure better tolerable in both adults [52] and children [58]. In spite of these facts, Pes measurement has not been widely applied yet, due to either the dread of discomfort from patients or the hesitancy of PSG technologists. Some new techniques have recently been introduced in the detection of sleep events. One of them is the electric prediction of pleural pressure from the pulse wave signals [59]. Inter-costal EMG signals are used to pick up the respiratory variations, with quite promising results [60]. In the near future, simpler and less invasive techniques are expected for measuring even subtler changes in respiratory efforts.

In EEG findings, UARS patients present more alpha frequency time [61, 62] and more RERAs [62] during sleep than patients with OSAHS. A new analytical approach was designed to quantify the so-called "respiratory cycle-related electroencephalographic changes (RCREC)" breath-by-breath, and to correlate delta, theta, and alpha EEG powers with respiratory cycle variations. This may allow detection of more subtle respiratory related sleep EEG changes [63]. Scoring of cyclic alternating patterns (CAPs) is another novel approach evaluating the quality of sleep in UARS. CAPs could be used to recognize abnormal sleep even without visually scored alpha EEG arousal [31], but CAP can only be studied during NREM sleep. A higher frequency of CAPs is noted in UARS compared to age and gender matched controls [64, 65]. By using power spectrum analysis, the comparison of the EEG among the EEG of UARS, OSAHS and normal control subjects during sleep, UARS subjects showed a higher amount of high theta and low alpha powers (i.e. 7-9 Hz bandwidth) during NREM sleep, and more delta powers during REM-sleep [61].

Treatment

Patients were successfully treated with nasal CPAP in the original report on UARS [3]. Thereafter, CPAP is often used as a therapeutic trial to demonstrate improvement of symptoms [42]. Nowadays, CPAP is still the first line treatment for UARS but compliance is poor and surgical treatment and dental appliances (treatment often combined) are more commonly used. Cognitive behavioral therapy (CBT) coupling with CPAP treatment has been shown beneficial for patients with chronic insomnia or psychosomatic symptoms secondary to UARS [42, 66] after appropriate treatment of the breathing syndrome and persistence of conditioning sleep onset insomnia. In a randomized study on UARS and chronic insomnia of postmenopausal female, radiofrequency reduction of nasal turbinates or turbinectomy, or a trial of CPAP showed better relief in daytime fatigue than behavioral treatment alone at 6 months after treatment [42]. Septoplasty and radiofrequency reduction of hypertrophic inferior nasal turbinates , with or without pharyngeal lateral walls resection can be successful in treating UARS. Satisfactory results were also seen in the management of oral appliances for UARS patients [67].

The cause of abnormal breathing would be the anatomical issues involving soft tissue in the nasopharynges, orophayrnges, hypopharynges, larynges and/or the bony structures of maxillae and mandibles. Failure in correction of the primary cause of the abnormal breathing will leave patients worsening of "functional" symptoms, and potentially may lead to the development of local polyneuropathy. The classic surgical procedures have often been considered too aggressive for treatment of UARS. However, treatment must address the cause of the syndrome and avoid progression of untreated pathologies. There are some studies reporting the surgical outcome for UARS [68, 69]. Uvulopalatal flap technique [70] has been helpful in the treatment of UARS. Orthodontic approaches such as rapid maxillary distraction are conveniently performed in children and teen-agers. Distraction osteogenesis applied to SDB

patients showed promising clinical improvement [71, 72]. This procedure is directly applicable in adults despite complete ossification of the maxilla and mandible. Midline incisions of the maxilla and mandible are necessary prior to the placement of internal jaw distractors. This combined surgical and orthodontic treatment is much less invasive than the traditional jaw advancement surgery. However, patients have to wear braces for an extended period of time (12 to 18 months) post treatment to bring teeth in an esthetic position.

In summary, treatment options for UARS include those currently available for OSAS patients. However, it may be more demanding than treating OSAS as patients tolerate nasal CPAP less and become quickly non-compliant. Correction of the underlying upper airway anatomical problems is the usual approach that may consist of treatment of nasal allergy, nasal surgery, orophayngeal surgery, surgery for the base of tongue, jaw surgery, or the use of dental devices.

Conclusion

As the evolution of the field of sleep medicine, more clinicians recognize UARS as a clinical syndrome that has distinct features from OSAHS. It is critical to recognize the associated symptoms and signs with UARS, in comparison with those of OSAHS. UARS may be present early in life and may be responsible for behavioral problems in children, from tiredness and fatigue, to hyperactivity, inattention, poor school results, attention deficit-hyperactivity disorder, sleepwalking, night terrors, enuresis and bruxism. Considering that prevention is much less costly to society than treatment of a syndrome with permanent lesions, recognition and treatment of UARS should be a priority. With better understanding of breathing during sleep, and better monitoring technology, it becomes clear that the existence of "benign snoring" should be questioned. We should evaluate not only children for snoring, as emphasized by the American Academy of Pediatrics [73], but also adults because many of them will be proved to have UARS if properly evaluated.

References

1. **Gastaut H,** Tassinari CA, and Duron B, Polygraphic study of diurnal and nocturnal (hypnic and respiratory) episodic manifestations of pickwick syndrome. *Rev Neurol* (Paris), 1965. 112: p. 568-579.
2. **Jung R** and Kuhlo W, Neurophysiological studies of abnormal night sleep and the pickwickian syndrome. *Prog Brain Res,* 1965. 18: p. 140-159.
3. **Guilleminault C**, Stoohs R, and Clerk A, A cause of excessive daytime sleepiness: the upper-airway resistance syndrome. *Chest,* 1993. 104: p. 781-787.
4. **Gold AR,** Marcus CL, and Dipalo F, Upper airway collapsiblity during sleep in upper airway resistance syndrome. *Chest,* 2002. 121: p. 1531-1540.
5. **Douglas NJ,** Upper airway resistance syndrome is not a distinct syndrome. *Am J Respir Crit Care Med,* 2000. 161: p. 1413-1416.
6. **Guilleminault C** and Chowdhuri S, Uupper airway resistance syndrome is a distinct syndrome. *Am J Respir Crit Care Med,* 2000. 161: p. 1412-1413.
7. AASM, International Classification of Sleep Disorders: Diagnostic & Coding Manual. 2 ed. 2005, Westchester, IL: *American Academy of Sleep Medicine.*
8. **Guilleminault C,** Tilikan A, and D. WC., The sleep apnea syndromes. *Annu Rev Med.,* 1976. 27: p. 465-484.
9. **Bao G** and Guilleminault C, The upper airway resistance syndrome - one decade later. *Curr Opin Pulm Med,* 2004. 10: p. 461-467.
10. **Gold AR,** Dipalo F, Gold MS, et al., The symptoms and signs of upper airway resistance syndrome: a link to the functional somatic syndromes. *Chest,* 2003. 123: p. 87-95.
11. **Guilleminault C,** Faul JL, and Stoohs R, Sleep-disordered breathing and hypotension. *Am J Respir Crit Care Med,* 2001. 164: p. 1242-1247.
12. **Guilleminault C,** Kirisoglu C, Poyares A, et al., Upper Airway Resistance Syndrome: an outcome study on a retrospective cohort. *J. Psych. Res.,* in press.
13. **Kimoff RJ,** Sforza E, Champagne V, et al., Upper airway sensation in snoring and obstructive sleep apnea. *Am J Respir Crit Care Med,* 2001. 164: p. 250-255.
14. **Guilleminault C,** Li K, Chen NH, et al., Two-point palatal discrimination in patients with upper airway resistance syndrome, obstructive sleep apnea syndrome, and normal control subjects. *Chest,* 2002. 122: p. 866-870.
15. **Virkkula P,** Silvola J, Maasilta P, et al., Esophageal pressure monitoring in detection of sleep-disordered breathing. *Laryngoscope,* 2002. 112: p. 1264-1270.
16. **Norman RG,** Ahmed MM, Walslebel JA, et al., Detection of respiratory events during NPSG: nasal cannula/pressure sensor versus thermistor. *Sleep,* 1997. 20: p. 1175-1184.
17. **Edstrom L,** Larson H, and Larson L, Neurogenic effects on the palatopharyngeal muscle in patients with obstructive sleep apnea: a muscle biopsy study. *J Neurol Neurosurg Psychiatry,* 1992. 55: p. 916-920.
18. **Woodson BT,** Garancia J, and Toohill RJ, Histopathologic changes in snoring and obstructive sleep apnea syndrome. *Laryngoscope,* 1991. 101: p. 1318-1332.
19. **Series F,** Simoneau JA, St Pierre S, et al., Characteristics of the genioglossus and musculus uvulae in sleep apnea-

hypopnea syndrome and in snorers. *Am J Resp Crit Care Med,* 1996. 153: p. 1870-1874.

20. **Friberg D,** Answed T, and Borg K, Histological indications of a progressive snorer disease in upper airway muscle. *Am J Respir Crit Care Med,* 1998. 157: p. 586-593.
21. **Friberg D**, Gazelius B, Holfelt T, et al., Abnormal afferent nerve endings in the soft palatal mucosa of sleep apnoics and habitual snorers. *Regul Pept,* 1997. 71: p. 29-36.
22. **Friberg D**, Heavy snorer's disease: a progressive local neuropathy. *Acta Otolaryngol.*, 1999. 119: p. 925-933.
23. **Nguyen ATD,** Jobin V, Payne R, et al., Laryngeal and velopharyngeal sensory impairment in obstructive sleep apnea. *Sleep,* 2005. 28: p. 585-593.
24. **Guilleminault C,** Huang YS, Kirisoglu C, et al., Is obstructive sleep apnea syndrome a neurological disorder? A continuous positive airway pressure follow-up study. **Ann Neurol.**, 2005. [Epub ahead of print].
25. **Davenport PW,** Friedman WA, Thompson FJ, et al., Respiratory-related cortical potentials evoked by inspiratory occlusion in human. *J. Appl. Physiol,* 1986. 60: p. 1843-1848.
26. **Afifi L,** Guilleminault C, and Colrain I, Sleep and respiratory stimulus specific dampening of cortical responsiveness in OSAS patients. *Respir Physiol Neurobiol,* 2003. 136: p. 221-234.
27. **Dematteis M,** Lévy P, and Pépin J-L, A simple procedure for measuring pharyngeal sensation: A contribution to sleep apnoea diagnosis. *Thorax,* 2005. 60: p. 418-426.
28. **Chen W** and Kushida CA, Nasal obstruction in sleep-disordered breathing. *Otolaryngol Clin North Am,* 2003. 36: p. 437-60.
29. **Gold AR,** Dipalo F, Gold MS, et al., Inspiratory airflow dynamics during sleep in women with fibromyalgia. *Sleep,* 2004. 27: p. 459-466.
30. **Woodson BT,** Expiratory pharyngeal airway obstruction during sleep: a multiple element model. *Laryngoscope,* 2003. 113: p. 1450-1459.
31. **Terzano MG,** Parrino L, Chervin R, et al., Atlas, rules and recording techniques for the scoring of the cyclic alternating pattern (CAP) in human sleep. *Sleep Med,* 2001. 2: p. 537-554.
32. **ASDA,** EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep, 1992. 15: p. 173-184.
33. **Zwillich C,** Devlin T, White D, et al., Bradycardia during sleep apnea: characteristics and mechanism. *J Clin Invest,* 1982. 69: p. 1286-1292.
34. **Guilleminault C,** Poyares D, Rosa A, et al., Heart rate variability, sympathetic and vagal balance, and EEG arousal in upper airway resistance and mild OSA. *Sleep Med.*, in press.
35. **Peppard PE,** Young T, Palta M, et al., Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med,* 2000. 342: p. 1378-1384.
36. **Hu FB,** Willett WC, Manson JE, et al., Snoring and risk of cardiovascular disease in women. *J Am Coll Cardiol,* 2000. 35: p. 308-313.
37. **Hung JEG,** Whitford R, Parsons W, et al., The association of sleep apnea with myocardial infarction in men. *Lancet*, 1990. 338: p. 261-264.
38. **Wolk R,** Kara T, and Somers VK, Sleep-disordered breathing and cardiovascular disease. *Circulation,* 2003. 108: p. 9-12.
39. **Gami AS,** Pressman G, Caples SM, et al., Association of atrial fibrillation and obstructive sleep apnea. *Circulation*, 2004. 110: p. 364-367.
40. **Narkiewicz K,** Kato M, Phillips BG, et al., Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. *Circulation,* 1999. 100: p. 2332-2335.
41. **Guilleminault C** and Bassiri A, Clinical features and evaluation of obstructive sleep apnea-hypopnea syndrome and the upper airway resistance syndrome. 4th ed. Principles and Practice of Sleep Medicine, ed. Kriger MH, Roth T, and Dement WC. 2005, Philadelphia: WB Saunders.
42. **Guilleminault C,** Palombini L, Poyares D, et al., Chronic insomnia, post menopausal women, and SDB. Part 2: Comparison of non drug treatment trials in normal breathing and UARS post menopausal women complaining of insomnia. *J. Psychosomat Res,* 2002. 53: p. 617-623.
43. **Czeisler CA,** Richardson GS, Coleman RM, et al., Chronotherapy: resetting the circadian clock of patients with delayed sleep phase insomnia. *Sleep,* 1981. 4: p. 1-21.
44. **Guilleminault C,** Kirisoglu C, Palombini L, et al., Continuous NREM sleep state instability in sleepwalking. J *Sleep Res,* in press.
45. **Lewin DS** and Pinto MD, Sleep disorders and ADHD: shared and common phenotypes. *Sleep,* 2004. 27: p. 188-9.
46. **Guerrero M,** Lepler L, and Kristo D, The upper airway resistance syndrome masquerading as nocturnal asthma and successfully treated with an oral appliance. *Sleep Breath,* 2001. 5: p. 93-96.
47. **Guilleminault C,** Faul JL, and Stoohs R, Sleep-disordered breathing and hypotension. *Am J Respir Crit Care Med,* 2001. 164: p. 1242-1247.
48. **Guilleminault C,** Khramtsov A, Stoohs RA, et al., Abnormal blood pressure in prepubertal children with sleep-disordered breathing. *Pediatr Res,* 2004. 55: p. 76-84.
49. **Guilleminault C** and Khramtsov A, Upper airway resistance syndrome in children: a clinical review. *Semin Pediatr Neurol,* 2001. 8: p. 207-215.
50. **Mallampati SR,** Gatt SP, Gugino LD, et al., A clinical sign to predict difficult tracheal intubation: a prospective study. *Can Anaesth Soc J,* 1985. 32: p. 429-434.
51. **Resta O,** Barbaro MPF, Bonfitto P, et al., Low sleep quality and daytime sleepiness in obese patients without obstructive sleep apnoea syndrome. *J Intern Med,* 2003. 253: p. 536-543.
52. **Epstein MD,** Chicoine SA, and Hanumara RC, Detection of

upper airway resistance syndrome using a nasal cannula/ pressure transducer. *Chest,* 2000. 117: p. 1073-1077.

53. **Ayap I,** Norman RG, Krieger AC, et al., Non-invasive detection of respiratory effort- related arousals (RERAs) by a nasal cannula/pressure transducer system. *Sleep,* 2000. 23: p. 763-771.
54. **ASDA,** Atlas Task Force EEG arousals: Scoring rules and examples: A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep,* 1992. 15: p. 173-184.
55. **Guilleminault C,** Poyares D, Palombini L, et al., Variability of respiratory effort in relationship with sleep stages in normal controls and upper airway resistance syndrome patients. *Sleep Med,* 2001. 2: p. 397-406.
56. **AASM,** Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep.,* 1999. 22: p. 667-689.
57. **Black J,** Guilleminault C, Colrain I, et al., Upper airway resistance syndrome: central EEG power and changes in breathing effort. *Am J Respir Crit Care Med,* 2000. 162: p. 406-411.
58. **Serebrisky D,** Cordero R, Mandeli, et al., Assessment of inspiratory flow limitation in children with sleep-disordered breathing by a nasal cannula pressure transducer system. *Pediatric Pulmonol,* 2002. 33: p. 380-387.
59. **Nanba S,** Ohsaki R, and Shiomi T, Apparatus and method for electronically predicting pleural pressure from pulse wave signals. United States Patent Application, 2002. US2002/0143261: p. A1.
60. **Stoohs RA,** Blum HC, Knaack L, et al., Non-invasive estimation of esophageal pressure based on inter-costal EMG monitoring. IEEE J, in press.
61. **Guilleminault C,** Kim YD, Chowdhuri S, et al., Sleep and daytime sleepiness in upper airway resistance syndrome compared to obstructive sleep apnea syndrome. *Eur Respir J,* 2001. 17: p. 1-10.
62. **Poyares D,** Guilleminault C, Rosa A, et al., Arousal, EEG spectral power and pulse transit time in UARS and mild OSAS subjects. *Clin Neurophysiol,* 2002. 113: p. 1598-1606.
63. **Chervin RD,** Burns JW, Subotic NS, et al., Correlates of respiratory cycle-related EEG changes in children with sleep-disordered breathing. *Sleep,* 2004. 27: p. 116-121.
64. **Guilleminault C,** Lee JH, and Chan A, Pediatric obstructive sleep apnea syndrome. *Arch Pediatr Adolesc Med,* 2005. 159: p. 775-85.
65. **Lopes MC** and Guilleminault C, Cyclic alternating pattern in adults with upper airway resistance syndrome. *Sleep*, 2005. 28(S1): p. A184.
66. **Krakow B,** Melendrez D, Lee SA, et al., Refractory insomnia and sleep-disordered breathing: a pilot study. *Sleep Breath*, 2004. 8: p. 15-29.
67. **Yoshida K,** Oral device therapy for the upper airway resistance syndrome patient. *J Prodthet Dent,* 2002. 87: p. 427-430.
68. **Newman JP,** Clerk AA, Moore M, et al., Recognition and surgical management of the upper airway resistance syndrome. *Laryngoscope,* 1996. 106: p. 1089-93.
69. **Utley DS,** Shin EJ, Clerk AA, et al., A Cost-Effective and Rational Surgical Approach to Patients With Snoring, Upper Airway Resistance Syndrome, or Obstructive Sleep Apnea Syndrome. *Layngoscope,* 1997. 107: p. 726-734.
70. **Powell N,** Riley R, Guilleminault C, et al., A reversible uvulopalatal flap for snoring and sleep apnea syndrome. *Sleep,* 1996. 19: p. 593-599.
71. **Guilleminault C** and Li KK, Maxillomandibular Expansion for the Treatment of Sleep-Disordered Breathing: Preliminary Result. *Laryngoscope,* 2004. 114: p. 893-896.
72. **Pirelli P,** Saponara M, and Guilleminault C, Rapid maxillary expansion in children with obstructive sleep apnea syndrome. *Sleep,* in press.
73. American Academy of Pediatrics - Section on Pediatric Pulmonology - Subcommittee on Obstructive Sleep Apnea Syndrome, Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics,* 2002. 109: p. 704-712.