Comparison of Respiratory Polysomnographic Parameters in Matched Cohorts of Upper Airway Resistance and Obstructive Sleep Apnea Syndrome Patients*

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Objective: To compare respiratory nocturnal polysomnography (NPSG) characteristics between matched cohorts of upper airway resistance syndrome (UARS) and obstructive sleep apnea syndrome (OSAS) patients.

Methods: All patients received 13-channel NPSG, including esophageal pressure (Pes) manometry. By definition, OSAS patients had an apnea-hypopnea index (AHI, number of apneas/hypopneas per hour total sleep time) ≥ 15, and UARS patients had an AHI < 5. Respiratory effort-related arousal (RERA) was defined as the absence of apnea/hypopnea with ≥ 10 s duration of progressive negative Pes, culminating in an arousal or microarousal. UARS patients, by definition, had ≥ 15 RERAs per hour. Fifteen consecutively diagnosed UARS patients were matched with OSAS patients on the basis of body mass index (BMI) and gender.

Results: Respiratory disturbance index (sum of the AHI and RERA per hour) was the same for both cohorts: UARS, 36 ± 4; OSAS, 42 ± 6 (p = 0.34). There were no differences between cohorts for mean inspiratory Pes nadirs for each 30-s epoch of sleep compared for each sleep stage over an entire night. For randomly selected breaths from supine stage 2 sleep, the mean inspiratory Pes nadir was the same for the cohorts: UARS, −16.6 ± 2 cm H₂O; OSAS, −16.1 ± 3 cm H₂O (p = 0.30). Differences between cohorts for each parameter fell within respective 95% confidence intervals.

Conclusion: With the exception of AHI, respiratory NPSG parameters were the same for UARS and OSAS patients when BMI and gender were controlled for.

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Key words: obstructive sleep apnea; polysomnography; upper airway resistance syndrome

Abbreviations: AHI = apnea/hypopnea index; BMI = body mass index; CI = confidence interval; NPSG = nocturnal polysomnography; OSAS = obstructive sleep apnea syndrome; Pes = esophageal pressure; RDI = respiratory disturbance index; RERA = respiratory effort-related arousal; UARS = upper airway resistance syndrome

The spectrum of severity for sleep-disordered breathing ranges from minimal, primary snoring, to the more severe obstructive sleep apnea syndrome (OSAS). Upper airway resistance syndrome (UARS) is considered a mild variant of OSAS, positioned as an intermediate on this spectrum.1 However, OSAS patients tend to be more obese than UARS patients.2 Prior studies have demonstrated the independent effect of obesity on the impairment of nocturnal respiratory function in OSAS patients.3-4 The current study seeks to determine whether UARS is a mild variant of OSAS by comparing characteristics of the nocturnal respiratory events of UARS and OSAS patients when the variables of obesity and gender are controlled for.

Patients with UARS typically present with complaints of excessive daytime sleepiness and snoring, and do not have OSAS on evaluation with standard nocturnal polysomnography (NPSG) using an oronasal thermocouple to measure airflow.6 For UARS patients, esophageal pressure (Pes) manometry demonstrates progressive negative pressures followed by
frequent arousals or microarousals.7 The prevalence of UARS in an asymptomatic population is unknown, but recent studies estimate that approximately 10 to 15% of all patients presenting to sleep disorder centers with snoring and excessive daytime sleepiness have UARS.8,9

It is more difficult to diagnose UARS accurately than OSAS. Although a number of novel techniques appear to have promise for diagnosing UARS without measuring Pes, there are few validation studies for these techniques.10–12 The “gold standard” for the diagnosis of UARS, Pes measurement, requires the use of an esophageal catheter. Few of the clinical sleep centers in the United States measure Pes routinely, possibly due to associated patient discomfort or added technical requirements and expense.13 There are few studies that demonstrate morbidity associated with UARS, other than excessive daytime sleepiness. Thus, another plausible explanation for the infrequent application of Pes measurement is that many physicians do not believe UARS requires treatment. Although case series14 and experimental models15 suggest that hypertension may be a consequence of untreated UARS, to our knowledge, no systematic studies of UARS patients evaluate this possible association.

In contrast to UARS, there are many studies that have assessed the outcomes of untreated OSAS.16 The majority of these studies have had methodologic flaws leading to controversy as to whether untreated OSAS results in increased morbidity and mortality.17 The ongoing Sleep Heart Health Study, which tracks cardiovascular outcomes, has evaluated 6,600 patients with NPSG and should elucidate the possible risks of untreated OSAS.18 However, the identification and study of UARS patients is not a component of this large-scale study. In lieu of UARS outcome data, it is important to consider whether UARS and OSAS patients are similar with respect to the severity of potential pathophysiologic mechanisms. If prospective studies affirm the need to treat OSAS patients, and there are minimal differences in the nocturnal respiratory characteristics of these matched patient cohorts, such data would support the need to diagnose and treat UARS in patients.

**Materials and Methods**

**Patients**

Following protocol approval by the Walter Reed Army Medical Center Department of Clinical Investigation and Institutional Review Board, informed, written consent was obtained from all patients involved in this study, which occurred between November 1997 and March 1998. During this period, 127 adult patients presented to the Walter Reed Army Medical Center Sleep Disorders Center and received an initial NPSG for the clinical evaluation of excessive daytime sleepiness, snoring, and/or bedpartner-witnessed apnea/hypopnea. The criteria for a second NPSG were an apnea/hypopnea index (AHI) < 5 on the initial NPSG and the absence of other sleep disorders, such as narcolepsy or movement disorders. Eighteen patients received a second NPSG, including Pes monitoring, but only 15 patients had UARS as defined by ≥ 15 respiratory effort-related arousals (RERAs) per hour. The UARS cohort was matched on the basis of gender and body mass index (BMI; measured in kilograms per square meter) with a cohort of 15 OSAS patients selected from 52 OSAS patients who also received diagnostic NPSGs, including Pes manometry completed during the same period.

**NPSG and Pes Measurement**

All UARS and OSAS patients underwent an initial 12-channel NPSG (SomnoStar 4100 system; SensorMedics; Yorba Linda, CA), which included the following standard parameters: central and occipital EEG; right and left electro-oculogram; digastric and tibialis electromyogram; continuous airflow by oronasal temperature thermistor; chest-wall excursions by thoracic and abdominal inductance plethysmography; heart rate and rhythm by ECG; oxyhemoglobin saturation by pulse oximetry; and acoustic monitoring of snoring sounds. The NPSGs were scored using 30-s epochs following the Rechtschaffen and Kales16 criteria for sleep/wake determination and sleep staging. Arousals were defined as ≥ 3 s of a shift to alpha or theta EEG activity from a slower background frequency. Microarousals were defined as < 3 s and ≥ 0.5 s, respectively, of a shift to alpha or theta EEG activity from a slower background frequency. Sleep efficiency was calculated as the percentage of total sleep time observed for the entire NPSG recording.

On the following night, a second NPSG was performed, which included a standard 12-channel recording montage, along with the additional measurement of Pes, performed with a 2.7-mm diameter electronic pressure catheter (Gaeltec; Hackensack, NJ), with the tip positioned in the midesophagus as verified by radiograph. The Pes transducer was referenced to atmospheric pressure and was calibrated with a water manometer (series 477; Dwyer Corp; Michigan City, IN) to ± 50 cm H2O.

**Respiratory Event Definitions and Analysis**

Apnea was defined as the cessation of airflow for ≥ 10 s, and hypopnea was defined as a recognizable, transient reduction but not a complete cessation of breathing for ≥ 10 s. Hypopnea was scored with a ≥ 50% decrease in the amplitude of oronasal thermocouple airflow or a < 50% amplitude reduction, which was associated with either an oxygen desaturation of ≥ 3% or an arousal. A RERA was an event characterized by increasing respiratory effort for ≥ 10 s leading to an arousal or microarousal from sleep that did not fulfill the criteria for hypopnea or apnea. A RERA was detected with nocturnal Pes manometry, which demonstrated a pattern of progressive negative Pes terminated by a change in pressure to a less negative pressure level associated with an arousal or microarousal.20 Examples of a RERA from a UARS patient and an apnea from an OSAS patient are presented in Figure 1.

By definition, OSAS patients had an AHI ≥ 15 and UARS patients had an AHI < 5. UARS patients, by definition, had ≥ 15 RERAs per hour. The respiratory disturbance index (RDI) was the sum of the AHI and the number of RERAs per hour.

For each patient, the Pes nadir for each 30-s epoch of sleep was determined, and the mean of these measurements was calculated for wake and each sleep stage without regard to body position.
The mean Pes nadir also was determined for each patient using 40 randomly selected breaths during supine stage 2 sleep. The Pes nadir for the entire NPSG for each patient was also evaluated.

For each patient, the lowest nocturnal oxygen saturation was determined for the entire NPSG. The percentage of sleep time at ≤90% and mean nocturnal oxygen saturation were also evaluated.

Statistical Analysis

Values are expressed as the mean ± SEM. Mean values of various parameters were compared between the UARS and OSAS cohorts using independent group t tests by computer software (SigmaStat; SPSS; Chicago, IL). The level of significance was set at p < 0.05. For all outcome measures, 95% confidence intervals were calculated for the differences between the cohorts.

Results

Demographics

Table 1 contains the demographic characteristics of the 15 UARS and matched OSAS patients. There was no significant difference in BMI for the UARS compared to the OSAS cohort (30.1 ± 1 kg/m² vs 28.4 ± 1 kg/m², p = 0.19). The OSAS cohort was older than the UARS cohort (47.3 ± 3 years old vs 39.5 ± 2 years old, p = 0.045). All patients were male.

Respiratory Events

The AHl was 33 (range, 16 to 87) for the OSAS cohort and 2.8 (range, 0 to 4) for the UARS cohort. The RDI was not significantly different between the cohorts: OSAS, 42 ± 6; UARS, 36 ± 4; p = 0.34; confidence interval (CI), −4 to 28 (a difference of 6). Figure 2 presents a comparison of these obstructive respiratory indexes for the two cohorts.

Pes Measurement

The mean Pes inspiratory nadir for each 30-s epoch of the NPSGs for the UARS and OSAS cohorts is shown in Figure 3. These measurements were not adjusted for body position. The greatest magnitude Pes occurred for both cohorts with slow-wave sleep (stages 3 and 4), and the least magnitude occurred with wakefulness and stage 1. There were no statistically significant differences for the Pes for each sleep stage and wakefulness when the cohorts

Table 1—Cohorts Matched for BMI

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<th>BMI, kg/m²</th>
<th>UARS</th>
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were compared, with the differences between the cohorts well within the 95% CIs. There was no difference in the mean inspiratory Pes nadir for randomly selected breaths occurring in supine stage 2 sleep (UARS, $-16.6 \pm 2$ cm H\textsubscript{2}O; OSAS, $-16.1 \pm 3$ cm H\textsubscript{2}O; $p = 0.30$; CI, $-7.6$ to $6.5$ [a difference of $-0.5$]). The most negative Pes value recorded for the entire NPSG was the same for the two cohorts (UARS, $-30.1 \pm 8.3$ cm H\textsubscript{2}O; OSAS, $-31.3 \pm 8.3$ cm H\textsubscript{2}O; $p = 0.70$; CI, $-7.6$ to $5.5$ [a difference of $-1.2$]).

Nocturnal Pulse Oximetry

There was no significant difference between the cohorts for lowest nocturnal oxygen desaturation (UARS, $88.3 \pm 5$%; OSAS, $84.7 \pm 5$%; $p = 0.08$; CI, $-7.4$ to $2.0$ [a difference of $-3.6$]). The mean nocturnal oxygen saturation for the total duration of the NPSG was the same for both cohorts (UARS, $96.0 \pm 1$%; OSAS, $95.0 \pm 1$%; $p = 0.06$; CI, $-2.0$ to $1.5$ [a difference of $1.0$]). The total number of minutes during the NPSG with oxygen saturation $<90\%$ did not significantly differ between the cohorts (UARS, $0.6 \pm 1$; OSAS, $3.1 \pm 6$; $p = 0.11$).

Sleep Structure

The total arousal index was increased for the OSAS cohort compared to the UARS cohort: $53 \pm 23$ vs $32 \pm 13$, respectively; $p = 0.005$; CI, $7$ to $35$ (a difference of $21$). Sleep stage distribution was the same for the two cohorts. For the OSAS and UARS cohorts, total sleep time ($307 \pm 23$ min vs $335 \pm 17$ min, respectively; $p = 0.34$; CI, $-87$ to $31$ [a difference of $-28$]) and sleep efficiency ($81 \pm 13\%$ vs $86 \pm 13\%$, respectively; $p = 0.31$; CI, $-14$ to $5$ [a difference of $-5$]) did not differ.

**DISCUSSION**

This study compared the NPSG respiratory parameters of BMI and gender-matched cohorts of UARS and OSAS patients. The most important finding of this study is that the UARS cohort demonstrated the same abnormal nocturnal respiratory measurements as the OSAS cohort, with the exception of the AHI. The UARS cohort comprised consecutive patients who were referred with symptoms suggestive of OSAS but who did not have OSAS on standard polysomnography using an oronasal thermocouple to estimate flow. When RERAs, events detected on the basis of Pes measurement, were included in the RDI, the number of obstructive respiratory events for the two cohorts was the same. The OSAS cohort had a mean AHI of approximately 40, which most sleep medicine specialists would consider severe enough to warrant life-long treatment with continuous positive airway pressure. This finding runs counter to the notion that UARS is a mild variant of OSAS and, therefore, requires less intensive efforts at diagnosis and treatment.

Additional important findings are that these cohorts had the same Pes values overall, after adjusting for sleep stage and supine positioning. These findings suggest that if there are deleterious cardiovascular sequelae of OSAS mediated to some degree by an increase in the intermittent variation of intrathoracic pressure, both OSAS and UARS patients may be at increased risk. A potential confounding factor, which we did not evaluate, was the Pes nadir of obstructive events of similar duration, as it is possible that the rate of change of Pes is also an important factor.

The cohorts demonstrated the same degree of nocturnal oxyhemoglobin desaturation measured by pulse oximetry. However, this finding could be a consequence of the lack of sensitivity of $\text{SaO}_2$ as an estimate of $\text{Po}_2$ when it is measured on the flattened, right-hand portion of the oxyhemoglobin desaturation curve in the young and middle-aged adults.
included in the current study. OSAS patients intuitively seem more likely to experience oxyhemoglobin desaturation with the occurrence of apneas resulting in complete airflow obstruction, compared to UARS patients, who maintain partial airflow during a RERA. An animal study by Chen et al.\textsuperscript{23} demonstrates the robust effect of hypoxemia in augmenting the pressor response to periodic apneas. A study including the measurement of serial, nocturnal blood gases is necessary to characterize nocturnal hypoxemia in UARS patients accurately.

The total arousal index was increased in the OSAS cohort compared to the UARS cohort. The cause for this increase is not obvious, because both cohorts had the same number of obstructive respiratory events during sleep, as measured by NPSG with the addition of Pes manometry. Prior studies suggest that the arousal threshold increases in patients with more severe forms of sleep-disordered breathing, resulting in a decreased propensity for arousals.\textsuperscript{24} The lower total arousal index of the UARS cohort may be further evidence of the severity of this syndrome. Microarousals, defined as arousals of < 3 s duration,\textsuperscript{25} were not quantified as a part of the current study. Some investigators suggest that UARS is characterized by an increased number of microarousals compared to those in normal patients,\textsuperscript{26} although no studies (to our knowledge) have yet compared these microarousals in cohorts of UARS and OSAS patients.

Clinical predictors alone have not been shown to distinguish OSAS patients from normal patients adequately, and in the current study population of young and middle-aged adults, it may even be more difficult to distinguish these groups.\textsuperscript{27} Twelve-channel NPSG with oronasal thermocouple airflow measurement has not been demonstrated to be an adequate technique to distinguish UARS patients from normal ones. Data from our Sleep Center suggest that 31% of patients who did not have OSAS but did have crescendo snoring and a total arousal index of > 20, which is suggestive of UARS, did not have UARS when Pes manometry was performed.\textsuperscript{9} Recent studies suggest that measurements of critical pharyngeal closing pressure,\textsuperscript{10} nasal pressure waveform,\textsuperscript{11} and quantitative respiratory inductive plethysmography, when integrated with standard NPSG,\textsuperscript{12} are promising techniques for the diagnosis of UARS in patients. Until these newer techniques are validated in studies with larger patient numbers, Pes manometry should still be used to evaluate patients with suspected UARS.

In conclusion, the current study suggests that UARS is not a mild variant of OSAS, based on the lack of differences observed with respect to obstructive respiratory event frequency and the magnitude of fluctuations in the inspiratory Pes nadir. The separation of UARS and OSAS patients into different therapeutic approaches may not be appropriate. This study suggests that the classification of sleep-disordered breathing patients into the diagnostic categories of UARS or OSAS may be an artificial distinction based on the inability of the thermocouple to detect more subtle airflow limitation in UARS patients. Further diagnostic efforts should be made to detect sleep-disordered breathing in suspected OSAS patients with a low AHI on standard polysomnography.

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