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Nocturnal seizures are associated with more severe hypoxemia and increased risk of postictal generalized EEG suppression

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SUMMARY

Epilepsy patients have more than twentyfold greater risk of sudden death when compared to the general population. Uncontrolled seizures is the most consistent risk factor, and death often occurs at night or in relation to sleep. We examined seizure-related respiratory disturbances in sleep versus wakefulness, focusing on peri-ictal oxygen saturation. Respiratory measures were examined in 48 recorded seizures (sleep, $n = 23$ and wake, $n = 25$) from 20 adult epilepsy patients. Seizures from sleep were associated with lower saturation, as compared to seizures from wakefulness, both during ictal (sleep median = 90.8; wake median = 95.5, $p < 0.01$) and postictal periods (sleep median = 94.3; wake median = 96.9, $p = 0.05$). Compared to wake-related seizures, seizures from sleep were also associated with a larger desaturation drop (sleep median = -4.2 ; wake median = -1.2 , $p = 0.01$). Postictal generalized EEG suppression (PGES) occurred more frequently after seizures from sleep (39%), as compared to wake-related seizures (8%, $p = 0.01$). Our findings suggest that nocturnal seizures may entail a higher SUDEP severity burden, as they are associated with more severe and longer hypoxemia events, and more frequently followed by PGES, both factors implicated in sudden death.

Keywords

Epileptic seizures; sleep; oxygen desaturation; PGES; SUDEP

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Disclosure

Dr White is a consultant to Philips Respironics and NightBalance and was until recently the Chief Medical Officer for Apnicure. Dr. Dworetzky is a consultant for SleepMed providing ambulatory EEG interpretations. The remaining authors have no conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is one of the leading causes of death in young adult individuals with epilepsy. These persons have a more than twentyfold greater risk of death when compared with the rest of the general population.^{1,2} While the precise mechanisms underlying SUDEP are still unclear, it has been suggested that cardiac and respiratory dysfunction may play a role.^{3–5} Some studies have reported seizure-related oxygen desaturations in adult epilepsy patients, either with focal or generalized seizures.^{6–8} Ictal desaturations were often accompanied by central apneas.⁹ These ictal hypoxemia events, presumably resulting from centrally mediated ventilatory dysfunctions, might have implications for SUDEP.^{6,7}

SUDEP most often occur during the nocturnal hours, and presumably in relation to sleep.^{4,5} Indeed, epilepsy patients with a history of nocturnal seizures have a more than twofold greater risk of SUDEP as compared to patients with a strictly diurnal seizure pattern.¹⁰ With regards to its unique underlying processes, sleep might act as a ‘window of vulnerability’ in individuals with epilepsy. However, to our knowledge, no study to date compared oxygen saturation levels during seizures from sleep versus in wakefulness in adult epilepsy patients. As SUDEP most often occur during the night, studying seizure-related respiratory disturbances during sleep might help identify some predisposing factors to sudden death.

The current study aimed to investigate whether nocturnal seizures are more likely to be associated with respiratory compromise, such as more severe oxygen desaturation as compared to seizures from wakefulness. To do so, we examined oxygen saturation before, during, and after seizures occurring either during sleep or wakefulness in adult epilepsy patients undergoing long term video-EEG monitoring.

METHODS

All adult individuals consecutively referred, between October 2010 and August 2011 to the long-term monitoring (LTM) unit at Brigham and Women’s Hospital underwent video-EEG recordings for the evaluation of seizures. Recording methodology of these adult epilepsy patients has been published previously.¹¹ Briefly, all patients underwent standard video-EEG monitoring, including whole-night sleep EEG (with scalp electrodes using the international 10–20 system) and electrocardiographic recordings. Respiration was monitored continuously, using respiratory inductance plethysmography belts (ProTech Diagnostics, Pittsburgh, PA, USA) and finger pulse oximetry sensors (Masimo Corp, Irvine, CA, USA).

EEG data were analyzed by board-certified epileptologists (MP, SK). Patients with nonepileptic events were excluded from the study. Seizure activity was established by standard video-EEG and clinical criteria. Only seizures with a clear ictal EEG pattern were included in the analyses. Duration of seizure activity was determined by marking seizure onset and termination on the EEG. Seizures were classified using the 2017 International League against Epilepsy guidelines.¹² As part of the standard LTM protocol, antiepileptic drugs (AEDs) were reduced by 50% on day 1 and completely withdrawn by day 2.

Oxygen saturation (SaO₂) levels were analyzed before seizure onset, during, and after each seizure. SaO₂ levels before and after seizures were examined during a 10-s window (data for each 1-s averaged over the 10-s period). As seizure duration varied greatly, only maximal and minimal SaO₂ values were analyzed during the ictal period. For each recorded seizure, the following measures were computed: maximal, minimal, and average SaO₂ before and after seizures, as well as ictal and postictal desaturation (from baseline pre-ictal saturation levels). Desaturation was calculated to reflect ‘saturation recovery’ postictally (values close to zero would indicate good recovery after a seizure).

Postictal generalized EEG suppression (PGES) was defined as a generalized attenuation of background EEG activity no higher than 10 μ V, lasting $\geq$ 10 s, and which did not result from muscle, movement, breathing or electrode artifacts. Ictal apneas were defined as at least 10 s of absent breathing, and characterized as central or obstructive. In some cases where respiratory data were missing, review of the video to assess respiratory effort helped in differentiating obstructive from central sleep apnea. This study was approved by the human research committees at Harvard Medical School and all subjects gave their written informed consent before participating.

Statistical analysis

Independent sample t-tests or their nonparametric equivalent, and Pearson’s Chi-square tests were performed to compare seizures characteristics, occurrence of PGES, and ictal apneas according to sleep and wake states. Mann-Whitney U tests were performed to compare SaO₂ measures between the groups (sleep vs wake-related seizures), and therefore median values are presented. Significance level was set at $p < 0.05$.

RESULTS

Twenty-two adult epilepsy patients had recorded seizures during video-EEG monitoring. One patient was excluded from the analysis for status epilepticus (waking state). Six seizures (sleep, $n = 1$; wake, $n = 5$) were excluded due to insufficient recorded SaO₂ measures. Consequently, 20 epilepsy patients aged between 22 and 53 years old (mean, 36.4 ± 11.1 years) were included in the analysis. Eleven patients were women. Mean duration of epilepsy was 19.7 ± 11.7 years (range 2–47), and average seizure frequency per month was 15.0 ± 24.5 (range 0.33–75). All patients had focal seizures, with a detailed description in Table 1. Four patients took one AED, 12 took two, and all others took three or more AEDs. Among patients who had undergone magnetic resonance imaging (MRI) scans, 14 had lesions, and 4 did not.

Seizures were categorized according to behavioral state at event onset (sleep or wake). Forty-eight seizures were analyzed, of which 23 (48%) occurred during sleep and 25 (52%) during wakefulness (Table 1). Seizure characteristics (including seizure duration and frequency of secondary convulsive seizure) did not differ between the groups. None of the patients had ictal obstructive apneas, and although occurrence of ictal central apneas was slightly higher during sleep, no differences were found between the groups. Of note, some seizures were associated with pen-blocking (amplitude saturation) or movement artifacts within the respiratory channels (sleep, $n = 6$ and wake, $n = 6$), and 3 seizures (sleep, $n = 2$

and wake, $n=1$) were also associated with a brief loss of the oxygen saturation signal. This was seen more frequently with seizures that evolved to convulsion (focal to generalized), but did not differ in sleep versus wakefulness.

PGES occurred significantly more frequently following seizures from sleep as compared to wakefulness ($p = 0.01$). Although the sample size did not allow direct statistical comparison of PGES duration between sleep and wake seizures ($n = 9$ and $n = 2$, respectively), mean PGES duration was slightly longer following seizures from sleep (mean, 46.0 ± 41.5 s), as compared to wake-related seizures (37.5 ± 34.6 s).

Saturation changes in sleep versus wake seizures

During the ictal state, significant differences were observed in maximal ($U = 192.0$, $p = 0.05$) and minimal ($U = 166.5$, $p = 0.01$) SaO_2 levels of sleep and wake seizures. As shown in Figure 1A and 1B, seizures from sleep were associated with lower maximal (median = 97.5) and minimal (median = 90.8) SaO_2 , as compared to seizures from wakefulness (maximal: median = 99.0, minimal: median = 95.5). Seizures from sleep were also associated with a larger desaturation drop (median = -4.2), as compared to wake-related seizures (median = -1.2 ; $U = 149.0$, $p = 0.01$ [Figure 1C]). Moreover, during the postictal period, significant differences were seen in both minimal ($U = 193.0$, $p = 0.05$) and average ($U = 189.0$, $p = 0.04$) SaO_2 levels of sleep and wake seizures. As presented in Figure 1D and 1E, SaO_2 levels remained significantly lower after seizures from sleep (minimal: median = 94.3, average: median = 94.9) than seizures from wakefulness (minimal: median = 96.9, average: median = 97.7). No significant differences were found between the groups for any baseline pre-ictal SaO_2 measure, or postictal desaturation drop and postictal maximal SaO_2 (data not shown).

To test whether multiple seizures from the same patient may contribute differently to SaO_2 changes, one-way ANOVAs with two independent factors (group: sleep vs wake, and seizure recurrence: 1 vs 2) were performed. No significant interaction was found for any SaO_2 measure (data not shown).

Moreover, we performed Spearman correlations between duration of PGES and SaO_2 measures among sleep and wake seizures, however results were non-significant.

DISCUSSION

In this prospective study, we found that seizures occurring during sleep are associated with lower SaO_2 nadir and larger oxygen desaturation drop, as compared to seizures from wakefulness in adult epilepsy patients. Moreover, during nocturnal seizures, SaO_2 levels remained significantly lower even a few seconds after seizure termination, suggesting that seizures from sleep are associated with poorer saturation recovery than seizures from wakefulness. Additionally, we found that PGES occurred more frequently after seizures from sleep, as compared to seizures from wakefulness.

Our results add to prior reports of postictal oxygen desaturations in adult epilepsy patients.⁶⁻⁸ They differ from a recent study by Jaychandran et al.¹³ which did not find significant

SaO₂ changes in relation to seizure activity. However, in this latter study, as is the case in most previous studies, no mention was made in regards to the behavioral state during which seizures occurred, and it is likely that events were analyzed only during the waking state. Only one study examined whether the presence of oxygen desaturation (below 90%) could be predicted by the seizure's onset behavioral state (wake vs sleep) in a regression model, but results did not reach significance.⁷ To our knowledge, this is the first study that examined seizure-related oxygenation during sleep as compared to wakefulness in adult epilepsy patients.

How sleep contributes to ictal and postictal respiratory disturbances is unclear. Previous evidence shows that ictal desaturations were often accompanied by central apneas.⁹ In our study, 44% of nocturnal seizures were associated with central apneas, and although the difference did not reach significance, a smaller fraction of wake-related seizures were accompanied by central apneas (28%). It is possible that the decreased chemosensitivity and increased upper airway resistance, along with a decrease in respiratory drive in sleep might be responsible for the frequent central apneas as well as the more severe desaturation. Moreover, baseline oxygen saturation normally falls by approximately 2% during sleep as compared to the waking state. If the minute ventilation falls due to a seizure, then the desaturation would fall even further due to the shape of the oxyhemoglobin desaturation curve. However, in our study pre-ictal SaO₂ levels did not significantly differ between seizures from sleep and wakefulness, and therefore it is unlikely that it fully explains our results.

The finding of more frequent and slightly longer PGES with nocturnal seizures was unexpected, though one previous study reported an increased prevalence of PGES (> 20 s) after convulsive seizures arising from sleep.¹⁴ The association of PGES in conjunction with more severe desaturation with seizures from sleep raises the question of whether factors specific to sleep as a physiological state may account for a more severe impact of seizures with a higher vulnerability to cerebral shutdown in this state and a consequent compromise of vital functions. Further studies with a more detailed focus on respiratory function related to seizures can test this hypothesis.

There are several limitations to our study. We had a relatively small number of patients, which precluded the use of advanced statistical analysis such as mixed-effect models to control for the effects of multiple seizures on saturation changes, or more detailed analysis according to seizure characteristics. In addition, all the measurements included in this study were performed in clinical conditions, and thus effects of medications and hospital interventions may not be excluded. Most importantly, we did not measure CO₂ to quantify hypoventilation during and after seizures. Transcutaneous CO₂ monitoring would be strongly recommended in future studies.

The advantages of our study include comprehensive measures of respiratory function in sleep versus wakefulness, and strict inclusion criteria. Our study shows that seizures emanating from sleep are associated with worse respiratory measures, as well as higher rate of PGES. These results remain to be tested for replication in larger cohorts of epilepsy patients. Future prospective studies will allow further investigation of potential predictors of

sleep-related respiratory disturbances and their relation to cerebral shutdown or risk of SUDEP.

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Figure 1.

Box plots (median and quartiles) showing that nocturnal seizures are associated with decreased oxygen saturation as compared to wake seizures. **(A)** Maximal oxygen saturation during seizures. **(B)** Minimal oxygen saturation during seizures. **(C)** Desaturation from baseline (pre-ictal) during the ictal period. **(D)** Minimal oxygen saturation after seizures. **(E)** Average oxygen saturation after seizures. * $p < 0.05$.

Table 1

Characteristics of seizures from sleep and wake state.

Characteristics	Sleep n = 23	Wake n = 25	<i>p</i>
Seizure duration (s) ^a	79.2 ± 57.7	106.6 ± 149.5	0.87
Focal, evolving to bilateral convulsive seizure (%)	9 (61)	12 (48)	0.54
Initial seizure semiology			
Astatic	1	2	
Atonic	1	2	
Automotor	8	5	
Dialeptic	0	1	
Gelastic	3	3	
Myoclonic	2	1	
Psychic aura	2	6	
Tonic	3	1	
Tonic-clonic	3	4	
IED localization (%)			
Frontal	6 (26)	5 (20)	0.62
Temporal	13 (57)	19 (76)	0.15
Occipital	1 (4)	0 (0)	0.29
Multiple	3 (13)	1 (4)	0.26
IED laterality (%)			
Left	12 (52)	10 (40)	0.40
Right	6 (26)	14 (56)	0.04
Both	5 (22)	1 (4)	0.06
PGES (%)	9 (39)	2 (8)	0.01
Ictal central apnea (%)	10 (44)	7 (28)	0.26

^aU Mann-Whitney.

IED: Interictal epileptiform discharges; PGES: Postictal generalized electroencephalographic suppression. Results are expressed as mean ± standard deviation.