

The Cyclic Alternating Pattern Demonstrates Increased Sleep Instability and Correlates With Fatigue and Sleepiness in Adults with Upper Airway Resistance Syndrome

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Objective: To clarify the relationship between sleep instability and subjective complaints in patients with upper airway resistance syndrome (UARS).

Methods: Thirty subjects (15 women) with UARS and 30 age- and sex-matched controls in a prospective, single-blind, case-control study. Blinded cyclic alternating pattern (CAP) electroencephalogram analysis and scales of fatigue and sleepiness were completed.

Analysis: Mann-Whitney U tests for independent, nonparametric variables between groups and χ^2 tests for nonparametric variables with defined standard values.

Results: Patients with UARS had significantly more complaints of fatigue and sleepiness, compared with controls, demonstrated on their Fatigue Severity Scale ($P < 0.001$) and Epworth Sleepiness Scale ($P < 0.001$). By design, the mean apnea-hypopnea index was normal in both groups, whereas the respiratory disturbance index was greater in patients with UARS than in those without (14.5 ± 3.0 vs 9 ± 5.2 , respectively [$P < 0.001$]). CAP analysis demonstrated abnormal non-rapid eye movement sleep with abnormally increased CAP rate, electroencephalogram arousals, A2 index, and A3 in-

dex. Decreased A1 index in controls was consistent with their more normal progression of sleep. CAP rate correlated with both the Epworth Sleepiness Scale ($r = 0.38$, $P < 0.01$) and the Fatigue Severity Scale ($r = 0.51$, $P < 0.0001$), and there was a positive trend between the Fatigue Severity Scale and phase A2 index ($r = 0.29$, $P < 0.05$).

Conclusion: Compared with age- and sex-matched controls, patients with UARS have higher electroencephalogram arousal indexes and important non-rapid eye movement sleep disturbances that correlate with subjective symptoms of sleepiness and fatigue. These disturbances are identifiable with sensitive measures such as CAP analysis but not with traditional diagnostic scoring systems.

Keywords: Upper airway resistance syndrome, chronic snoring, cyclic alternating pattern, fatigue, sleepiness, sleep disturbance.

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SLEEP-DISORDERED BREATHING CAUSES SLEEP DISRUPTION, FATIGUE, SLEEPINESS, AND LAPSES IN AROUSAL, ATTENTION, AND CONCENTRATION THAT compromise quality of life and can even result in accidents at work or while driving. Although conspicuous in obstructive sleep apnea, abnormal breathing during sleep may be harder to recognize in patients presenting with upper airway resistance syndrome (UARS).^{1,2} Additionally, the sleep electroencephalogram (EEG) changes associated with UARS appear much less dramatic than those noted with obstructive sleep apnea, and repetitive apneic events terminating in awakenings are often not apparent in the polysomnograms of patients with UARS.³

Further complicating the care of these patients is the fact that the complaints associated with this syndrome are often described as “functional.” Although this term indicates that a clear etiology is not yet diagnosed, it may inappropriately imply that there is no underlying medical cause. Such symptoms include complaints of sleep maintenance insomnia, chronic fatigue, chronic pain symptoms, fibromyalgia, morning headache, and cognitive difficulties

or parasomnias, such as chronic sleepwalking or bruxism.^{4,5} Inevitably, these frustrating symptoms are out of proportion to breathing events and sleep disruption depicted by routine scoring of the diagnostic polysomnogram. This may be, in part, secondary to loss of resolution from batching sleep into 30-second epochs for routine scoring of the polysomnogram and the lack of accounting for arousals shorter than 3 seconds in duration. Although unaccounted for with the standard technique, these additional disruptions in non-rapid eye movement (NREM) sleep may have clinical significance.

We report findings from a single-blinded, prospective, age- and sex-matched, case-control study of patients with UARS evaluated for sleep disruption with cyclic alternating pattern (CAP) analysis of the EEG. We hypothesized that patients with UARS would have CAP-analysis indexes demonstrating greater sleep disruption, compared with controls. We also hypothesized that this more-sensitive measure of sleep disruption would correlate with scales of their subjective complaints of sleepiness and fatigue.

METHODS

Subjects

Patients were referred by community physicians for complaints of tiredness, fatigue, unrefreshing sleep, sleep maintenance insomnia, joint pain, decreased cognitive performance, or morning headaches longer than 6 months in duration. Patients were without clear etiology for the above complaints despite appropriate internal medicine work-up and symptomatic-oriented treatments. Treatment trials included antidepressant medications (trazodone or serotonin reuptake inhibitors) in 80% ($n = 22$) of patients. All

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This is not an industry supported study. Drs. Guilleminault, Lopes, Hagen, and Rosa have indicated no financial conflicts of interest.

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subjects were medication free for at least 60 days at entry into the protocol. Age-matched (± 1.5 years) and sex-matched controls, in general good health with regular nocturnal sleep habits, no sleep complaints, and no recent or chronic medication use (except oral contraceptives), were recruited from the community. Controls and patients underwent identical evaluation and testing in the Stanford Sleep Disorders Clinic between September and December 2004. Participants were asked to complete 10 days of sleep diaries, indicating sleep habits and disturbances.

Measures

All participants completed the Sleep Disorder Questionnaire,⁶ the Epworth Sleepiness Scale (ESS),⁷ and the Fatigue Severity Scale (FSS).⁸ The FSS is a validated fatigue scale designed to assess functional outcomes related to fatigue in conditions such as chronic fatigue, multiple sclerosis, and systemic lupus erythematosus.⁸ This is a 9-item questionnaire with responses measured on a Likert scale from 1 to 7, where 1 indicates no impairment and 7 indicates severe impairment, such that higher FSS scores suggest greater fatigue. Its clinical utility, reliability, and validation criteria are reported elsewhere.⁸

All subjects completed a thorough sleep medicine evaluation, including assessment of craniofacial anatomy and orthodontic problems associated with upper-airway narrowing. This included quantification of body mass index, nasal septum deviation, inferior turbinate enlargement, external and internal nasal valve insufficiency, neck circumference, airway class with the Mallampati scale, and the Friedman et al tonsil size scale.^{9,10}

Polysomnography

The first diagnostic polysomnogram included esophageal manometry (Pes) for the diagnosing of UARS. Monitoring included EEG (C3/A2, C4/A1, O1/A1, Fp1/A1, Fz/A1-A2), chin and leg electromyogram, electrocardiogram (V2 lead), right and left electrooculogram, nasal cannula-pressure transducer system, mouth thermistors, esophageal pressure (Pes), thoracic and abdominal piezoelectric bands, neck microphone, finger pulse oximetry, and position sensor. Recordings were analyzed the following morning using American Sleep Disorders Association guidelines and the definitions outlined in Table 1A. Apneas and hypopneas were scored based on nasal-cannula recording such that hypopnea was defined as flow reduction by at least 30% for 10 seconds, compared with normal breathing, and associated with a decrease in oxygen saturation by at least 3% or an EEG arousal of 3 seconds' duration. Flow limitation was defined as a pattern demonstrating a reduction in the inspiratory flow by 3% to 29% (see Figure 1). These flow-curve findings were associated with Pes crescendos and continuously increased inspiratory effort on the Pes lead for at least 4 successive breaths to determine abnormal breathing events. From these data, a respiratory disturbance index was calculated reflecting the number of abnormal respiratory events per hour of sleep.¹¹ Subjects meeting criteria for obstructive sleep apnea or periodic limb movements were excluded from further study. All participants in the remaining UARS group fit the criteria outlined by Bao and Guilleminault for UARS:² complaining subjects must have had an apnea index of 0, a hypopnea index of 5 or less, an apnea-hypopnea index of 5 or less, and a minimum oxygen saturation greater than 92% during nocturnal sleep.

Table 1A—Scoring criteria for respiratory variables

Term	Definition
Apnea	Absence of airflow at nose and mouth for longer than 2 breaths, independent of desaturation or change in EEG. Subdivided into central, mixed, or obstructive based on airflow and Pes recording.
Hypopnea	Reduction by at least 30% in nasal flow-signal amplitude for a minimum of 2 breaths. Scored independently from SaO ₂ drop or EEG arousal. Often but not always associated with snoring.
Abnormal respiratory effort	Reduction in nasal flow of less than 30% with flattening of nasal-cannula signal (flow limitation) and decrease in the mouth signal (thermistor). Often seen with snoring and increased effort shown on Pes signal defined as:
Pes Crescendo ¹¹	Sequence of 4 or more breathes that show increasingly negative peak end inspiratory pressure. May be seen with flow limitation on nasal cannula.
Continuous sustained effort ¹¹	Repetitive, abnormally negative, peak end inspiratory pressures, ending at same negative inspiratory pressure without a crescendo pattern. Associated with discrete flow limitation on nasal cannula or pressure transducer signal, with "flattening" of the breath-signal curve for at least 4 successive breaths.
Pes Reversal ¹²	Termination of abnormal increase in respiratory effort with abrupt switch to a less-negative peak end inspiratory pressure.
Respiratory Event-Related Arousals	As defined by the AASM: Patterns of progressively negative pressure terminated by both a sudden change in pressure to a less-negative level as well as an arousal event lasting 10 seconds or more. ¹²
Tachypnea	Increase in respiratory rate, above that seen during quiet unobstructed breathing, by minimum of 3 breaths per minute in NREM sleep, or 4 breaths per minute in REM sleep, for 30 seconds or more. No changes in oxygen saturation, Pes, or EEG were required. ¹¹

EEG refers to electroencephalogram; Pes, esophageal pressure; AASM, American Academy of Sleep Medicine; NREM, non-rapid eye movement; REM, rapid eye movement

A second nocturnal polysomnogram without esophageal manometry was performed the second night to rule out sleep disturbance induced by esophageal manometry and to permit subject accommodation to the lab environment before collecting data for CAP analysis.¹¹⁻¹³ Control subjects and patients with UARS underwent the same series of polysomnograms. Both were continuously video monitored during sleep. The time of lights out for each study was selected according to the subjects' preceding sleep dairies, and sleep lasted a minimum of 7.5 hours. Patients signed informed consent for anonymous usage of data in research,

Patient Name: 100029 x, x
 Subject Code: x
 Study Date: 11/07/2006



Figure 1—Example of recording in a patient with upper-airway resistance syndrome (UARS). Electroencephalogram (EEG) (4 channels) chin electromyogram, electrooculogram (2 channels), electrocardiogram, leg electromyogram (2 channels), SaO₂, microphone (note mild snoring recording middle of figure), nasal cannula, mouth thermistor, chest and abdomen movements (2 channels). Note the succession of higher amplitude bursts (ie phase A indicated between arrows) followed by return to lower amplitude desynchronized EEG during stage 2 non-rapid eye movement sleep (Phase B). Note also fluctuation in amplitude of nasal cannula curve—inspiration signal: upward with normal breaths near center of figure and decrease in amplitude of successive breaths on right and left side of figure.

and controls signed informed consent and were remunerated for participation. All recordings were performed using the same computerized sleep system (Sandman TM-Kanata, ONT. Canada).

CAP analysis

Recordings of the second night (without Pes) for both groups were copied in European data format to CD-ROMs with indication of lights out and lights on. All CDs were coded for anonymity and blinding, then scored by a single scorer blinded to all subject-specific information (arm of study, age, sex, etc). Each record was first analyzed by 30-second epochs according to standardized criteria, with sleep latency defined as the first epoch of at least 16 seconds of any stage of sleep,¹⁴ and sleep efficiency as total sleep time divided by total recording time, from sleep onset until lights on. EEG arousals were scored based on the American Sleep Disorders Association criteria.¹⁵

CAP was first scored automatically using the Somnologica™ automatic scoring system based on the C3/A2 EEG and was then visually verified and corrected based on all recorded EEG leads

according to the CAP consensus report.^{16,17} CAP was scored during each NREM sleep period and included CAP cycles based on the presence of 2 successive phases A and B and CAP sequences, such as repetitive clusters of stereotyped EEG features formed by at least 2 consecutive CAP cycles.

Phase A lasts from 2 to 60 seconds. Subdivision of phase A into subtypes (A1, A2, A3) and phase B of a CAP cycle is based on the percentage of EEG desynchronization (Table 1B). Subtype A1 is scored as a change from baseline EEG to synchronized EEG activity that is less than 20% desynchronized and includes delta bursts, K-complexes, vertex sharp waves, and polyphasic bursts. Subtype A2 is scored as 20% to 50% desynchronized EEG activity. Subtype A3 characterizes a NREM EEG that is more than 50% desynchronized and comprises low-amplitude fast rhythms such as K-alpha complexes, EEG arousals, and polyphasic bursts. CAP rate (percentage of CAP cycle in total NREM sleep time), CAP time, CAP sequences and duration, CAP phase A count and duration, CAP phase B count and duration, and phase A subtype index (percentage of phase A1, A2, or A3 per hour of total NREM sleep) were calculated.

Table 1B—CAP scoring criteria^a

CAP	
Phasic EEG events	
Abrupt EEG shift—slow or fast—from the sleep EEG background activity	
Duration of events: lasting more than 2 and less than 60 seconds	
CAP sequence	
Sequences of 2 phasic EEG events alternating with EEG background activities	
Each CAP sequence: at least 2 CAP cycles in succession	
CAP Cycle	
Each CAP cycle includes Phase A (phasic events) + Phase B (recurring periods of EEG background activities)	
Phases A	
Phase A1:	Phases A consisting exclusively of synchronized EEG patterns (intermittent alpha rhythm in stage 1; sequences of K-complexes or of delta bursts in the other NREM stages)
Phase A2:	Phases A consisting of desynchronized EEG patterns preceded by slow high-voltage waves (ie, K-complex sequences with alpha and beta activities, K-alpha)
Phase A3:	Phases A with desynchronized EEG patterns alone (ASDA arousals; fast activities)
Phase B	
Phase B:	EEG background activities according to each sleep state
ASDA arousal	
Abrupt EEG shift toward fast activity, such as 8-13 Hz (alpha) or > 16 Hz (beta)	
Duration: lasting more than 3 and less than 15 seconds	

According to international criteria¹⁷

CAP refers to cyclic alternating pattern; EEG electroencephalogram; ASDA, American Sleep Disorders Association.

Table 2—Subjects' clinical characteristics

Clinical characteristic	Patients (n = 30)	Controls (n = 30)
Men/women, no.	15/15	15/15
Age ^a , y		
BMI ^a , kg/m ²	22.8 ± 1.6	23.0 ± 1.8
ESS ^a	8.5 ± 2.0 ^b	4.0 ± 1.5
FSS ^a	4.9 ± 0.9 ^b	2.3 ± 1.0
Clinical Complaints, no.		
Chronic fatigue	30	0
Daytime impairment	29	0
Non-refreshing sleep	28	0
Disrupted nocturnal sleep	26	0
Morning headache (at least 2/week)	18	0

^aData are presented as mean ± SD. BMI refers to body mass index; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale.

^bP = 0.001

CAP data comparison between controls and patients were performed using Mann-Whitney U tests and percentages with known standardized values were analyzed using χ^2 statistics. Associations between CAP parameters and clinical variables were performed with Pearson correlation tests.

RESULTS

Subject characteristics are summarized in Table 2. Although controls were without the following clinical complaints, all patients with UARS (n = 30) reported chronic fatigue, 28 reported nonrefreshing sleep, 26 reported disrupted nocturnal sleep, 17 reported morning headache, and 29 reported daytime performance impairment. The body mass index for the UARS and control subjects was the same at 22.8 ± 1.6 kg/m² and 23.0 ± 1.8 kg/m², respectively. Using the World Health Organization protocol and assessing between the 09:45 and 11:00, low blood pressure (defined as 90/60 mm Hg or lower) was present in 11 subjects.¹⁸

Anatomic findings involving abnormal nasal valve, small maxilla or mandible, and narrow upper airway with elongated pharyngeal soft tissue were noted in all patients. Only 1 control subject presented with retroposition of the maxilla, but this individual was without soft-tissue findings to suggest a narrow airway. The mean ESS was 8.5 ± 2.0 for patients, compared with 4.0 ± 1.5 for controls (P = 0.001). The mean FSS score for patients was 4.9 ± 0.9, compared with 2.3 ± 1.0 for controls (P = 0.001).

Night 1 total sleep time was insignificantly shorter than night 2 (363 ± 70.5 minutes vs 374.2 ± 64.7 minutes). Presence of intermittent or continuous nocturnal snoring was noted in 26 patients and intermittently in 1 control. Although there were no apneas recorded in any subject, hypopneas were present, and the apnea-hypopnea index therefore reflected a "hypopnea index." The mean ± SD apnea-hypopnea index was 2.6 ± 1.5 in patients with UARS and 0.6 ± 0.7 in control subjects (P = 0.0001). The respiratory disturbance index, calculated from nasal cannula and Pes findings as described earlier, was appropriately elevated in the UARS patients (9.1 ± 2.6 vs 0.9 ± 0.8), as expected. In both patients and controls, the lowest oxygen saturation was always above 92%. The results of polysomnography are summarized in Table 3. As shown in Table 3, the nocturnal sleep of patients with UARS was disturbed, with a greater arousal index; this index included all arousals of 3 seconds or longer in duration and was associated with a decrease in slow wave sleep and sleep efficiency.

Results of the CAP analyses indicate significant reductions in the integrity of NREM sleep in patients with UARS, compared with controls, with elevated CAP rate (57% ± 9% vs 34% ± 6%), CAP time (172 ± 41 seconds vs 77 ± 25 seconds) and CAP cycles (374 ± 101 vs 148 ± 76), respectively (Table 4). Phase A1, which is seen with normal progression into slow wave sleep, was higher in controls than in patients with UARS (P = 0.01). Phases A2 and A3 both indicated greater sleep instability in patients with UARS (P = 0.01). Phase A2 was greater in patients with UARS (25 ± 9 vs 19 ± 12.5), compared with controls, as was Phase A3 (16.1 ± 7 versus 11 ± 7.4).

There was a significant positive correlation between CAP rate and ESS score (r = 0.38, P = 0.01) as well as CAP rate and FSS score (r = 0.51, P = 0.0001). A positive trend was found between Phase A2 index and FSS (r = 0.29, P = 0.05). Pearson correlations for the remaining CAP indexes are presented in table 5.

DISCUSSION

As we hypothesized, CAP analysis demonstrated an even greater instability of NREM sleep than was appreciated with standard scoring. Furthermore, this indicator of sleep instability was correlated with subjective symptoms of sleepiness and fatigue, whereas both the apnea-hypopnea index and arousal index

Table 3—Sleep variables in patients with UARS and controls

Variable	Patients	Controls
Apnea Index, no./h	0	0
Hypopnea Index, no./h	2.6 ± 1.5*; 2.4	0.6 ± 0.7; 0.6
RDI, no./h	9.1 ± 2.6*; 9.2	0.9 ± 0.8; 0.88
TST, min	374.2 ± 64.7; 380	377.2 ± 75.5; 379
Sleep efficiency, %	85.0 ± 9.6****; 86.4	90.6 ± 4.6; 91.1
Stages 3-4 NREM, %	14.9 ± 6.12***; 14.8	25.4 ± 6.7; 25.7
REM sleep, %	7.9 ± 7.7; 17.76	19.4 ± 4.7; 19.4
Arousal Index, no./h	14.5 ± 3.0**; 14.6	9 ± 5.2; 9.4

Data are presented as mean ± SD; median

*P = 0.0001, (U-test)

**P = 0.001 (U-test)

***P = 0.00001 (χ^2)

****P = 0.04 (χ^2)

UARS, upper-airway resistance syndrome; Respiratory Disturbance Index (RDI), flow limitation with nasal cannula signal and esophageal pressure + apnea-hypopnea index; TST, total sleep time; NREM, non-rapid eye movement; REM, rapid eye movement.

Table 4—CAP variables

	UARS (n=30)	Controls (n=30)
CAP rate, %	57 ± 9*	34 ± 6
CAP time, sec	172 ± 41*	77 ± 25
CAP cycles, no.	374 ± 101*	148 ± 76
Index of CAP subtypes %		
A1	59 ± 13*	68 ± 16
A2	25 ± 9*	19 ± 12.5
A3	16.1 ± 7*	11 ± 7.4

Data are presented as mean ± SD. CAP refers to cyclic alternating pattern; UARS, upper-airway resistance syndrome.

*P = 0.01 Mann Whitney U test

failed to correlate with these common symptoms in patients with UARS. CAP analysis provided a more-sensitive measure of sleep instability in these subjects. Other factors, such as environmental stimuli, other sleep disorders, or a hypothetical reduction in arousal threshold, could also cause increased arousals. The patients with UARS, however, all had disordered breathing secondary to an abnormal airway as the source of sleep instability; other sleep disorders were excluded by polysomnogram, and the testing conditions were identical for both groups.

To be enrolled in the UARS arm of the study, patients needed to have an abnormal recording and meet criteria for UARS on the first polysomnogram. Therefore, by design, there was a significant difference in arousal index between patients and normal controls. This is an artifact of the study design and is noninformative, as our aim was to describe sleep disruption underappreciated by standard scoring criteria and its effects on daytime symptoms of sleepiness and fatigue.

Subjective scales of symptom severity (FSS and ESS) indicated both a statistically significant and clinically relevant elevation in fatigue and sleepiness in our patients with UARS. Although the mean ESS score of 8.5 in patients with UARS was not in the categorically abnormal range, it is over twice the ESS score of controls. This is consistent with our clinical sense that, although many patients with UARS may not necessarily fall asleep inadvertently during waking hours, they do suffer from more sleepiness than do controls. The mean difference in FSS score between groups was also both clinically and statistically significant. Additionally, this difference was likely minimized somewhat because FSS scores in controls were moderately higher than those of controls that have been previously published.⁸ The mean FSS score of 4.9 ± 0.9 in our patients with UARS was beyond the clearly abnormal benchmark of 4.0 for this scale.

The phase A index is defined by the number of EEG patterns defining a specific phase A per hour of NREM sleep time. Phase A2 is a desynchronized segment insufficient to qualify for an arousal by American Sleep Disorders Association criteria and, therefore, is not integrated in the standard scoring system. This index, along with CAP rate and CAP time, was significantly greater in patients with UARS. All 3 were also correlated to some degree with scores

of sleepiness and fatigue, thus supporting our hypothesis that UARS and its associated sleep fragmentation likely accounts for the frustrating and elusive complaints of sleepiness and chronic fatigue that are common in patients with UARS.

Delta bursts or delta clusters are EEG patterns noted in subjects with sleep complaints. Some consider these clusters as indicative of “disturbances” of sleep, whereas others deny any pathologic significance.¹⁹ Consistent with a pathologic significance to these findings, it has been shown that upper-airway occlusion during sleep can be associated with these delta clusters without intervening alpha or beta EEG occurrence.²⁰ The CAP system integrates these bursts during NREM sleep and the reoccurrence of synchronization-desynchronization EEG patterns in a comprehensive framework.

There is normally an increased progression during NREM sleep toward neuronal synchronization that culminates in the appearance of slow-wave sleep in the sleep EEG. If peripheral disturbances occur, this normal progression of delta and other high-amplitude waves will be interrupted with the reappearance of EEG desynchronization. This manifests as a phase A, which will ultimately be interrupted by a phase B of variable duration, as shown in Figure 1. Delta or other synchronized EEG bursts do not by themselves indicate abnormal sleep or arousal but, rather, in the context described above, represent the interruption of the normal evolution of EEG synchronization toward slow-wave sleep during NREM sleep. The Phase A1 index is related to this normal progression into slow-wave sleep, and the lower A1 index in patients with UARS is therefore consistent with our hypothesis. It must be emphasized that the CAP system does not take into consideration disturbances occurring during rapid eye movement sleep. This is the period wherein more-obvious disordered breathing and associated EEG arousals are more prevalent. Although the overall arousal index reflects both NREM and rapid eye movement sleep disturbances, CAP analysis describes the nature of only NREM sleep fragmentation. Previous studies have shown that NREM sleep instability can be the background on which parasomnias occur, including sleepwalking, sleep terrors, and bruxism. In these studies, as in the study presented here, a decrease in the percentage of phase A1 was observed.

Although phase A1 is inversely related to sleep instability, phases A2 and A3 are both directly related to sleep instability. The elevation in both of these indicators was statistically significant in our patients with UARS relative to controls. However, because phase A3 includes EEG arousals as defined by American Sleep Disorders Association criteria, this increase does not

Table 5—Pearson coefficient correlation analyses

Parameter	ESS (r)	FSS (r)
TST	0.10	0.15
Percentage of REM sleep	0.03	0.04
AHI	0.06	0.05
AI	0.17	0.20
CAP rate	0.38**	0.51***
CAP time	0.39**	0.53***
Phase A ¹ Index	-0.18	-0.20
Phase A ² Index	0.20	0.29*
Phase A ³ Index	0.17	0.20

ESS refers to Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; TST, total sleep time; REM, rapid eye movement; AHI, apnea-hypopnea index; AI: arousal index (number of 3 seconds or larger electroencephalographic arousal by hour of sleep); CAP, cyclic alternating pattern.

*P = 0.05

**P = 0.01

***P = 0.0001

describe additional disturbance beyond that accounted for by the arousal index. As mentioned above, phase A2 is not accounted for in standard sleep scoring and indicates a further disruption of NREM sleep.

Pes monitoring was associated with a nonsignificant decrease in total sleep time; however, our analysis was performed on a second night of recording without Pes monitoring to avoid any decrease in total sleep time. A validation of both the automatic CAP scoring system (Somnologica TM, Medcare; Reykjavik, Iceland) and human interscorer reliability has been described.²¹ Based on this previous study, we used the Somnologica TM scoring system as a first detection of CAP and then utilized the single best scorer of our clinic to be the blind scorer for the present study. As in the current study, the interscorer and automated scoring validation study was performed on subjects without Pes monitoring.²¹ The second night of recording in our study also permitted a night for accommodation to the testing environment.

Although it is difficult to demonstrate which proportion of subjective symptoms are attributable to the elevated CAP parameters versus the disturbance accounted for in the respiratory disturbance index, the fact that the CAP rate and A2 index are the only 2 indicators of disruption that correlated with fatigue and sleepiness is informative. We've demonstrated that the CAP system provides a more-sensitive analysis for problematic NREM sleep disruption that accounts for daytime symptoms otherwise unexplained by the standard scoring technique.

Black et al²⁰ used quantitative EEG analysis to show that there was significant increase in delta power before the reopening of the upper airway terminating obstructive breathing events and that reopening of the airway may occur without increase in alpha and beta EEG frequencies. Chervin et al²² used a computerized algorithm to show that changes in the EEG can be seen with many of the breaths seen during development of airway occlusion during sleep. These findings indicate that changes in the EEG can be many more than the short EEG arousals associated with termination of obstructive events. Thomas et al have used the CAP scoring system to affirm the appropriateness of nasal continuous positive airway pressure titration in patients with obstructive sleep apnea. These authors demonstrated that normalization of oxygen

saturation and flow, using currently available techniques, does not affirm complete return to normal breathing because persistence of upper airway resistance will still lead to an abnormally high level of CAP and persistence of daytime complaints.²³

There is often a misconception that all subjects with sleep-disordered breathing are overweight, resulting in failure of the primary care physician to recognize and refer patients with UARS for further evaluation. Many patients with UARS are sent to a sleep clinic as an afterthought and may not even be recognized by sleep laboratories if less-sensitive sleep- and breathing-recording techniques are used.²⁴ Even if UARS is recognized, undertreatment occurs when disruption in sleep due to flow limitation and increased effort is not appreciated. This is unfortunate because the current study demonstrates that these patients have increased sleep fragmentation that correlates with the severity of the subjective symptoms when tested with a more-sensitive indicator, such as CAP analysis.

Despite their less striking presentation, patients with UARS have a substantial amount of disturbed sleep. Chronic sleep disturbances are very much scrutinized today, given that, we are recognizing, beyond curtailing sleep, additional consequences on human well being, including learning, memory, performance, and other medical problems. Use of the CAP system permits more-sensitive detection of sleep disturbance and contributes to our understanding of the basis for subjective complaints described by patients with UARS. Future studies utilizing this technique are needed to elucidate the relationship between UARS and its complex constellation of common complaints.

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