Epilepsia, 49(12):2063–2068, 2008
doi: 10.1111/j.1528-1167.2008.01681.x

FULL-LENGTH ORIGINAL RESEARCH

Sleep staging and respiratory events in refractory epilepsy patients: Is there a first night effect?

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Summary

Purpose: We performed this analysis of possible first night effects (FNEs) on sleep and respiratory parameters in order to evaluate the need for two serial night polysomnograms (PSGs) to diagnose obstructive sleep apnea (OSA) in epilepsy patients.

Methods: As part of a pilot multicenter clinical trial investigating the effects of treating sleep apnea in epilepsy, two nights of PSG recording were performed for 40 patients with refractory epilepsy and OSA symptoms. Sleep architecture was examined in detail, along with respiratory parameters including apnea/hypopnea index (AHI) and minimum oxygen saturation. Analysis included two-tailed t-tests, Wilcox sign rank analysis, and Bland Altman measures of agreement.

Results: Total sleep time differed between the two nights (night 1,363.8 min + 59.4 vs. 386.3 min + 68.6, $p = 0.05$). Rapid eye movement (REM) sleep and percentage of REM sleep were increased during night two (night 1: 12.3% + 5.9 vs. night 2: 15.5% + 6.2, $p = 0.007$), and the total minutes of slow-wave sleep (SWS) were increased (night 1: 35.6 + 60.7 vs. night 2: 46.4 + 68.1, $p = 0.01$). No other sleep or respiratory variables differed between the two nights. Given an AHI inclusion criterion of five apneas per hour, the first PSG identified all but one patient with OSA.

Discussion: Respiratory parameters showed little variability between the first and second nights. Sleep architecture was mildly different between the first and second PSG night. Performing two consecutive baseline PSGs to diagnose OSA may not be routinely necessary in this population.

KEY WORDS: First night effect, Polysomnogram, Epilepsy, Obstructive sleep apnea, Rapid eye movement (REM) sleep, Slow-wave sleep (SWS).

In patients with epilepsy, studies of sleep architecture and respiratory disturbances have been a fruitful area of clinical investigation. Treatment of sleep apnea in those with refractory seizures may improve seizure frequency, quality of life, and daytime sleepiness (Wyler & Weymuller, 1981; Devinsky et al., 1994; Vaughn et al., 1996; Malow et al., 1997; Koh et al., 2000). One of the challenges, however, to investigators conducting polysomnogram (PSG)-based research in patients with epilepsy is the possibility of a first-night effect, and the possible need for two consecutive nights of polysomnography. The first night effect (FNE) is well-studied in the normal population and was first described in 1966 (Agnew et al., 1966). In control subjects, the first PSG night often has a longer sleep latency, less rapid eye movement (REM), and decreased sleep efficiency than subsequent nights of study, and this phenomenon is usually felt to represent habituation to the sleep environment (Toussaint et al., 1997). Respiratory parameters have also been demonstrated to change over repeated nights of testing (LeBon et al., 2000), and variations in the apnea/hypopnea index (AHI) on the second

Accepted April 22, 2008; Early View publication May 30, 2008.
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The study was presented in part at the Associated Professional Sleep Societies Meeting (APSS), Salt Lake City, Utah, June 2006.

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PSG are seen in children and the elderly as well as normal adult subjects (Waquier et al., 1991; Scholle et al., 2003; Li et al., 2004). However, the FNE seems to vary in different disease states—for instance, psychiatric inpatients have a much less pronounced FNE than controls (Toussaint et al., 1995).

The differences that have been noted in the sleep architecture of epilepsy patients may influence the degree of FNE in this population. The amount of REM sleep is often less than that noted in control populations, while stage 1 sleep may be increased (Marzec et al., 2005), and epileptiform activity is present mainly during non-rapid eye movement (NREM) sleep and may prove disruptive (Samaritano et al., 1991; Malow et al., 1998). These patients may be more prone to a FNE than the general population because they are more prone to disturbed sleep even outside of the laboratory, (DeWeerd et al., 2004), and already have a lower percentage of REM sleep. On the other hand, prior experience with EEG testing may allow them to acclimate more readily to the testing environment. Epilepsy patients have significantly increased daytime somnolence (Salinski et al., 1996), and their sleep latency and stage 1 sleep could be shorter than that of controls on their first night.

In our prior analysis of sleep architecture in 53 patients with medically refractory epilepsy studied at one site, during the second night of PSG compared to the first, patients exhibited a mild increase in slow-wave sleep (SWS) and a trend toward increased total sleep time (Marzec et al., 2005). In planning a pilot trial to evaluate treatment of obstructive sleep apnea (OSA) in patients with medically refractory epilepsy, we wished to confirm these findings in an independent cohort of patients studied at four different sites and also wished to include respiratory parameters (AHI and minimum oxygen saturation). Our hypothesis was that one night of PSG would be sufficient to make the diagnosis of OSA in a cohort of patients suspected of having OSA based on screening questionnaires and clinical evaluation.

Methods

Adult patients with refractory epilepsy were identified for enrollment in a study of the effects of treating sleep apnea on seizure frequency. Inclusion criteria included a frequency of two or more seizures per month (partial or generalized, auras excluded) that could be accurately quantified and a high clinical suspicion for OSA based upon a questionnaire addressing risk factors for OSA including BMI, snoring, and other clinical symptoms (for detail, see references Douglass et al., 1994; Weatherwax et al., 2003). Institution Review Board approval was obtained to study the effects of identification and treatment of sleep apnea in these subjects, and a detailed informed consent was obtained.

Patients enrolled in this fashion at four centers underwent two consecutive nights of research polysomnography. The PSGs were recorded on 32 channel digital systems. Recording montages were standardized to include chin electromyography (EMG), electrocardiogram (EKG), Limb EMG, nasal/oral airflow (thermocouples), thoracic and abdominal excursion (piezo-electric bands), electro-oculograms, pulse oximetry, and monitoring of snoring. The EEG montage was an extended eight channel parasagittal montage. Sleep studies were scored in 30 s epochs according to the usual standard guidelines, and all were scored in a blinded fashion by one coauthor and subsequently verified by a second coauthor (Rechtshaffen & Kales, 1968).

Analysis of the data included evaluation of the median, mean, and standard deviation of the following variables for the first and the second night of study: total sleep time, sleep efficiency, sleep latency, wakefulness and arousals, total stage 1 sleep, stage 2 sleep, stages 3 and 4 sleep (SWS), REM sleep, AHI, and percent minimum oxygen saturation. Wilcoxon signed-rank tests were conducted to compare the first night to the second night sleep parameters for each of these variables. No medication changes were made between the first and second nights of recording. Adjustment for multiple comparisons was avoided in order to screen most effectively for any possible clinically-significant differences between nights. A Bland–Altman agreement plot was also performed to compare the first and second night apnea-hypopnea indices 21 (Bland & Altman, 1986).

Results

Forty-three subjects were recruited for the study, but three were eventually excluded from analysis of FNE because of seizures that occurred in one of the two study nights. The average age of the group was 40 years (range 19–61, see standard deviations in Table 1). There were 21 women and 19 men enrolled, with an average BMI of 32.4. Six patients had a generalized epilepsy syndrome and the rest had refractory partial epilepsy, based on imaging, prior EEG, and semiologic characteristics. Mean baseline seizure frequency was 13 per month, and average

Table 1. Patient demographics

Variable	Mean (± SD)
Age	40.2 (±12.2)
Sex M/F	19/21
BMI	32.4 (± 8.1)
Partial/generalized epilepsy	34/6
Baseline monthly seizure frequency	12.5 (±23.9)
Age at onset	15.9 (±13.7)
Number of antiepileptic drugs (AEDs)	1.90 (±0.67)
Number of non-AED psychoactive medications	0.70 (±0.88)

Table 2. Sleep architecture/AHI comparisons, first versus second night

Variable	Median	Mean value	Standard deviation	Significance (2-tailed, Wilcoxon Signed-Rank test)	Normative range (Carskodon, 2000)
Total sleep time (TST)					
Night1	365.0	363.8	60.70	**p = 0.05**[a]	
Night 2	376.7	386.3	68.06		
Sleep efficiency (TST/record time)					
Night1	81.8	79.9	10.87	p = 0.40	
Night2	82.3	81.9	9.63		
Sleep latency (minutes)					
Night 1	12	21.5	24.65	p = 0.69	
Night 2	12.8	21.4	27.40		
Wake after sleep onset (minutes)					
Night 1	64.7	73.1	47.7	p = 0.58	
Night 2	58.7	69.3	48.4		
Stage 1 (min)					
Night 1	35.7	46.2	35.4	p = 0.92	
Night 2	37.5	43.1	26.0		
Stage 1%					
Night 1	9.7	13.5	11.8	p = 0.78	2–5%
Night 2	10.8	12.6	9.9		
Stage 2 (min)					
Night 1	241.6	230.9	74.1	p = 0.76	
Night 2	228.0	234.4	67.3		
Stage 2%					
Night 1	64.9	62.1	14.5	p = 0.18	44–55%
Night2	59.8	60.0	13.1		
Stages 3–4 (SWS min)					
Night 1	28.0	35.6	31.8	**p = 0.01**[a]	
Night 2	42.8	46.4	37.9		
Stages 3–4 (SWS)%					
Night 1	8.8	11.7	10.2	p = 0.37	13–23%
Night 2	10.7	12.2	9.8		
REM (min)					
Night 1	39.5	48.7	27.3	**p = 0.02**[a]	
Night 2	61	60.9	30.7		
REM%					
Night 1	10.3	12.3	5.9	**p = 0.007**[a]	20–25%
Night 2	16.1	15.5	6.2		
AHI (apnea hypopnea index)					
Night 1	11.6	13.5	10.3	p = 0.66	
Night 2	10.6	13.1	10.2		
Oxygen saturation (minimum)					
Night 1	87.0	85.4	7.5	p = 0.18	
Night 2	87.0	87.0	4.0		

[a]Significant differences at two-sided 0.05 significance level based Wilcoxon signed-rank test.

age of onset was 16. These patients were receiving an average of two antiepileptic drugs (16 patients were on monotherapy, see Table 1) and one other psychoactive medication (including medicines for anxiety and depression). All subjects underwent two consecutive nights of polysomnography in a research setting. Three of these patients had a seizure during one of the two nights of baseline recording, and were therefore excluded from analysis of the FNE, given concerns about possible disruption of sleep architecture and respiratory patterns after the seizure. In these subjects with seizures (one had seizures on both nights and two had seizures only on night one), it was noted that the AHIs were above 5 on both nights.

Table 2 lists the means and standard deviations for sleep and respiratory parameters assessed and compared over the two nights. These include sleep latency, minutes and percentages of stages 1 and 2 sleep, REM and SWS, arousals, AHI, and minimum oxygen saturation. Compared to normative adult data, our epilepsy patients had more stages 1 and 2 sleep on both nights, and less REM and SWS on both nights than the usual control subjects (Carskodon & Dement, 2000). Differences between the first and the second night of PSG were seen in the average REM sleep time in minutes, in the proportion of REM sleep, and in the total minutes of SWS, all of which were higher on the second night than the first. The total sleep

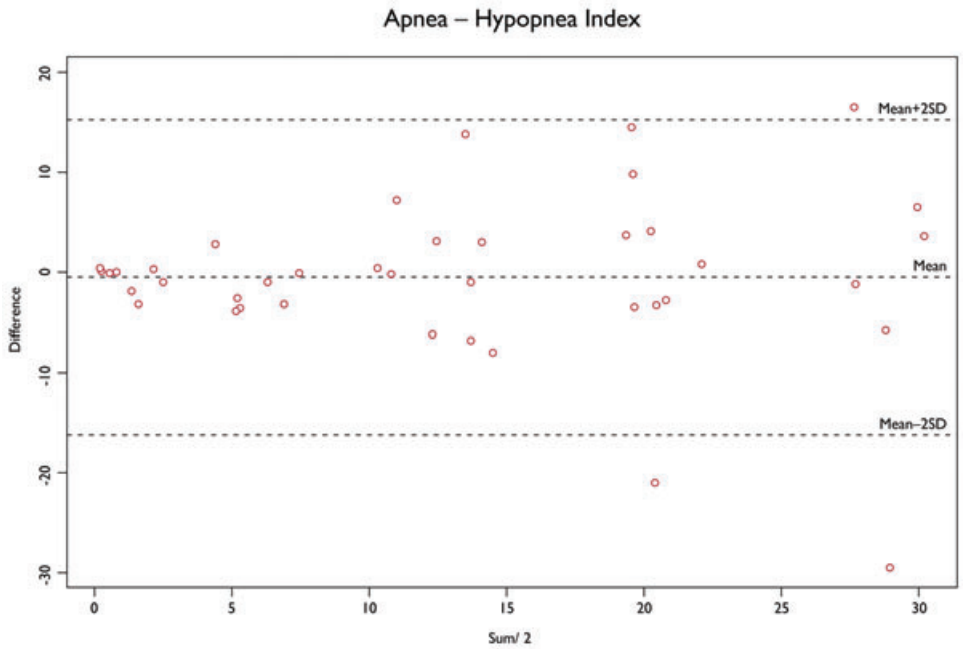

Figure 1.
Bland–Altman agreement plot of night 1 and night 2 AHI. The differences of AHI from nights 1 and 2 are plotted against the averages of the two measurements. Horizontal lines are drawn at the mean difference, and at the mean difference plus and minus two times the standard deviation of the differences. The funnel pattern in the plot shows larger AHI values tended to be more variable between the nights. (However, this should not affect results of nights 1 and 2 AHI comparison because the nonparametric Wilcoxon signed-rank test used is robust to this departure from normality.)
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time was at the limit of significance ($p = 0.05$). The most important change was an increase in the percentage of REM sleep during the second night (16% vs. 12% on night 1). Minutes spent in SWS also increased, although the proportion of the night spent in SWS did not, as the total sleep time increased overall.

The AHI did not show a significant difference between the two nights of recording. The absolute AHI difference ranged from 0 to 52, but the median difference was 3.25 (95% CI: 2.7–4) and the differences were primarily seen in those with high AHI scores (Fig. 1). The overall percentage of agreement between the AHI on the two nights was 90% (8 ± 28), with a kappa score of 0.73 (95% CI: 0.50–0.98) indicating moderate agreement between the two nights. AHIs on the two nights had correlation coefficients of rho (Spearman) = 0.73 and $p = 0.55$. There were no significant differences in AHI during REM or NREM sleep between the two nights.

The threshold for diagnosis of OSA in these patients was an AHI of 5 or greater. Only one patient met criteria for OSA on the basis of the second night alone (AHI 3 in night one and 5.8 in night two). Three patients had AHI >5 on the first night's study, but not the second. A total of 29 patients had an AHI over 5 on both nights and seven patients had an AHI below 5 both nights.

Discussion

In our cohort of refractory epilepsy patients undergoing PSG within a multisite pilot clinical trial, the differences in sleep architecture between first and second night PSG studies were limited to a borderline increase in total sleep time and an increase in REM sleep and SWS during the second night. Our findings are comparable to our prior work demonstrating a trend for higher total sleep time and higher proportion of SWS on night 2. Previous studies of FNEs in control groups have shown substantial sleep latency changes (Tamaki et al., 2005) that were not apparent in this epilepsy group. Our population showed sleep architecture differences from control subjects similar to those that have been described previously in epilepsy (Sammaritano & Therrien, 2002). Specifically, our patients had more light sleep, shorter sleep latency, and less REM and SWS than normal control subjects. Sleep latency in those with increased daytime somnolence may be more rapid on the first laboratory night, and previous

experience with EEG testing might make the setting less challenging. Still, the amount of REM and SWS increased significantly during the second night of recording in our epilepsy patients. The differences we noted between the first and second nights of recording may be relevant for detailed subsequent studies in this population; studies of sleep architecture may benefit from a two-night paradigm.

This is the first study to comprehensively analyze respiratory parameters in this population; we found no significant differences in AHI between the first and second night of study despite increased REM sleep on night 2. One might have anticipated that nights with increased REM sleep would have shown a higher AHI, but this was not the case. In the normal adult population, in children, and in the elderly, deeper sleep and higher AHI has been reported during the second night of study in some series (LeBon et al., 2000; Li et al., 2004). In our patients with epilepsy, neither total AHI, nor AHI in REM and NREM, nor minimum oxygenation documented any significant differences between the two nights. Although the Bland–Altman analysis did show greater variability in those with higher AHIs between the two nights, there was no substantial FNE on the ability to diagnose sleep apnea in this population of refractory epilepsy patients. Possible explanations for the lack of significant difference in respiratory parameters in this group may include the fact that sleep is disrupted at baseline by epileptiform discharges or changes in sleep maintenance. The effects of sleep disruption in a laboratory on respiratory parameters may be significantly less than the effects of altered cerebral electrophysiologic function in this group of patients with epilepsy and exposure to diverse medications with CNS effects.

Several other subgroups have been studied in whom the FNE may not cause substantially lower recognition of OSA after a single sleep study. In children, sleep architecture was different, but OSA did not differ by night in one series (Scholle et al., 2003) and another author proposed that it was probably not necessary to study pediatric patients for two nights (Li et al., 2005). Most recently, it has been discovered that older children had much less FNE for respiratory parameters than younger ones (Verhulst et al., 2006). A study of psychiatry patients also showed they have significantly less marked FNE than controls (Toussaint et al., 1995).

Whatever the cause of the milder FNE on sleep architecture and respiration in this epilepsy population, we have documented that the second night of PSG evaluation adds little to the overall detection of sleep-disordered breathing in our sample of patients with epilepsy. In our sample, 36 patients were ultimately randomized to treatment for OSA; only one with very mild apnea would have been excluded without a second night of polysomnography, and overall the agreement between the two nights for those with lower or borderline AHIs was very good. In some unusual clinical situations, a second night of polysomnography may be useful. However, given the cost and burden of an additional night of study to the research subject, the second night may not be necessary for further studies in this refractory epilepsy population.

Acknowledgments

The study has been supported by NINDS RO1 NS 042698 (BAM) and CGRC grants M01 RR00095 (Vanderbilt), RR00041 (University of Michigan) and RR00046 (University of North Carolina).

Conflict of interest: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with these guidelines. Author disclosures include the following: Ronald Chervin holds a professorship established in part by a contribution from Respironics, Inc. He serves on the scientific advisory board for Pavad Medical, Inc. and has consulted for Alexza Pharmaceuticals, Inc. Dr. Vaughn has research support from GSK, OM, Eisai, and has been a speaker for GSK. Dr. Foldvary-Schafer has grant support from Schwarz pharma, Cepahlon, Inc., UCB, Inc., GSK, and is on the advisory board for GSK. The remaining authors have no conflicts of interest.

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