ORIGINAL RESEARCH

The Association of Nocturnal Seizures and Interictal Cardiac/Central Autonomic Function in Frontal Lobe Epilepsy: Heart Rate Variability and Central Autonomic Network Analysis

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Purpose: Patients with epilepsy frequently experience autonomic dysfunction, closely related to sudden unexplained death in epilepsy (SUDEP). SUDEP occurs most often at night or during sleep, and frequent nocturnal seizures are an established risk factor. This study investigated the influence of nocturnal seizures on autonomic dysfunction in epilepsy.

Patients and Methods: This retrospective study enrolled frontal lobe epilepsy (FLE) patients who performed 24-hour EEG monitoring. All participants were divided into nocturnal FLE (NFLE, > 90% of seizures occurring during sleep) or diurnal FLE (DFLE) groups. EEG and ECG signals were simultaneously obtained during waking and sleep stages. EEG current density source and connectivity analysis of the autonomic network were performed. ECG was analyzed across time and frequency domains heart rate variability (HRV) analysis method was used. The obtained parameters were compared between the NFLE and DFLE groups.

Results: Fifteen NFLE and 16 DFLE patients were enrolled with no significant difference in age, sex, disease duration, seizure frequency, or the number of anti-seizure medications between the two groups. During sleep, a decrease in HRV parameters and an increase of the beta-1 (13–22 Hz) current source density power in the bilateral paracentral lobule (BA4,5,6), precuneus (BA7), and cingulate (BA31) were observed in the NFLE group compared to DFLE group. The NFLE group also showed hyperconnectivity in the central autonomic (12 edges distributed over 10 nodes), sympathetic (2 edges distributed over 3 nodes), and parasympathetic (4 edges distributed over 6 nodes) beta-1 frequency band networks during sleep. During wakefulness, central and cardiac autonomic variables were not significantly different between the NFLE and DFLE groups.

Conclusion: Interictal cardiac and central autonomic dysfunction occurred simultaneously and can be attributed to the brain-heart autonomic axis. Our findings suggest that nocturnal seizures may contribute to interictal autonomic dysfunction during sleep in people with epilepsy.

Keywords: nocturnal seizure, heart rate variability, central autonomic network, sleep, autonomic dysfunction

Introduction

Patients with epilepsy frequently experience autonomic symptoms during seizures, including changes in heart rate, respiration, and gastrointestinal, urogenital, and pupillary functions.[1,2] Autonomic dysfunction is a risk factor for mortality and morbidity in people with epilepsy and is closely related to Sudden Unexpected Death in Epilepsy (SUDEP).[3] SUDEP is a prevalent cause of death in epilepsy, accounting for up to 17% of all deaths in epilepsy.[4] Although the pathophysiology of SUDEP is still uncertain, autonomic dysfunction is presumed to play an important role. The autonomic nervous system modulates cardiorespiratory function, and its dysfunctions are associated with sudden

death in cardiac disease.[5–7] Repetitive seizures in people with epilepsy may promote cardiorespiratory dysregulation and subsequent fatal cardiac arrhythmia and respiratory failure.[8]

The cardiac autonomic nervous system is modulated by the central autonomic network (CAN), which integrates afferent cardiac autonomic information. The CAN is composed of various forebrain and brainstem structures, and each CAN structure has a feedback circuit via close interconnection.[9] Autonomic dysfunctions develop during the ictal period as a result of ictal propagation to CAN structures.[1] Previous studies reported that central autonomic dysfunction in epilepsy is related to dysregulations of cardiac and respiratory autonomic nerve systems.[10,11] Cardiac autonomic dysfunction could be evaluated using heart rate variability (HRV), which is a fluctuation of time intervals between adjacent heartbeats that is used as a marker of the autonomic nerve system, cardiac mortality, and sudden cardiac death.[12,13] In people with epilepsy, significant HRV changes appear in temporal lobe epilepsy (TLE) and drug-resistant epilepsy. Furthermore, HRV is related to seizure severity and serves as a biomarker for increased SUDEP risk.[14,15] These findings imply that cardiac and central autonomic dysfunction occur in people with epilepsy, although a definitive link remains elusive.

Previous studies have reported that people with epilepsy may develop autonomic imbalances during sleep.[16–18] In addition, it is known that more than 40% of SUDEP is related to sleep, and frequent nocturnal seizures are recognized as its risk factor.[19–21] It could be supposed that sleep and frequent nocturnal seizures promote autonomic dysfunction in epilepsy. Nocturnal frontal lobe epilepsy (NFLE) is characterized by seizures that mostly occur during sleep and is thought to be associated with a higher risk of SUDEP as well as autonomic dysfunction during sleep.[22] Patients with frontal lobe epilepsy (FLE) have faster heart rates and lower parasympathetic drive compared to normal control during interictal periods, and NFLE patients show significant HRV changes during sleep compared to normal control.[23,24] However, most research on HRV has been conducted in TLE patients, and studies on other types of epilepsies, including FLE, are rare.[7]

The aim of this study was to investigate the influence of nocturnal seizures on the cardiac and central autonomic systems in FLE patients. The differences in HRV and CAN during sleep and waking stages between diurnal FLE (DFLE) and NFLE groups were studied.

Materials and Methods
Study Design and Subjects
This retrospective study was carried out in a single epilepsy center (Uijeongbu St Mary's Hospital, the Republic of Korea). The study protocol received approval from the Institutional Review Board of the Catholic University of Korea (Approval No. UC19RISI0146), which determined that informed consent was not required as the researchers did not collect any personally identifiable information while examining patient records. This study was conducted according to the principles of the Declaration of Helsinki. Participants confirmed with FLE after 24-hour EEG monitoring from 2013 to 2019 were enrolled. The diagnosis of FLE was based on previous routine or video EEG findings and seizure semiology. FLE was confirmed as interictal discharges exclusively in the frontal lobe during the 24-hour EEG, with no interictal epileptiform discharges observed in other regions. Seizure patterns, frequencies, and demographic information were collected through seizure diaries and clinical chart reviews. All FLE patients were classified into either DFLE or NFLE groups. Patients who experienced more than 90% of seizures during sleep were classified as NFLE, whereas the remaining patients were classified as DFLE.[25,26] The exclusion criteria were as follows: other neurologic, psychiatric, or cardiac disorders, abnormal brain imaging, hypertension, diabetes, renal failure, abnormal ECG findings, clinical/electrical ictal event during 24-hour EEG monitoring, or clinical seizure within 24 hours prior to the EEG monitoring.

ECG Acquisition and Analysis
The ECG signals were recorded simultaneously with waking and sleep EEG during 24-hour EEG monitoring. Artifact-free ECG data over 30 minutes were obtained during the stage 2 sleep and waking stages. The ECG signals were analyzed using Kubios HRV software (version 2.2, http://www.kubios.com) and MATLAB (MathWorks, Inc, Natick, MA, USA).[27] The QRS complex was identified automatically and confirmed manually. Subsequently, time- and

frequency-domain HRV parameters were obtained. The time-domain parameters included the mean of the R wave-to-R wave interval (meanRR), standard deviation of heart rate (SDHR), standard deviation of all Normal-to-Normal intervals (SDNN), standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN), SDNN index (SDNNI), the root mean square of the difference between successive normal intervals (RMSSD), number of successive NN interval pairs that differ more than 50ms (NN50), NN50 divided by the total number of NN intervals (PNN50), the integral of the NN interval histogram divided by the height of the histogram (HRV triangular index), and the baseline width of the NN interval histogram (TINN). The frequency-domain parameters included total power, very low frequency (VLF, ≤ 0.04 Hz), low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15–0.4 Hz) band power, and the ratio between LF and HF band power (LF/HF).

EEG Acquisition and Data Preparation

During 24-hour EEG monitoring, the EEG signal was obtained using a routine 10–20 scalp electrode system (GRASS technology; West Warwick, RI, USA). The sampling rate was 200 Hz, and 19 electrodes (Fp1, Fp2, F3, F4, C3, C4, P3, P4, F7, F8, T3, T4, T5, T6, O1, O2, Fz, Cz, and Pz) were used. The ground and reference electrodes were placed at FPz and FCz, respectively. All participants showed interictal discharges limited to the frontal lobe without recorded EEG seizures. The stage 2 sleep EEGs were obtained from the data between 04:00 and 08:00 a.m. Two neurologists (SH. Kim, and HJ. Lee) independently reviewed the waking and sleep EEG signals. The waking and sleep stages were confirmed by the American Academy of Sleep Medicine (AASM) scoring criteria.[28]

EEG Current Source Density Analysis

Waking and sleep EEG data were visually reviewed, and the epoching procedures were performed using the Insight II software package (Persyst Development Corporation, Prescott, AZ, USA). Two-second epochs without ictal discharge or artifacts were selected in each participant's waking and sleep EEG signals. All epoched EEG data were analyzed using standardized low-resolution brain electromagnetic tomography (sLORETA) software (http://www.uzh.ch/keyinst/loreta).[29] sLORETA utilized a three-spherical head model based on the Montreal Neurological Institute 152 template with the 3D solution space restricted to the cortical gray matter as determined by the probabilistic Talairach atlas. It revealed an area in solution space that consisted of 6239 voxels at 5 mm spatial resolution.[30,31] Electrode coordinates were made for the calculation of the transform matrix, which was created by registration and interpolation of 19 scalp electrodes to the average head model. After then, cross spectra were calculated, and the corresponding 3D cortical distribution of the electric neuronal generators was computed for each participant and each frequency band. The difference in current source density between NFLE and DFLE in each waking and sleep stage was investigated, and the following EEG frequency domains were analyzed: delta (1–4 Hz), theta (4–8 Hz), alpha-1 (8–10.5 Hz), alpha-2 (10.5–13 Hz), beta-1 (13–22 Hz), and beta-2 (22–30 Hz).[29]

Connectivity Analysis of the Central Autonomic Network

The connectivity of the CAN between pairs of regions of interest (ROIs) was analyzed using sLORETA software. Autonomic function-related brain regions were defined as 13-central autonomic, 9-central sympathetic, and 8-central parasympathetic ROIs (Supplementary Tables 1–3).[32] For analysis, each ROI was defined by "ROI maker 1" with the "all voxels within a radius of (15 mm)" option. The functional connectivity for each pair of ROIs was calculated using the linear similarity method (lagged-linear connectivity). The obtained connectivity was compared between NFLE and DFLE groups in each waking and sleep stage. The final results were visualized using BrainNet viewer (https://helab.bnu.edu.cn/DOWNLOADS/BrainNetViewer/index.htm).[33]

Statistical Analysis

Demographic and characteristic variables were compared using the appropriate statistical methods, including the Mann–Whitney U-test or the chi-square test with Fisher's correction. In each waking and sleep stage, the HRV parameters were compared between the NFLE and DFLE groups using the Analysis of Covariance (ANCOVA) method to adjust for age. The non-parametric ANCOVA were used when appropriate. The localization of current source density (CSD) power and

connectivity between pairs of ROIs was performed using the sLORETA software statistics tool. Significant differences between the NFLE and DFLE groups were assessed in the six frequency bands using *t*-tests, and multiple comparison-corrected critical probability threshold values were calculated using the nonparametric randomization method based on empirical probability distributions.[29,34] All statistical analyses were performed using the R software package (version 3.5.1) and the statistics tool of sLORETA software.

Results

Demographics and Seizure Characteristics

A total of 31 subjects with FLE were enrolled in this study, including 21 males with a median age of 24 years (range, 14–65 years). Fifteen participants were confirmed to have NFLE, including 12 males with a median age of 23 years (range, 14–54 years) and a seizure frequency of 2.7±3.8/month. Sixteen participants were diagnosed with DFLE, including 9 males with a median age of 30 years (range, 15–65 years) and a seizure frequency of 1.5±2.6/month (Figure 1). All subjects were taking anti-seizure medication (ASMs) during the study period. Demographics and seizure characteristics including age, sex, disease duration, seizure frequency, and the number of ASMs were not significantly different between the NFLE and DFLE groups (Table 1).

Heart Rate Variability

During the sleep stage, there were significant differences in HRV parameters between the two groups. The time domain analysis showed that the SDHR ($p<0.019$), SDNN ($p<0.044$), and triangular index ($p<0.033$) were lower in the NFLE compared to the DFLE group. Similarly, frequency domain analysis showed lower LF ($p<0.041$), and total power ($p<0.031$) in the NFLE group compared to the DFLE group. However, during the waking stage, there were no significant differences in HRV parameters between the two groups (Table 2).
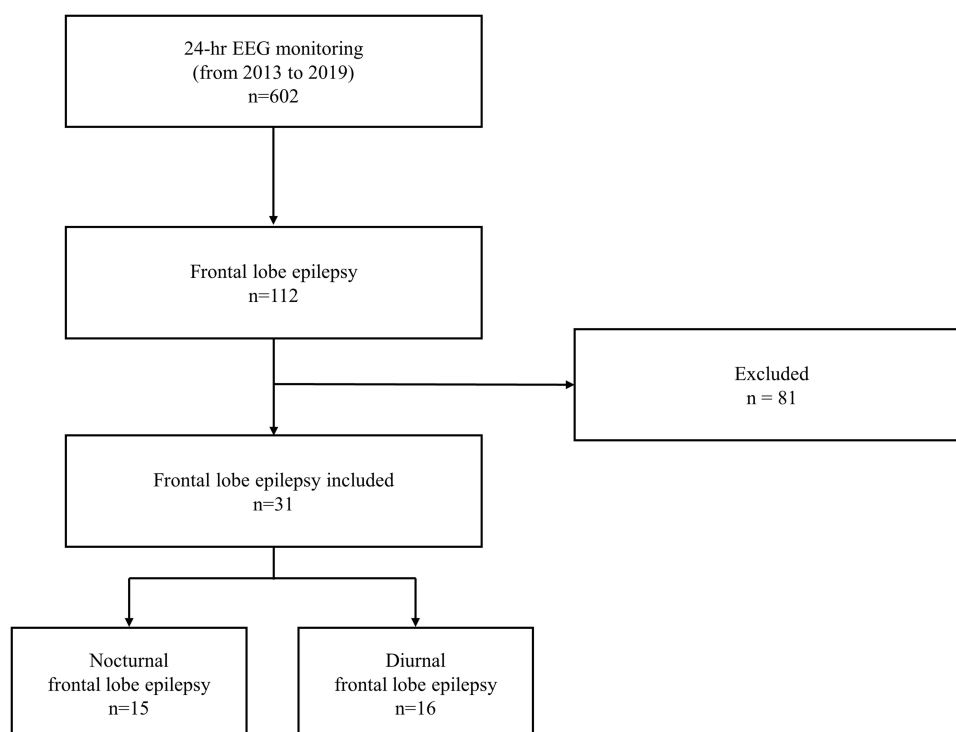

Figure 1 The flow chart of participants included in this study.

Table 1 Demographics and Clinical Information

	Diurnal FLE (n = 16)	Nocturnal FLE (n = 15)	p
Age (median, years)	30 (19.0; 41.5)	23 (20.0; 24.5)	0.251
Sex (male, %)	9 (56.3%)	12 (80.0%)	0.252
Disease duration (months)	48 (4.5; 143.5)	48 (29.5; 72)	0.842
Seizure frequency (per month)	1.5± 2.6	2.7±3.8	0.491
Nocturnal seizure (%)	0%	95.4%	<0.000
Etiology (%)	Unknown (100%)	Unknown (100%)	
Lateralization (%)			0.416
Right	1 (6.3%)	2 (13.3%)	
Left	7 (43.8%)	3 (20.0%)	
Bilateral	8 (50.0%)	10 (66.7%)	
Number of ASMs (mean)	1.13	1.00	0.489

Notes: Data are presented as the median (quartile), or n (%).
Abbreviations: FLE, frontal lobe epilepsy; ASMs, anti-seizure medications.

Table 2 HRV Parameters During Wake and Sleep and Periods Between NFLE and DFLE Groups

	Wake			Sleep		
	DFLE	NFLE	p	DFLE	NFLE	p
meanHR	72.00 (2.44)	72.04 (2.52)	0.990	60.26 (2.06)	58.28 (2.13)	0.518
meanRR	874.514 (30.515)	848.392 (31.558)	0.565	1020.92 (37.05)	1051.57 (38.31)	0.578
SDHR	6.76 (0.49)	5.78 (0.50)	0.184	5.47 (0.48)	3.70 (0.50)	0.019*
SDNN	74.77 (5.61)	64.08 (5.80)	0.205	79.19 (5.86)	60.99 (6.06)	0.044*
RMSSD	40.99 (4.13)	31.35 (4.28)	0.124	54.29 (5.08)	49.54 (5.26)	0.529
NN50	335.54 (57.73)	235.22 (59.71)	0.336	564.5 (69.68)	463.2 (72.07)	0.331
PNN50	18.55 (3.37)	11.53 (3.48)	0.167	33.74 (4.82)	28.69 (4.98)	0.481
SDANN	30.71 (4.62)	25.02 (4.78)	0.180	29.41 (4.11)	20.10 (4.25)	0.178
SDNNI	66.71 (4.78)	57.62 (4.94)	0.206	69.94 (4.94)	55.39 (5.11)	0.055
Triangular index	17.15 (1.54)	15.41 (1.59)	0.446	16.59 (1.11)	12.93 (1.15)	0.033*
TINN	298.97 (21.58)	281.76 (22.32)	0.591	205.89 (28.88)	156.38 (29.87)	0.253
VLF (ms^2)	3457.82 (498.08)	2609.1 (515.11)	0.282	3583.35 (587.88)	1744.54 (607.98)	0.082
LF (ms^2)	1277.44 (170.74)	787.74 (176.58)	0.123	1084.08 (118.32)	711.59 (122.36)	0.041*
HF (ms^2)	601.14 (112.47)	364.3 (116.31)	0.307	1186.64 (186.65)	932.51 (193.03)	0.470
LF/HF	2.63 (0.69)	3.91 (0.72)	0.938	1.65 (0.48)	1.310 (0.50)	0.836
Total power	5338.2 (674.85)	3762.6 (697.93)	0.123	5855.53 (740.22)	3389.87 (765.53)	0.031*

Notes: Data are presented as the mean ± standard error (SE) adjusted for age. *Indicates statistically significant difference (p<0.05).
Abbreviations: DFLE, diurnal frontal lobe epilepsy; NFLE, nocturnal frontal lobe epilepsy; meanHR, mean heart rate; meanRR, mean of the R wave-to-R wave interval; SDHR, the standard deviation of heart rate; SDNN, the standard deviation of all Normal-to-Normal intervals; RMSSD, the root mean square of difference between successive normal intervals; NN50, the number of successive NN interval pairs that differ more than 50ms; PNN50, NN50 divided by the total number of NN intervals; SDANN, standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording; SDNNI, SDNN index; Triangular index, the integral of the NN interval histogram divided by the height of the histogram; TINN, the baseline width of the NN interval histogram; VLF, very low frequency band power; LF, low frequency band power; HF, high frequency band power; LF/HF, the ratio between LF and HF band power.

Current Source Density and the CAN

During the sleep stage, the NFLE group showed a significant increase in beta-1 CSD power ($p<0.05$) in several brain regions including the bilateral frontal paracentral lobule (BA4,5,6), precuneus (BA7), and cingulate (BA31) compared to the DFLE group (Figure 2). There was no significant difference in other frequency bands, and no decrease in CSD was observed in any frequency band analyses.

In the analysis of CAN connectivity during the sleep stage, the NFLE group showed CAN hyperconnectivity in the beta-1 frequency band ($p<0.05$, $t=4.0971$), involving 12 edges distributed over 10 nodes, with most connections in the Rt
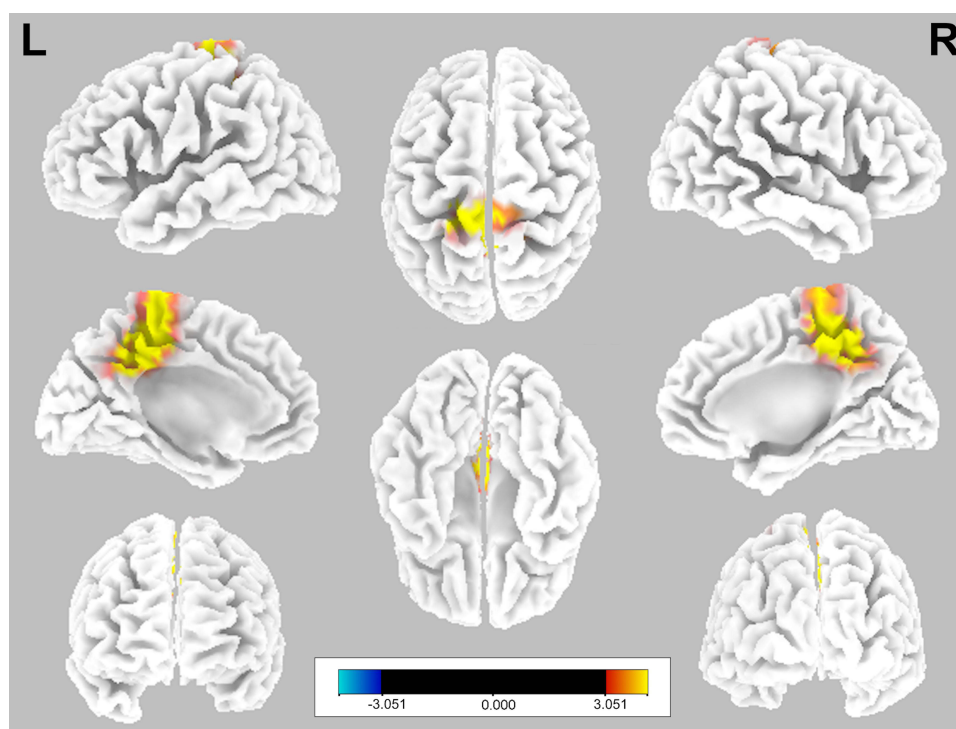
Figure 2 Representative image of current source density analysis during sleep.
Notes: The NFLE group shows a significant increase in beta-1 (13–22Hz) CSD power (p<0.05) in the bilateral frontal paracentral lobule (BA4,5,6), precuneus (BA7), and cingulate (BA31) compared to the DFLE group. Yellow and red colors indicate voxels with significantly increased activity in the NFLE group compared to the DFLE group (p<0.05, t=3.051).

and mid anterior cingulate gyri (5 edges). The mid anterior cingulate gyrus_1, Rt anterior cingulate gyrus, Lt para-hippocampal gyrus, Rt insula gyrus, Rt parahippocampal gyrus, Lt insula gyrus_1, Lt rectal gyrus, mid anterior cingulate gyrus_2, Rt supramarginal gyrus, and Lt insula gyrus_2 were the involved nodes (Figure 3).

In addition, the NFLE group showed hyperconnected central parasympathetic-associated and central sympathetic-associated networks in the beta-1 frequency band, involving 4 edges distributed over 6 nodes (p<0.05, t=4.0282) and 2 edges distributed over 3 nodes (p<0.05, t=3.9691), respectively. The Lt parahippocampal gyrus, Lt insula gyrus, Lt precentral gyrus, Rt superior temporal gyrus_1, Rt superior temporal gyrus_2, and Rt insula gyrus were the involved parasympathetic nodes. The involved sympathetic nodes were the mid anterior cingulate gyrus, Lt orbital gyrus, and Lt insular gyrus, and CAN hypoconnectivity was not observed during sleep.

During the waking stage, no significant differences were found in CSD or in central autonomic, sympathetic, or parasympathetic networks between the two groups.

Discussion

In this study, more severe cardiac and central autonomic abnormalities in the interictal period were observed in the NFLE group compared to the DFLE group. Cardiac and central autonomic dysfunctions occurred in a simultaneous manner and were more pronounced during sleep.

Interictal Autonomic Dysfunction

Autonomic dysfunction during the interictal period is well documented in people with epilepsy.[2,35] Previous studies have reported significant differences in HRV parameters, such as SDNN, LF, HF, and LF/HF, between people with epilepsy and normal controls.[36–38] In previous studies, TLE patients exhibited autonomic dysfunction and lower HRV parameters compared to age-matched normal controls.[36,38] FLE patients also showed lower HRV parameters, which were correlated with the risk of SUDEP.[39] Although autonomic dysfunctions in FLE have been reported, most studies investigated TLE,
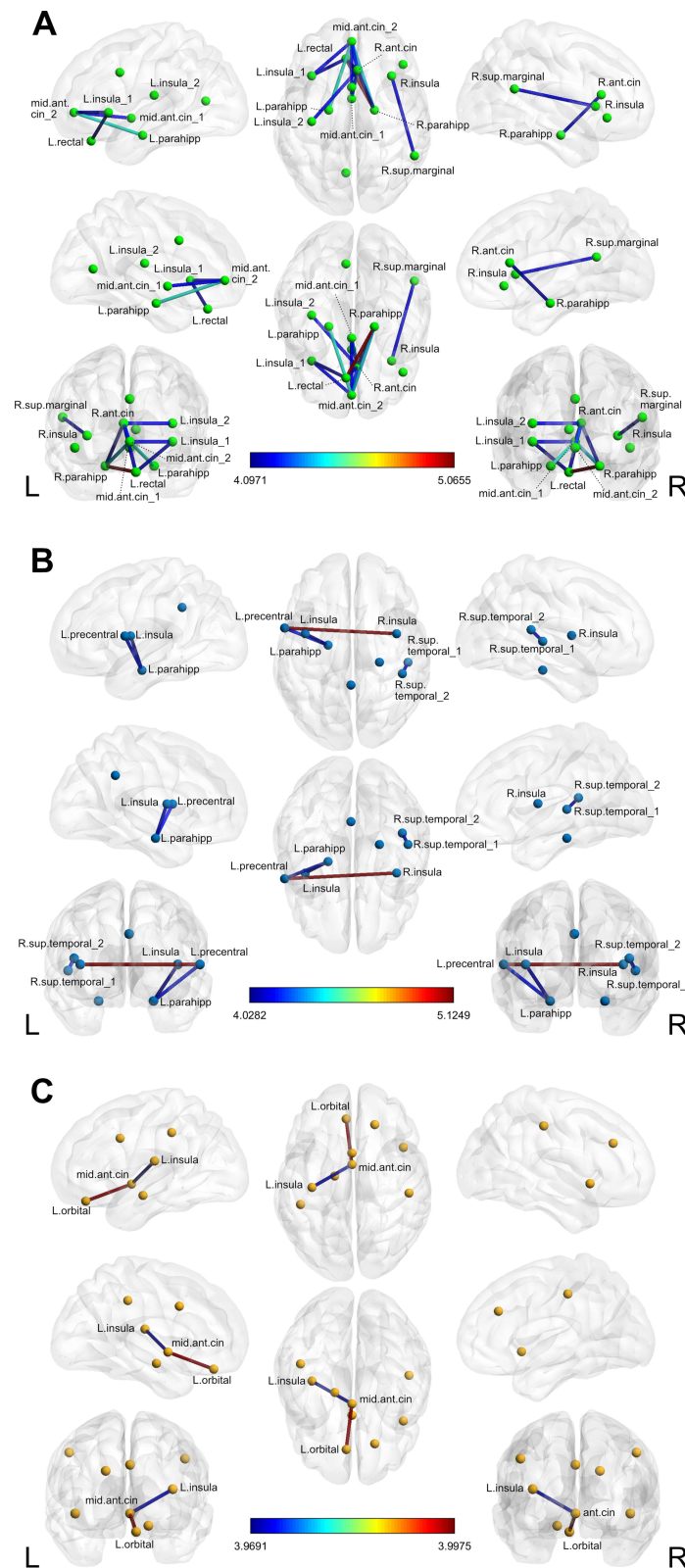
Figure 3 EEG connectivity analysis of central, parasympathetic, and sympathetic network during sleep.
Notes: (**A**) Central autonomic network. The NFLE group shows beta-1 frequency band network hyperconnectivity (p<0.05, t=4.0971, 12 edges distributed over 10 nodes). (**B**) Parasympathetic network. The NFLE group shows a beta-1 hyperconnectivity (p<0.05, t=4.0282, 4 edges distributed over 6 nodes). (**C**) Sympathetic network. The NFLE group shows beta-1 hyperconnectivity (p<0.05, t=3.9691, 2 edges distributed over 3 nodes).
Abbreviations: R, right; L, left; ant, anterior; post, posterior; sup, superior; cin, cingulate; parahipp, parahippocampal.

and the evidence in FLE patients has been limited.[2,23] Our study showed significantly lower HRV parameters in the NFLE group compared to the DFLE group during the interictal period, consistent with previous studies. SDNN is widely used as the gold standard for assessing cardiac risk, and lower SDNN values are indicative of increased mortality and reduced mobility. SDNN reflects the combined influence of both the sympathetic and parasympathetic nervous systems.[12] The triangular index is closely linked to arrhythmias, and a low triangular index in atrial fibrillation is associated with higher mortality rates.[12,40] While SDHR is associated with mortality risk in heart disease, it is not commonly employed as a standalone measure.[41] LF represents the frequency component ranging from 0.04 to 0.15 Hz. Total power encompasses energy across the ULF, VLF, LF, and HF frequency bands. LF reflects the combined function of both the sympathetic and parasympathetic nervous systems and reduced LF values have been associated with sudden cardiac death.[12,42] Our results suggest that cardiac autonomic dysfunction could occur, even during the interictal period, in NFLE patients.

The involvement of CAN structures in seizure may result in severe cardiac arrhythmia, which could be associated with SUDEP.[9] Abnormalities in the medial thalamus and superior temporal gyrus, which are structures of the CAN, have been observed in postmortem studies of SUDEP.[43] These structural abnormalities were observed even before SUDEP events, indicating that CAN dysfunction could occur during the interictal period in people with epilepsy.[44] We employed EEG source and connectivity analysis to assess the CAN. These techniques provide insights into the activation of specific brain regions or networks and are commonly utilized to investigate various neurological diseases.[29,45,46] In our study, changes in central autonomic, sympathetic, and parasympathetic network activity were seen during the interictal period in NFLE patients. Our findings also showed that the parasympathetic network was more extensively activated than the sympathetic network. Previous studies reported increased sympathetic tone and decreased HRV during sleep in people with epilepsy.[18,47] However, our study focused on preganglionic CAN activity rather than the autonomic output of the CAN. The results of our HRV analysis are consistent with previous studies. As a result, our structural and network analysis findings indicate that the dysregulation of the CAN occurred even during the interictal period in NFLE.

In our study, the NFLE group showed significant activation of the bilateral paracentral lobule, precuneus, and cingulate during the interictal period.[48] The paracentral lobule and cingulate are involved in baroreflex function.[49] The precuneus has a sympathetic vasoconstrictive wakefulness drive to resting muscles, and the precuneus and paracentral lobule have extensive connections with the prefrontal and insular areas.[50,51] Our findings suggest that cardiac and central autonomic dysfunction develop simultaneously during the interictal period in people with epilepsy.

Sleep, Nocturnal Seizure, and Autonomic Dysfunction in Epilepsy

Sleep promotes synaptic renormalization and downscaling, which is related to autonomic system homeostasis. During normal non-REM sleep, parasympathetic drive increases while sympathetic drive decreases, resulting in BP dipping, respiratory depression, and an increase in HRV parameters. Meanwhile, during REM sleep, there are fluctuations in blood pressure and respiration, and the autonomic state is similar to that during wakefulness.[52] People with epilepsy, exhibit interictal autonomic dysfunction and HRV changes that are more pronounced during sleep.[7] HRV parameters decrease during sleep in patients with FLE and intractable epilepsy, indicating autonomic alterations.[18,39] The current study found that central and cardiac autonomic alterations in NFLE patients were more pronounced than DFLE group only during sleep, implying that autonomic function is more vulnerable during sleep in people with epilepsy.

Autonomic changes are frequently observed in people with epilepsy. During the ictal or peri-ictal stage, these changes are resulted from the propagation of the epileptic activity into the CAN. The exact mechanism underlying interictal autonomic dysfunction remains unclear. However, it is hypothesized that repetitive seizures can potentially induce alterations in the CAN, thereby contributing to interictal autonomic dysfunction.[1,53] Frequent seizure is a risk factor of SUDEP and is associated with autonomic dysfunction.[3] HRV was observed to be lower in the refractory TLE group than in normal controls but not in those with well-controlled TLE.[54] In our study, more severe autonomic dysfunction developed in the NFLE group than in the DFLE group, although there was no significant difference in total seizure frequency between the two groups. Moreover, the DFLE group did not show significant changes in autonomic alteration during waking compared to the NFLE group. Our findings suggest that nocturnal seizures may have a greater impact on interictal autonomic alteration. The exact mechanism by which nocturnal seizures cause autonomic dysfunction remains

unclear, but there are several possible explanations. Some studies reported that epileptiform discharges cause arousal, cortical activation, and transient autonomic activation in people with epilepsy.[18,55] Other studies have found that autonomic activation precedes phasic EEG changes, cortical activation, and arousal.[56,57] Nocturnal seizures and interictal epileptiform discharges may interfere with sleep processes, potentially causing autonomic alteration.[58,59] Therefore, frequent nocturnal seizures are likely to cause frequent arousal and autonomic fluctuations, resulting in chronic autonomic dysfunction. Our findings suggest that nocturnal seizures during sleep, which is a vulnerable stage for autonomic function, may have a greater influence on autonomic dysfunction in people with epilepsy.

Brain-Heart Autonomic Axis

In our study, concurrent cardiac and central autonomic dysfunction occurred during sleep. HRV is generated by heart-brain interactions and dynamic non-linear autonomic nervous system (ANS) processes.[12] Stimulation of the left and right insula induces bradycardia and tachycardia, respectively.[60] Sympathetic activation is associated with tachyarrhythmia during the ictal and peri-ictal stages of epilepsy, whereas parasympathetic activation is associated with bradyarrhythmia and dyspnea.[53,61] Furthermore, alterations in the CAN have been reported in SUDEP and high-risk SUDEP patients.[10,11,43] In a patient with Takotsubo syndrome, a catecholamine-induced reversible cardiomyopathy, as well as alterations in the CAN and limbic network, was seen.[62,63] These findings imply that autonomic changes occur through the brain-heart autonomic axis during the interictal stage in people with epilepsy.

Our study has several limitations. Firstly, we applied strict enrollment criteria, resulting in a relatively small number of subjects. Secondly, the study groups were not compared to an appropriate normal control group. The current study aimed to investigate the influence of nocturnal seizures on autonomic function in epilepsy and involved only FLE patients with the same characteristics except for the frequency of nocturnal seizures. Thirdly, the type of ASM, which may have affected ANS, was not considered.

Conclusion

Our findings suggest that nocturnal seizure might be the most pronounced factor for interictal autonomic dysfunction during sleep in FLE patients. Interictal cardiac and central autonomic dysfunction occurred simultaneously and can be attributed to the brain-heart autonomic axis. Further studies including a larger sample size and comparison to a normal control group would provide additional insight. Studies on the mechanism between nocturnal seizure and autonomic dysfunction are also needed.

Statement of Ethics

There is no potential for individual researcher access to personal information, and there is no element of human rights violation. The Institutional Review Board of the Catholic University of Korea determined that consent is not required because the researchers are not collecting any personally identifiable information (such as patient name, hospital identification number, or social security number) when examining patients' records.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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