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Upper airway resistance syndrome 2018: non-hypoxic sleep-disordered breathing

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ABSTRACT

Introduction: Upper airway resistance syndrome (UARS) as obstructive sleep apnea syndrome (OSAS) has been described as abnormal breathing during sleep, based on the recording technologies and knowledge of the time. These terms have advanced the field, but are they still useful?

Area Covered: Historically, the definition of UARS syndrome was aimed at recognizing pathology not covered by 'OSAS' and to prompt specialists to go further than the obvious. It aimed at pushing specialists to recognize pathologies earlier and to elicit research in the developmental features of sleep-disordered-breathing (SDB). The technology used to monitor SDB changed over-time, allowing recognition of SDB differently but not necessarily better.

Expert Commentary: Currently, we have a better understanding of the development of SDB, and its evolution with aging, leading to co-morbid-OSA. However, the real issue is to recognize the problems much earlier, and to understand what can be done to prevent its development. The notions of OSA, UARS, apnea hypopnea index are only historical. There is enough knowledge to date to go beyond these definitions, to recognize problems differently and to lead to the prevention of the factors leading to SDB. The recognition of non-hypoxic sleep-disordered breathing is a step in this direction.

1. Introduction: a historical view

While studying sleep apnea in pediatric patients in the 1970s Guilleminault et al. observed that during nocturnal polysomnogram (PSG) there were short (1–3 s) alpha (7–9 Hz) arousals preceded by 3–20 second periods of increasing intrathoracic pressure measured using an esophageal pressure probe or Pes [1–4]. Later the team showed that these arousals were not associated with oxygen desaturations, apneas, or hypopneas but the patients often exhibited increased respiratory effort with inspiratory flow limitation (IFL) during PSG and were experiencing significant daytime symptoms and developmental impairments [5]. Described as Upper Airway Resistance Syndrome (UARS) it was broadly introduced to the medical community when applied to adults in 1993 [6]. These patients were presenting differently than obstructive sleep apnea (OSA) patients. UARS patients were younger, leaner and had fewer comorbidities than OSA patients [7]. UARS patients were experiencing unrefreshing sleep and daytime sleepiness like OSA patients but were more likely to also suffer from a variety of less specific somatic, psychosomatic and psychiatric conditions (i.e. headache, inattention, hyperactivity, chronic fatigue syndrome, insomnia, anxiety, and depression) [6,8]. On their sleep studies UARS patients had clear arousals related to events seen with Pes, however, these were not considered 'scorable events' by traditional apnea and hypopnea definitions (AHI). Sleep-disordered breathing has become synonymous with obstructive sleep apnea and over the past 45 years, with the continued clinical under-appreciation and

the loss of the esophageal pressure probe(Pes) during routine PSG, the diagnosis of UARS has lost recognition.

One of the fundamental problems of sleep medicine has been to find an objective way to identify sleep disruption and a way to tell patients if their sleep is 'healthy'. The 'AHI,' or quantity of apneas and/or hypopneas per hour, is the tool used to measure the severity of sleep apnea. With sleep apneas' rapid prevalence growth due to increased clinical recognition, the scoring of AHI has become the marker of 'healthy sleep'. However, by focusing on the AHI, and ignoring the increasing or sustained (see Figures 1 and 2) respiratory effort that leads to EEG arousals, we are missing UARS and ignoring the cause of chronic complaints. The inability of the current scoring system to recognize UARS and be an accurate clinical tool with a low AHI remains a problem.

2. Upper airway resistance syndrome

UARS is defined on PSG as having an AHI < 5 and oxygen saturation nadir equal or greater than 92% [9]. UARS patients exhibit a breath by breath progressive increases in resistance to airflow in the upper airway associated with arousals from sleep. Guilleminault et. al determined that an arousal is often seen within one to three breaths of flow limitation associated with abrupt but limited reductions in the tidal volume (i.e. abnormal increase in upper airway resistance during sleep) [10,11]. UARS patients report chronic fatigue, daytime difficulties with concentration and performance, fragmented and/or unrefreshing sleep, complaints of sleep onset and
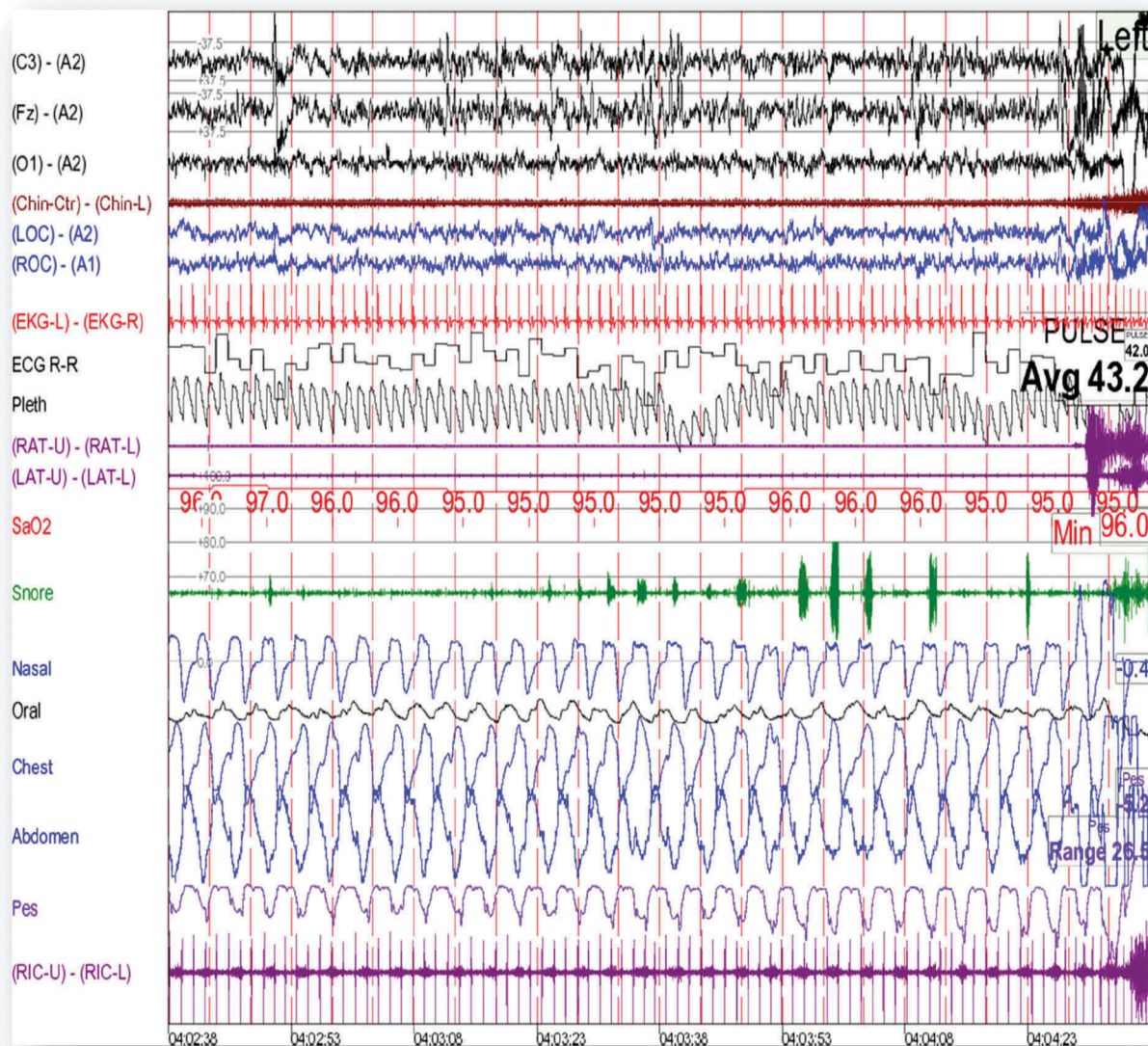
Figure 1. Example of a 2018 respiratory-event-related-arousal during a 120-s segment. From top to bottom:: channels 1–3: EEG, channel 4: chin EMG, channels 5 and 6: Eye movements (EOG), channel 7: ECG, channel 8: heart rate variation derived from channel 7, channel 9: finger plethysmography -Per convention sympathetic activation is shown with down movement of curve - There are two clear sympathetic activations-channels 10 and 11: leg movement from anterior tibialis muscles, Channel 12: Sp-O2 (oximetry), channel 13: snoring noise calculated from neck microphone monitoring power -Note there is a progressive increase in noise- Channel 14: nasal cannula-pressure transducer -The flow curve is abnormal from the beginning, except for the first two breaths, there is absence of the normal round upper part of the curve [per convention, inspiration is up-ward], there is presence of a cut of the peak inspiration curve with a flattening of the curve. The flattening of the inspiratory curve began before snoring is detected and became more obvious with increase in snoring noises. There is also a decrease in amplitude of the nasal pressure flow curve, but it never reaches a 30% decrease in amplitude and is not associated with any change in oxygen saturation (channel 12). The pattern of the nasal cannula curve has to be compared with the recordings obtained on channels 18 and 19: channel 18: recording of esophageal pressure – Pes- and 19 recording of 'intercostal/diaphragm activity'. As can be seen on these two channels the Pes indicates a progressively increasing effort with each breath: the peak-negative-Pes becomes more pronounced (i.e. more negative) indicating increased effort, the muscle recordings shows this increasing effort as well. Channel 15 indicates mouth breathing, which is continuous; channels 16 and 17 are the recording of chest and abdomen with inductive plethysmography bands- each band is monitored with opposite polarity here as can be seen in this, a non-hypoxic event that leads to cortical disruption as indicated at the end of the recording.

maintenance insomnia without obvious obstructive sleep-apnea symptoms. They have been misdiagnosed and mismanaged as documented in a 4.5-year longitudinal study of 94 UARS patients between 1995 and 1998 [12]. In this study, none of the subjects received appropriate treatment – at the time PAP therapy – because insurance companies would not accept UARS as a diagnosis. However, in follow up these patients reported worsening of their initial symptoms i.e. fatigue, insomnia, anxiety, depression, chronic fatigue syndrome,

fibromyalgia and had been prescribed symptomatic medications without addressing the underlying cause. To better differentiate UARS versus OSAS, comparative studies have emphasized difference in complaints and symptoms between both syndromes with UARS being more likely seen in premenopausal women, with less snoring and more complaints of 'daytime fatigue,' reports of unrefreshing sleep, difficulty performing at work, poor concentration, memory problems, unspecific muscle pain, and mood syndromes.
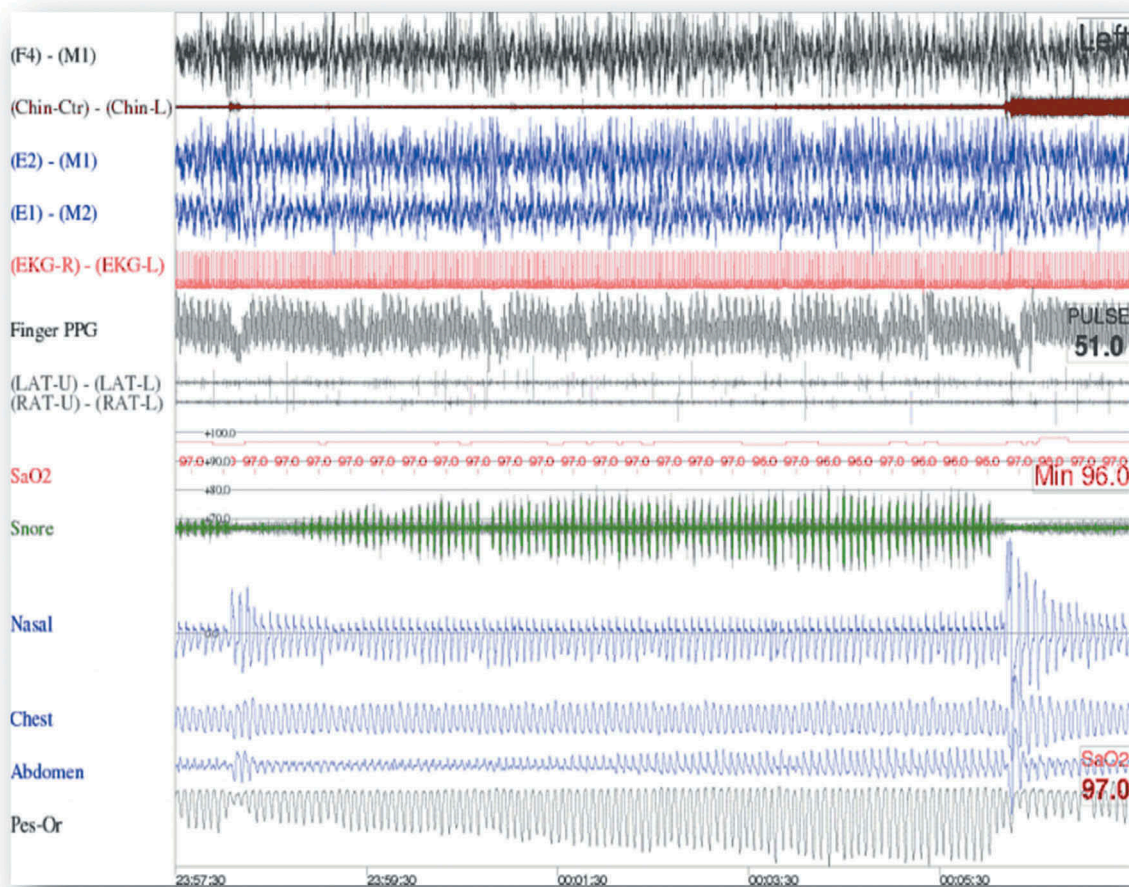
Figure 2. Increasing pes pressures leading to an arousal but not a 'scorable event' during a 15-min segment. From top to bottom: channel 1: EEG, with the presence of repetitive cyclic-alternative pattern A2 in NREM sleep but indication of EEG arousal only at end of recording (right part of slide). channel 2: chin EMG, channel 3 and 4: eye movements, channel 5: ECG, channel 6 Finger plethysmography with an indication of the presence of repetitive sympathetic activation event, channel 7 and 8: leg muscle recordings, channel 9: pulse oximetry showing no desaturation: NH-SDB. channel 10: progressive increase of snoring until arousal. channel 11: Nasal cannula with continuous flattening of the flow-curve, channel 12 and 13: thoracic and abdominal plethysmography bands, channel 14: progressive increase in effort indicated by Pes. Note that in association with CAPs type A2 there are moderate changes in effort as indicated by mild decreases in negative peak Pes and sympathetic activation (finger plethysmography) but the very limited arousals are not sufficient to end the event despite the indication of cortical disturbance.

3. Pathophysiology behind obstructive sleep apnea syndrome and UARS

In the 1990 and early 2000 years, studies focused on understanding the role of snoring in the development of OSA [13–18]. These studies emphasized that OSA was noted years after onset of snoring. Friber et al. suggested that OSA was the consequence of a 'snoring disease' based on histologic and neurophysiologic studies of upper-airway (UA) muscles [19–24]. These studies indicated that a local polyneuropathy involving small sensory and motor fibers innervating the UA, particularly tongue-muscles, was present in OSA patients. The most interesting finding was the involvement of the very small sensory fibers that may have a role as 'receptors' transmitting information to the 'brain-stem-controls' leading to UA muscle contractions with inspiration. As an example, Nguyen et al, using air-pulse stimulations on the pharynx and larynx compared to a control group, confirmed the neurophysiological findings reported initially by Friberg et al. and indicated that

not only the sensory responses in the pharyngeal region but also the aryepiglottic reflexes were disturbed in the chronic, loud snorers [18]. The Stanford group using two points-discrimination tests and three groups of subjects (OSA, UARS, normal controls) could not find difference in response between UARS and controls but did confirm the differences in OSA patients in palatal two-point discrimination [16]. Swedish researchers suggested that the mechanism of the local UA injury is like that seen in Hand-Arm Vibration Syndrome (HAVS) observed in manual laborers with prolonged use of low frequency hand-held vibrating tools. Interestingly, with HAVS patients, the frequency for vibrating tools to have the worst damage is 50–300 Hz, which is also seen within the range of snoring [24]. With chronic snoring, there is a progressive decreased sensitivity to vibration and temperature and a progressive local demyelinating neuropathy with hypertrophy of the muscle tissue. It was found by Nguyen et al. in 2005 that the severity of lesions correlated with the severity of OSA. In biopsies from the palate and posterior

pharynx, there was evidence of neurogenic lesions thought to be associated with blunting of the afferent upper airway receptors response to collapse [19–24]. In contrast, studied UARS patients maintain normal UA sensory responses similar to controls and thus would not have the impaired UA reflexes as seen in OSA patients [16].

It is believed that the continuous abnormal stimulation of the sensory-motor loop, because of the increased resistance in the UA, is a strong contributor to the sleep disturbance seen in UARS patients. This is supported by investigations of sleep structure and sleep EEG in matched OSA, UARS and control subjects. There are distinct changes beyond just the NREM arousal seen in the sleep architecture of UARS patients. They have decreased slow wave sleep and increased wake after sleep onset. Several studies were performed to support such hypothesis: Usage of the Cyclic-Alternating–Pattern (CAP) scoring system indicates increases in type A2 pattern during NREM sleep, while OSA present more phase A3 pattern, which is similar to the AASM definition of 'EEG arousal' [25]. In the study of CAP and UARS, the CAP rate was also shown to correlate with the daytime symptoms of sleepiness [26]. Another investigation using systematic analysis of all-night sleep EEG with fast Fourier transformations comparing age and gender-matched OSA patients, UARS, and normal controls indicated a clear difference in power density between the different subject groups during total sleep time, with UARS patients having a higher power density in both the slow alpha-EEG(7–9 Hz) and delta bands than patients with OSA and control subjects [11]. Such findings indicate continuous cortical disturbance toward arousal (increase alpha power) despite the persistence of EEG patterns of sleep with efforts to re-enforce sleep (delta power) [27,28]. This finding of increased stimulation of the 'arousal' mechanisms has been hypothesized to be responsible for maintaining a sufficiently open UA: with tendency to have abnormal UA resistance during sleep but with triggering of 'alertness circuits' as indicated by the increase in alpha (and at time beta) power and to lead to the absence of the traditional apnea or hypopnea with clear drop in oxygen saturation, and thus observation of UARS. This abnormal cortical involvement would be responsible for the report of unrefreshing/poor sleep and presence of a 'hyper-arousable CNS' during sleep manifesting not only with the above daytime symptoms but also with daytime performance impairments such as those shown by Stoohs et al. in 2006 demonstrating delayed reaction time in UARS [29]. Reaction time deficits related to OSA have already been reported but such tests support UARS patient's complaints of difficulty with performance and concentration.

4. Polysomnographic recognition of UARS

Early on esophageal manometry – Pes – was used to diagnose sleep disorder breathing as other techniques were judged inaccurate. However, despite the recognition of the inaccuracy of thermistors, with the increase in number of sleep laboratory, the usage of thermistors took-over in many places, and due to the inaccuracy of the initial non-invasive measurement of oxygen saturation (monitored on the ear-lobe) an association of a 50% decrease of the curve obtained from the thermistor and a drop of 3% to 4% of oxygen saturation was required to diagnose abnormal breathing during sleep. Despite clear technical improvements (usage of nasal cannula and more accurate pulse oximeters), such definitions are in part still used when performing PSGs. Pes allowed measurement of respiratory effort, something that even today is difficult to recognize in PSG. Measurement of inspiratory, i.e. diaphragmatic/rib-cage muscle activity was used by a few and gave much better information than thermistors, but few knew how to calibrate and use this information [30,31].

In the mid-1990s, the sleep community recognized that there was a need to further identify arousals that were occurring without apneas and hypopneas but were related to abnormal breathing during sleep. This recognition was related to the presence of loud snoring, sometimes with health complaints, but the absence of 'scorable' apnea-hypopneas identified on studies using pneumotachograph and/or Pes [32]. Investigation of snoring sounds was easy and there was recognition that important snoring sounds could be associated with EEG arousals and that often there was a crescendo pattern of the sound and termination with a loud snore and a 3 s or more arousal: This pattern was defined as a 'respiratory-event-related-arousal' or RERA and was the result of an international meeting of sleep researchers in Chicago in 1995, the so-called 'Chicago Criteria' (see Figure 3). In the late 1980s and early 1990s studies performed with not only Pes, but also face-mask and pneumotachograph had already demonstrated that flow limitation was present in sleep-disordered-breathing and that there was a direct relationship between increases in respiratory efforts, flow limitation and EEG arousals that avoided the occurrence of upper-airway collapse and maintained a non-hypoxic state [33] (see Figure 4). However, despite its great usefulness to recognize pathological breathing during sleep, the equipment was considered as difficult to keep all night in/ on patients and was only used in research protocols.

Introduction of the nasal cannula pressure transducer – in the late 1990s – allowed more accurate measurement of the nasal inspiratory-flow-curve [34,35] despite the fact that abnormal expiratory resistance and accurate identification of the expiratory-flow-
curve is poorly recognized with such equipment. Moreover, a decrease in the amplitude of the inspiratory flow curve does not differentiate between decreases or increases in diaphragmatic effort secondary to airflow limitation. The combination of recording inspiratory muscle effort and nasal cannula or, better, usage of a calibrated Pes, are the only way to associate respiratory effort and airflow limitation. Finally, several patterns were described using Pes to recognize limited but abnormal UA resistance: a 'Crescendo' pattern, most commonly seen during stages N1 and N2 and a 'continuous sustained effort' pattern, most commonly seen during stage N3. While these patterns are best appreciated with Pes, nasal cannula has brought about a better recognition of abnormal nasal flow. For example, RERAs are now calculated based on the amplitude decrease of the inspiratory flow curve obtained from the nasal cannula: When there is a 30% decrease of the amplitude of the nasal flow curve compared to adjacent breaths and a 3 or more second EEG arousal a RERA is scored despite absence of 3 or more percent drop in oxygen

saturation. Such PSG patterns should allow us to at least suspect presence of abnormal breathing during sleep without a clear drop in oxygen saturation. However, such a definition is still inadequate as the cortex will not take 3 or more seconds to react to an abnormal increase in UA resistance, as shown by CAP and EEG power analyses, which ignores the abnormal response of the cortex at the base of complaints for UARS patients.

Current sleep polysomnographic equipment, in laboratory or ambulatory, allows performance of more sophisticated nasal flow recordings than ever before- even if Pes is still a gold standard- and allows for more sophisticated analyses of recorded signals. The pattern of flow limitation described by Stooh et al. in 1991 [33] (see Figure 3) associated with increased respiratory effort, EEG arousals and absence of oxygen saturation drops can be easily detected and the definition of inspiratory-flow-limitation - IFL- is well-established. Furthermore, the nasal cannula is used widely in the sleep-medicine-world, but the advantage it brought in the recognition of abnormal breathing during sleep has not followed the technical advances. The nasal cannula allows continuous measurement of IFL, however, expiratory flow limitation (EFL) is mostly ignored.

The minimum scoring criteria for IFL have been studied in a general population sample at the Federal University of Sao Paulo [36]. This was an epidemiological study of sleep-disorders on subjects' representative of the city of Sao-Paulo. A total of 1048 subjects were completely analyzed. Subjects were investigated for one week including medical evaluations, questionnaires and performance of 7 days of actigraphy and one in-laboratory nocturnal PSG with nasal cannula but no Pes. The investigators used the PSG definition of 'flow limitation" from the literature and confirmed the validity of the definition and for the first time found normative data on the association between 'flow limitation' (i.e. subjects without apnea and hypopnea and oxygen drop of 3% or 4%) and presence of complaints. The study concluded that subjects with at least 30% of sleep time with flow limitation reported sleep-related complaints and had abnormal metabolic findings on blood analyses [36]. None of the subjects were diagnosed or treated. The cut-off point of 30% of sleep time with IFL is probably a too wide cut-off point but this is the first general population study giving a cut-off point for pathological breathing without apnea-hypopnea and oxygen saturation drops of at least 3%.

5. Vagal tone and UARS

There is a change in the autonomic balance with sleep onset and even more importantly with REM sleep. Sleep-onset is associated with a decrease in sympathetic activity and increase in vagal tone. Autonomic nervous system-ANS-activity can be followed when studying specific effectors such as heart rate-HR- blood-pressure-BP- and finger plethysmography-PPG. Arousals lead to a return of
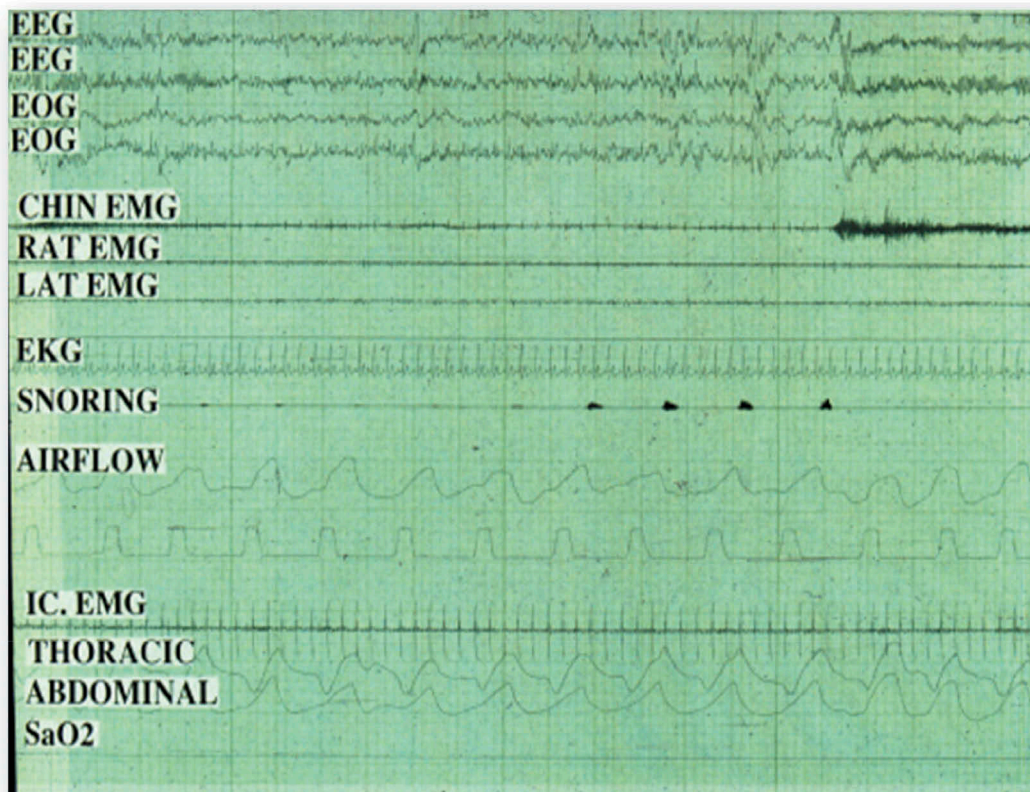

Figure 3. RERA based on snoring (1995). The different channels are indicated on the left of the recording performed on a Grass [TM] polygraph. The sample covers 60 s, on channel 9 from top is recording of snoring and snoring-power progressively increases and leads to an EEG arousal clearly seen on right side of figure with elimination of snoring.
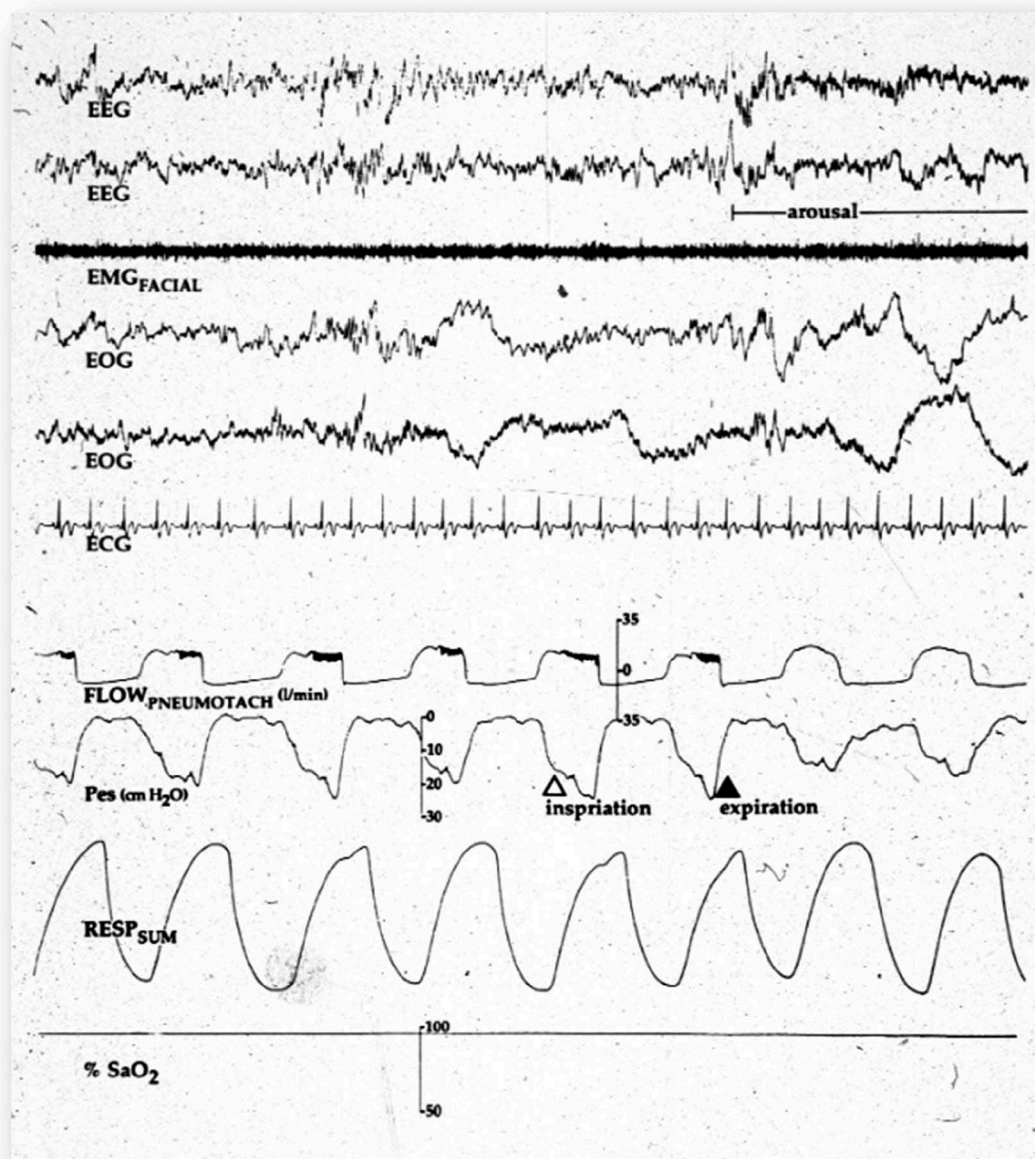
Figure 4. Flow limitation in 1990. Recording in 1990 of respiratory effort with calibrated Pes (channel 8 from top) with Pes calibration scale, numbers are negative numbers, nasal flow with a calculation of tidal volume with a pneumotachograph (channel 7). There is a development of flow-limitation with increasing effort indicated by Pes. Vibrations induced by snoring can be seen on the flow recorded with the pneumotachograph, the arousal leads to return to baseline. Channel I and 2: EEG with arousal on right side of figure, channel 3: chin EMG, channel 4 and 5: eye movement, channel 6: ECG lead, channel 9: monitor resultant of thoracic and abdominal movement using an equipment called 'Respitrace' and bottom channel #10 monitor oximetry [33].

increased sympathetic tone: this is clearly noted with investigation of ANS effectors such as HR or PPG changes. Drops in oxygen saturation are also associated with increases in sympathetic tone. Arousal from sleep is thus associated with change in HR, PPG, and BP that may indicate an arousal lasting less than 3 s. However, changes in autonomic balance may not always indicate a cortical arousal- the cause of the sleep disturbance and patient's complaints- but may indicate only an 'autonomic activation' i.e. a disturbance limited at brain-stem reflexes without passing the thalamic gate and without disturbance of the cortex.

The changes in ANS during sleep are often considered only in the context of OSA, i.e. presence of EEG arousals of at least 3

s and oxygen saturation drops. Such a combination always leads to a sympathetic activation that has been documented since the 1970s. However, the repetitive stimulation of the vagal tone during sleep with each breath without oxygen desaturation, leads to "sympathetic functional- de-afferentation' as demonstrated previously [37,38]. A large study of 4409 sleep-disorder patients looking at daytime BP changes, found out that a small subgroup (2.3%) presented an abnormally low blood pressure during the daytime with the presence of orthostatic intolerance and cold hands and feet. 98% of this subgroup were diagnosed with UARS [39]. To better understand how patients, mostly pre-menopausal women, with UARS presented with low blood pressure and symptoms of hyper-vagotomy, a study was

performed on 49 UARS subjects diagnosed using Pes. A breath-by-breath investigation based on the Hilbert-Huang-Transform exploring autonomic nervous system changes observed during IFL was performed [40]. Autonomic status was quantified from beat-to-beat heart rate analysis by high frequency (RR_{HF}), low frequency (RR_{LF}), and LF/HF ratio of each respiratory cycle. Based on respiratory-related mechanisms contained in the photo-plethysmography (PPG) signal, the respiratory-related oscillations (PPG_{res}) were further quantified. A hyperactivation of the parasympathetic system was demonstrated in the presence of inspiratory-flow limitation recorded in association with increased respiratory efforts and very short EEG sleep disruption. These often long-lasting respiratory changes had no or very limited impact on oxygen saturation- the common sympathetic activator [40], explaining the observation in some UARS patients the presence of daytime complaints.

6. Prevalence of UARS and flow limitation in the general population

The epidemiological study of the Federal university of Sao Paulo involving 1048 subjects looked at this issue. This study clearly defined the PSG pattern of 'flow-limitation', and as mentioned above, calculated based on their population a cut-off point of 30% of nocturnal sleep time spent with IFL as 'abnormal.' They calculated that 15% of their sample met their definition of 'UARS' [36]. These investigators also reported, based on age, a very different distribution of OSA and UARS. Young subjects have mostly UARS while OSAS is mostly unseen, with increasing age UARS is seen less while OSAS is observed more. These authors suggest that the shift from UARS to OSA occurs around age 40: at age 20–29 years 31% of subjects present with UARS while only 7.4% have OSAS, but at 60–69 years only 5.5% have UARS and 62% have OSA. At age 40 the prevalence of 24.6% of UARS versus 24.2% of OSAS. As this is not a longitudinal study, they can only suggest that a pathological process – perhaps as described by Friber et al. [24], occurs and leads to a passage from UARS toward OSAS. The only study looking at two different points separated by about 5 years – a follow-up that may not be long enough – shows that most UARS individuals (usually young adults) were usually not treated despite indication of pathology to referring physicians and clinically had a worsening of complaints, but only a few developed a diagnosis of OSAS after repeat PSG [41].

7. Patient care today

The increased use of the 'home study' has decreased the recognition of UARS, as EEG is not monitored, and quantification of sleep disturbance cannot be performed. Even with improved technology, findings are not extracted from PSG studies as they should: Nasal cannula allows recognition of IFL but is a poor detector of EFL. EFL is however an integral part of abnormal breathing during sleep. Lofaso et al. monitored both Pes and gastric pressure (Pga) and using the same approach as the New-York group testing nasal cannula and observing changes obtained with application of nasal continuous-positive-airway-pressure (CPAP) demonstrated the presence of expiratory abdominal muscle activity [EAMA] and showed presence of a rise in Pga with CPAP pressure [42]. The Stanford group replicated this finding and systematically studied the discharges of the abdominal expiratory muscles in patients with snoring and flow limitation. The Stanford group documented the presence of expiratory muscle discharges in subjects with apnea-hypopnea in 1978, a finding replicated by others [43–45]. Furthermore, Chronic snoring should be a clinical marker to raise concern in treating specialists as its impact on complaints and respiratory muscles has been documented for a long time [46,47].

Recognition of the EFL is difficult with nasal cannula indicated only by a decrease in the widening of the peak of the expiratory flow curve. The easiest way to indicate the presence of EFL is measurement of expiratory muscle discharges [48, 49]. Based on successive recordings the Stanford group found out that there is a temporal progression of flow limitation: In all studied subjects with clinical complaints of symptoms associated with UARS ($n = 50$), there was after sleep-onset, (1) Development of IFL, (2) then development of snoring, and (3) development of inspiratory and EFL . The progressive temporal occurrence was always noted, but the Stanford group had to review 400 UARS PSG to find 50 with the presence of EFL during a portion of the PSG, indicating that IFL was likely the more common pattern than EFL indicated by abnormal expiratory-abdominal-muscle discharges, which were not present in many cases. Increases in IFL often led to EEG changes before occurrence of EFL; but increase in inspiratory and expiratory muscle discharges followed a similar 'crescendo' pattern, and snoring became louder with each flow limited breath with a combination of simultaneous IFL and EFL.

Rimpila et al. [50] insisted in the recent past on the presence of CO_2 retention in association with 'flow limitation' and hypopneas. Looking at changes in transcutaneous CO_2 recordings, they analyzed a small number of well-characterized events and found that there was an increase in $TcCO_2$ curve about 20 s after the EEG arousals. The Stanford group analyzed the $TcCO_2$ curve with the individual events, but were unable to see the pattern reported by the authors with IFL. One possibility is the slow response of the transcutaneous electrode, an end-tidal CO_2 analysis would probably be more accurate, but the equipment already included a scoop for mouth breathing analysis and as nasal flow changes from nostril to nostril during sleep and as IFL is measured as the resultant of flow from both nostrils, the group did not monitor end tidal CO_2 in their UARS patients. The only time the Stanford group were able to see increases in TcCO2, 10–20 s after an arousal was with simultaneous presence of IFL and EFL and when such association had lasted for at least 90 s. The association of some limited increase in CO_2, may probably be explained by incomplete expiration associated with EFL. Further attention should be given to EFL and expired CO_2.

8. Conclusion

For many years' attention has been drawn only to 'hypoxic-sleep-disordered-breathing-H-SDB.' This is related to the very prominent presence of obesity with co-morbid OSA, and the easiness to use finger oximetry to diagnose patients. Furthermore, it has led to many four channel-ambulatory recorders, with very limited investigation of 'sleep-disordered-breathing.' Development of sophisticated equipment capable of treating any type of H-SDB, i.e. not only OSA but also REM-sleep-related hypoventilation or hypoventilation syndromes, and the demonstration-particularly in the hypoventilation syndromes- of the very successful outcome of decreases in hospitalization and improved quality of life, justify this effort.

But, for many SDB began very early in life. We have indicated how problems may be suspected at birth and recognized even in early infancy. Specialists should now recognize and treat not 'UARS' but 'non-hypoxic' SDB avoiding further evolution of health problem and probable slow worsening overtime. Current sleep polysomnographic equipment, in laboratory or ambulatory, allows us to perform more sophisticated recordings than ever before- even if Pes is still a gold standard- and allows us to perform appropriate analyses of recorded signals. The key issue is to monitor appropriately many variables and to know how to score them. The Brazilian group has defined on their population sample, the normative limits of 'flow limitation' in adults. Such investigation should be replicated, as nasal cannula allows appropriate recording of IFL, particularly when using a DC channel (see Figure 5). Appropriate investigation of the expiratory part of the breathing cycle may suggest the presence of abnormal airway resistance. Systematic analysis of mouth breathing during sleep should be mandatory, as mouth breathing always indicates an increase in airway resistance due to the tongue and mandibular position associated with mouth breathing supine, and any study of treatment should involve evaluation of appropriate nasal breathing during sleep, as restoration of normal nasal breathing is the only indication of successful treatment results.

9. Expert commentary

Since the description of 'obstructive apnea' in 1960 on two Pickwickian patients by Gerardy in Heidleberg, Germany [51], the notion of 'abnormal breathing during sleep' and how to recognize and treat it has evolved. Obstructive-Sleep-apnea-syndrome, Upper-airway-Resistance Syndrome, apnea-hypopnea-index represent steps in our progressive understanding of the problem. Technological Improvements in our ability to monitor breathing during sleep have led to these advances. Currently, we know that at birth and during the first few years of life, many already have indications of the factors leading to abnormal breathing during sleep [52]. Recognition of these factors should lead to much earlier treatment and avoidance of the end-stage of the problem
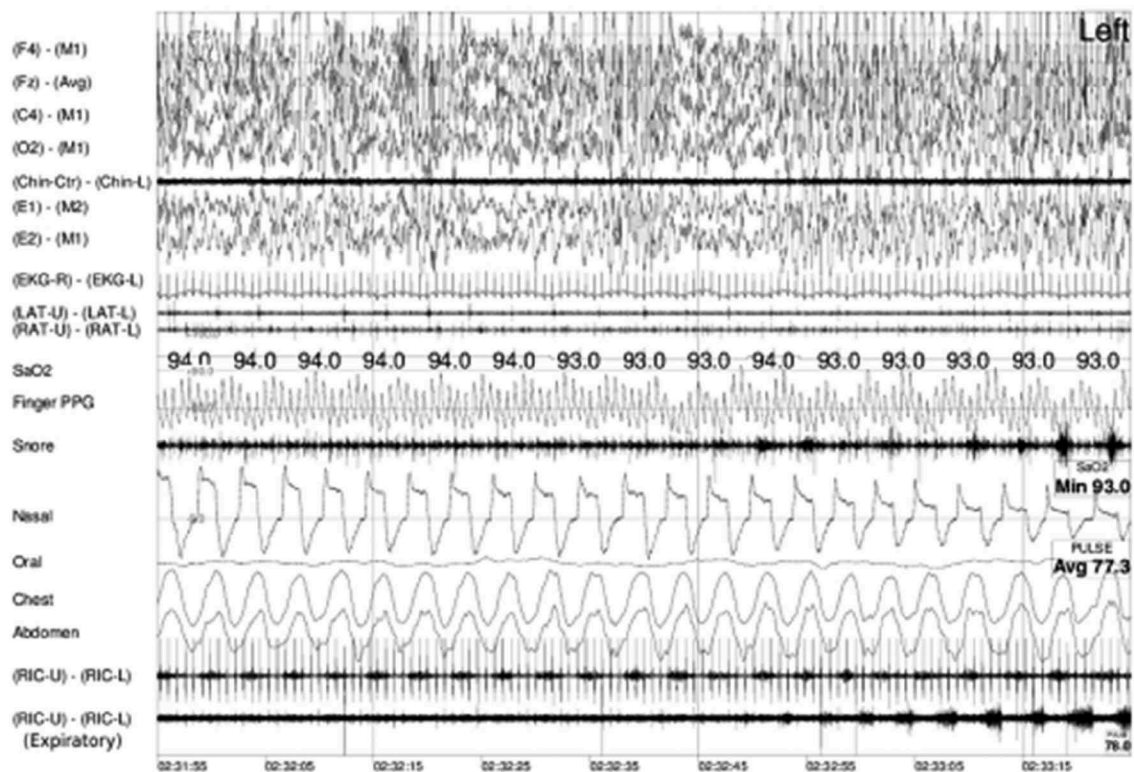

Figure 5. Polysomnographic recording of a UARS patient. Channels from top to bottom: channels 1–4: EEG leads, channel 5: chin EMG channel 6 and 7: 2 eye movements channel, channel 8: ECG, channel 9 and 10: 2 leg EMG, channel 11: oximetry, channel 12: Finger-plethysmography, channel 13: snore volume, channel 14: nasal cannula, channel 15: oral channel (scoop), channel 16 and 17: Thoracic and abdominal inductive plethysmography bands, channel 18: intercostal/diaphragm muscles recording, channel 19: oblique – expiratory- muscle recording channel. As can be seen at beginning of recording segment nasal cannula already indicate flow limitation that get worse over time but is not associated with 3% SaO2 drop. Progressive snoring is recorded and increases in power with occurrence of increasing expiratory muscle activity. The arousal occurs just at the very end of the presented segment.

i.e. 'Co-morbid-OSA'. AHI, OSA, UARS are historical names that showed the progresses that have been made. In clinical practice, many to date still do not recognize the very early indicators of the problems that will handicap an individual for the rest of his or her life, while prevention is something that could be done. UARS was a historical attempt at leading the field toward a better understanding of 'abnormal breathing during sleep' and to pull-it out of the marrams of OSA and the AHI. Advances in technology have allowed us to perform investigations not possible previously and to advance our field to earlier recognition of a problem that will only worsen over-time. Many to date only recognize co-morbid OSA and focus on the treatment of the co-morbidities. This is an important medical mission but the recognition of UARS has allowed us to progress from the 'end-stage' recognition of co-morbid OSA. Nomenclatures, obsolete scoring systems, insurance companies, and their financial demands, have been a burden in the advances in our quest to control abnormal breathing during sleep as early as possible. Our proposal of non-hypoxic SDB is nearly already past, but it will lead the field of Sleep Medicine to the prevention of the progressive development of symptoms and complications overtime during the life of the patient.

10. Five-year view

We must better define 'flow limitation' not only in adults but also in pre-pubertal children. Usage of the 'apnea-hypopnea index' has passed and several studies looking only at 'snoring', particularly in children, have found strong association with abnormal learning, memory, and behavior. As shown above, appropriate collection of signals during polysomnography and accurate analyses of these signals, explain why the AHI is less sensitive than a variable such as snoring. But we have to give normal ranges for different age groups. We have to work with technology to develop analyses of 'flow limitation,' possibly with EMG activity of inspiratory and expiratory muscles. Such efforts have already begun but have not been emphasized and generalized. These developments should be implemented in clinical practice after the development of normative data. Finally, information must be shared with health-care 'payers' (insurance companies, social-security administrators, and health policy-makers) as a clearly recognizable group of patients remain untreated.

Key issues

- Discuss the history of UARS.
- Define UARS.
- Discuss the pathophysiology of UARS and compare it to that of OSA.
- Discuss the limitations of identifying UARS on polysomnogram.
- Discuss vagal tone and UARS.
- Discuss the prevalence of UARS.
- Discuss current patient care.
- Discuss goals of the future for UARS: Non-Hypoxic Sleep Disordered Breathing.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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