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Effects of Vagus Nerve Stimulation on Sleep-Disordered Breathing, Daytime Sleepiness, and Sleep Quality in Patients With Drug-Resistant Epilepsy

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Background and Purpose This study aimed to determine the long-term effects of vagus nerve stimulation (VNS) on sleep-disordered breathing (SDB), daytime sleepiness, and sleep quality in patients with drug-resistant epilepsy (DRE). It also investigated the relationships among these main effects, clinical characteristics, and VNS parameters.

Methods Twenty-four patients were recruited. Paired *t*-tests and multiple linear regression analyses were performed to determine how the demographic and clinical characteristics of the patients influenced the variables that changed significantly after VNS treatment.

Results After VNS, the patients showed significant increases in the apnea-hypopnea index (AHI), respiratory disturbance index (RDI), apnea index, hypopnea index, and oxygen desaturation index (ODI), as well as a significant decrease in the lowest arterial oxygen saturation (SaO_2 nadir) ($p<0.05$). The multiple linear regression analyses demonstrated that the predictor of larger increases in AHI and RDI was being older at baseline, and that the predictor of a larger increase in apnea index was a longer epilepsy duration. The strongest predictor of a larger increase in ODI was a higher frequency of aura episodes at baseline, followed by a longer epilepsy duration. The strongest predictor of a larger decrease in SaO_2 nadir was a higher frequency of aura episodes at baseline, followed by a longer epilepsy duration.

Conclusions This study has confirmed that VNS improves seizure control in patients with DRE, whereas it increases obstructive sleep apnea (OSA). Furthermore, the increase in OSA is affected by age and the duration of epilepsy. Therefore, careful observation and monitoring of SDB is recommended in patients who undergo VNS.

Keywords epilepsy; vagus nerve stimulation; obstructive sleep apnea; apnea-hypopnea index; excessive daytime sleepiness.

INTRODUCTION

Vagus nerve stimulation (VNS) involves stimulating the vagus nerve with electrical impulses, and is a clinically safe and effective treatment for patients with epilepsy (PWE). It has been used primarily for focal epilepsy, as well as for certain types of generalized epilepsy as an adjunctive treatment when other treatments have not worked, since it can effectively reduce the seizure frequency by 50% or even more in drug-resistant epilepsy (DRE) patients.[1,2] Nonetheless, it can also cause several side effects, such as voice changes, hoarseness, throat pain, dyspnea, nausea, and cough.[3-5] The side effect that receives less attention is sleep-disordered breathing (SDB), including both obstructive and central sleep apnea episodes.[6-8]

Previous studies showed that VNS is associated with sleep disturbances.[6-15] In particular, changing certain VNS parameters (output current, duty cycle, and discharge frequency)[7,12]

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and/or turning VNS on and off[10,11] induces significant changes in SDB. One retrospective study found VNS-related obstructive sleep apnea (OSA) in eight of nine (89%) pediatric patients.[6] Another study found that 4 of 26 (15%) pediatric PWE had sleep apnea after the implantation of a VNS device.[7] Also, one prospective study found that OSA was associated with VNS treatment in 5 of 16 adult PWE.[10] In addition to potentially causing SDB, VNS promoted both wakefulness and rapid eye movement (REM) sleep in a cat depending on the balance between cholinergic and noradrenergic linkages.[16] However, a study of 10 adult PWE demonstrated that VNS treatment both significantly increased daytime alertness and significantly decreased nocturnal REM sleep.[17] Another study of 16 PWE found that VNS at a low intensity (≤1.5 mA) decreased daytime sleepiness and daytime REM sleep, even in patients with no reductions in seizure frequency.[18] In summary, VNS influences the interrelated network of SDB, epilepsy, and sleep, and so the present study investigated effects of long-term VNS treatment on OSA, sleep quality, and daytime sleepiness in patients with DRE.

METHODS

Patients

This prospective study was approved by the Samsung Medical Center Institutional Review Board (No. 2016-05-055) and obtained informed consents from the PWE undergoing VNS treatment. Twenty-four patients who underwent two overnight polysomnography (PSG) and completed a set of sleep-related questionnaires both at baseline and at follow-up were included in this study. All patients were asked to keep accurate seizure logs during the period between the baseline and follow-up PSG investigations. There were no drug changes in any patients throughout the study, including at the 2-month baseline assessment. All of the patients were drug-resistant and underwent a presurgical evaluation such as long-term video-EEG (electroencephalography) monitoring and brain magnetic resonance imaging (MRI). The patients had various types of seizures, including aura episodes, motor simple partial seizures (SPS), complex partial seizures (CPS), secondary generalized tonic–clonic seizures (2GTCS). Patients were excluded if they had cognitive impairments that were sufficiently severe to interfere with their ability to provide informed consent or to participate in the study.

Study design

This study was designed to evaluate the effects of VNS on the seizure outcome and sleep-related variables (SDB, daytime sleepiness, insomnia, and sleep quality). Baseline assessments were performed the day before the VNS device was implanted. All of the assessments performed at baseline were repeated when the output current of each patient reached ≥1.5 mA at least 3 months (range: 7–12 months) after surgery.

VNS treatment

VNS treatment was applied using the NeuroCybernetic Prosthesis stimulating electrode and stimulator manufactured by LivaNova (previously Cyberonics, Houston, TX, USA). The VNS device was implanted subcutaneously in the left chest and neck under general anesthesia, and the stimulator was switched on at 2–4 weeks after surgery when the surgical wounds had healed and showed no sign of infection. The initial stimulation started with an output current of 0.25 mA, a frequency of 30 Hz, a pulse width of 500 μs, and on/off cycles of 30 s on and 5 min off. The output current was gradually increased at each visit (i.e., every 2–4 weeks) over several weeks from 0.25 to ≥1.5 mA, depending on the tolerance and seizure outcome. Patients were supplied with a handheld VNS magnet that could be used to activate stimulation when they experienced an aura, to prevent its progression to seizure. When a patient complained about an adverse event related to stimulation, the pulse width was reduced to 250 μs or the output current was temporarily reduced with or without also decreasing the signal on-time to 21 or 25 s.

Overnight PSG

All patients were asked to abstain from alcohol and caffeinated beverages on the day before the sleep studies were conducted. Sleep recordings were made using the Somnologica device (Embla, Denver, CO, USA). PSG was performed using six-channel EEG (F3/A2, F4/A1, C3/A2, C4/A1, O1/A2, and O2/A1), four-channel electrooculography, electromyography (on submental, intercostal, and anterior tibialis muscles), and electrocardiography with surface electrodes. The following devices were also attached to the patients: thermistor (for monitoring oronasal airflow), nasal air pressure sensor, oximeter (for measuring oxygen saturation), piezoelectric bands (for determining thoracic and abdominal wall motions), and body-position sensor. Patients went to bed at 23:00 and were awakened at 07:00 the next day. Sleep architecture was scored in 30 s epochs, and sleep staging was interpreted in accordance with the criteria of Rechtschaffen and Kales.[19] Apnea and hypopnea episodes were defined based on standard scoring scales.[20] The American Academy of Sleep Medicine (AASM) rules published in version 2.0 of the AASM manual[20] were used for scoring a hypopnea episode as follows: >30.0% reduction in nasal pressure signal excursions from baseline that lasted >10 s with >3.0% desaturation from the pre-event baseline or arousal. An apnea episode was defined as a reduction in airflow of >90.0% in the thermistor lasting

≥10 s during which there was evidence of persistent respiratory effort. To grade the severity of sleep apnea, the total number of apnea and hypopnea episodes per hour was reported as the apnea-hypopnea index (AHI). OSA severity was defined as follows: AHI <5/hr, normal; AHI=5−15/hr, mild; AHI=15−30/hr, moderate; and AHI >30/hr, severe. The respiratory disturbance index (RDI) in this study was the sum of the AHI and the respiratory-effort-related arousal (RERA) index (number of RERAs per hour of sleep).[20] The oxygen desaturation index (ODI) was the number of times per hour of sleep that blood oxygen level decreased by ≥3.0% from baseline.

Sleep-related variable assessments

This study evaluated three sleep-related variables (daytime sleepiness, insomnia severity, and sleep quality) twice before and after VNS treatment. Excessive daytime sleepiness (EDS) was measured using the Epworth Sleepiness Scale (ESS),[21] insomnia severity was measured using the Insomnia Severity Index (ISI),[22] and sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI).[23] The ESS has been widely used to measure the sleep propensity of a subject across different situations in daily life during the preceding month with a simple self-administered eight-item questionnaire. Total ESS scores are divided into five subcategories: 0−5, lower-normal daytime sleepiness; 6−10, higher-normal daytime sleepiness; 11 or 12, mild EDS; 13−15, moderate EDS; and 16−24, severe EDS.[21] The ISI is measured using a self-report questionnaire of a subject's perception of insomnia severity. Total ISIs are divided into four subcategories: 0−7, no clinically significant insomnia; 8−14, subthreshold insomnia (mild severity); 15−21, clinical insomnia (moderate severity); and 22−28, clinical insomnia (severe).[22] The PSQI comprises 19 questions that are combined to form the following 7 components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. These seven components are combined to form a global score that varies from 0 to 21, where 0 indicates no difficulty and 21 indicates extreme difficulty. A common cutoff for the global score is 5.[23]

Seizure measurement

Seizure frequencies of aura episodes, SPS, CPS, and 2GTCS were assessed by analyzing the seizure diaries of patients throughout the study period. For all patients, changes in the frequencies of different seizure types at the follow-up were analyzed by comparing the post-VNS seizure frequency with the baseline seizure frequency.

Statistical analysis

Paired *t*-tests were used to assess changes in all variables (seizure frequency, PSG, and sleep questionnaires) between before and after long-term VNS treatment. In addition, two-samples independent *t*-tests were used to compare demographics, epilepsy-related, sleep-related, and VNS-related variables between patients with and without an increased AHI. Multiple linear regression analyses were used to identify the factors potentially associated with significant changes in PSG parameters, daytime sleepiness, insomnia severity, and sleep quality after VNS treatment. The dependent variables were changes in AHI, RDI, apnea index, the lowest arterial oxygen saturation (SaO_2 nadir), and ODI. Independent variables included age, sex, ESS score, ISI, and PSQI at baseline, epilepsy-related variables, and VNS-related variables. The epilepsy-related variables were age at the onset of seizures, duration of epilepsy, type of epilepsy and seizures, EEG findings, and existence of MRI lesions. The VNS-related variables were whether a VNS magnet was used, the stimulation voltage, and the duration of VNS treatment.

The associations between dependent and independent variables were quantified as the mean and 95.0%-confidence-interval values of unstandardized linear regression coefficients. All significant associations were ranked according to the absolute values of their standardized effects, quantified as standardized regression coefficients. The tests of statistical significance were two-tailed, and significance was defined by $p<0.05$. All statistical analyses were performed with SPSS software (version 25.0, IBM Corp., Armonk, NY, USA).

RESULTS

The demographic and clinical characteristics of the 24 included patients are summarized in Table 1. Their age at the time of implanting the VNS device was 30.6±9.6 years (mean±standard deviation), while the age at the onset of seizures was 9.9±7.3 years, the duration of epilepsy was 20.2±11.2 years, the number of antiepileptic drugs (AEDs) was 4.4±1.2, and the interval between baseline and follow-up PSG investigations was 11.0±1.9 months (range: 7−12 months). There was no significant change in body weight between the baseline and follow-up visits. All patients had bilateral or multifocal epilepsy. Fifteen patients experienced adverse events of VNS, comprising hoarseness (n=7), cough (n=2), shortness of breath (n=1), and neck tingling pain (n=5).

Paired *t*-tests revealed significant changes between before and after VNS treatment in AHI (4.9/hr to 8.7/hr, p=0.009), RDI (6.0/hr to 10.0/hr, p=0.013), apnea index (0.4/hr to 1.0/hr, p=0.021), hypopnea index (4.5/hr to 7.7/hr, p=0.015), SaO_2 nadir (90.6% to 88.0%, p=0.004), and ODI (4.3/hr to 8.3/hr, p=0.018). The baseline PSG revealed mild OSA (5≤AHI<15) in 2 patients, moderate OSA (15≤AHI<30) in 2, and normal

Table 1. Demographic and clinical characteristics of all patients

Pt no.	Age (yr)	Sex	BMI before VNS (kg/m^2)	BMI after VNS (kg/m^2)	Seizure onset age (yr)	Epilepsy duration (yr)	Seizure types	MRI lesion	Seizure frequency at VNS device implantation: Aura/MSPS/CPS/GTC (mon)	Seizure frequency at follow-up: Aura/MSPS/CPS/GTC (mon)	No. of AEDs	Duration of VNS at follow-up (mon)	VNS parameters: OC (mA)/SF (Hz)/PW (ms)/SOFT (sec, min)	EEG findings (ictal EEG)	Previous epilepsy surgery
1	25	F	21.4	21.4	16	9	Aura, CPS	WNL	33/0/5/0	1/0/3/0	7	8	2.0/30/500/30, 5	Rt or bilat. frontotemporal	No
2	23	M	22.0	21.7	8	15	Aura, CPS, 2GTC	WNL	3/0/2/2	1/0/1/1	3	12	2.0/30/500/30, 5	Bilat. frontopolar	No
3	46	F	22.8	20.8	15	31	Aura, CPS, 2GTC	Tumor in Lt TL	4/0/4/4	1.5/0/1.5/0	5	12	2.25/30/500/30, 5	Lt, Rt frontotemporal	No
4	25	M	25.7	26.4	12	13	CPS, 2GTC	WNL	1/0/2/1	0/0/1/0	6	10	2.0/30/500/30, 5	Bilat. frontotemporal	No
5	29	F	25.1	23.3	19	11	Aura, CPS, 2GTC	WNL	3.5/0/3.5/0	0/0/1/0	4	15	2.0/30/500/30, 5	Rt, Lt temporo-occipital	No
6	35	F	31.6	33.6	3	33	Aura, CPS	HTL	0/0/10/0	0/0/3/0	4	13	2.0/30/500/30, 5	Bilat. frontotemporal	Yes
7	21	M	29.4	31.5	16	5	Aura, CPS, 2GTC	WNL	0/0/6/0	5/0/2.5/0	3	9	2.0/30/500/30, 5	Lt, Rt frontotemporal	No
8	21	M	30.6	35.0	4	17	Aura, CPS, 2GTC	WNL	4/0/4/0	2/0/0/0	4	14	2.0/30/500/30, 5	Lt, Rt temporal	No
9	19	M	26.6	25.6	9	10	MSPS, 2GTC	WNL	0/200/0/0	0/64/0/0	4	10	2.0/30/500/30, 5	Bilat. frontocentral	No
10	38	M	27.5	27.5	1	37	CPS, 2GTC	WNL	0/0/10/2	0/0/1/0	5	21	1.5/30/500/30, 5	Rt, bilat. frontal	No
11	34	F	22.7	25.8	17	17	Aura, CPS, 2GTC	HS in Rt	20/0/20/0	3.5/0/12.5/0	4	20	2.0/30/500/30, 5	Rt, bilat. temporal	Yes
12	57	F	22.3	22.3	12	45	Aura, CPS	HSI in Lt OL	3.5/0/3.5/0	0/0/1.5/0	5	7	1.5/30/500/30, 5	Lt, Rt temporal	No
13	34	F	23.1	24.3	2	31	CPS	Pachygyria in Rt FC	0/0/2/0	0/0/1/0	3	17	2.0/30/500/30, 5	Lt, Rt frontotemporal	No
14	37	F	34.0	33.6	2	34	Aura, CPS	HTL	30/0/15/0	30/0/15/0	5	14	1.5/30/500/30, 5	Bilat. frontocentral	Yes
15	45	M	26.4	26.4	9	32	Aura, CPS, 2GTC	ENC in Lt FL	0/0/25/0	0/5/5/0	4	9	2.25/30/500/30, 5	Lt, Rt frontal	No
16	28	F	17.7	18.5	5	22	Aura, MSPS, CPS, 2GTC	WNL	1/1/1/1	0/0/0/0	3	22	2.5/30/500/30, 5	Rt, Lt frontotemporal	No
17	23	M	22.0	24.6	8	14	MSPS, CPS, 2GTC	WNL	0/1/8/1	0/1/4/0	4	14	1.75/30/500/30, 5	Bilat. frontocentral	No
18	27	M	28.1	27.7	11	15	Aura, CPS, 2GTC	WNL	0/0/3.5/0	0/0/2/0	5	13	1.75/30/500/30, 5	Lt, bilat. frontotemporal	No
19	26	M	34.5	34.5	17	8	CPS, 2GTC	WNL	0/0/2/2	0/0/1/0	6	9	2.0/30/500/30, 5	Lt, bilat. frontotemporal	No
20	32	F	22.8	23.7	1	30	Aura, CPS	WNL	3.5/0/10/0	0/0/7/0	7	32	2.5/30/500/30, 5	Bilat. nonlocalized	No
21	22	F	28.8	26.8	5	16	Aura, CPS, 2GTC	WNL	6/0/6/1	0/2/0/0	5	11	1.75/30/500/30, 5	Rt temporal	Yes
22	41	M	26.8	28.1	31	9	Aura, MSPS	Multiple CL	2/2/0/0	0/0/0/0	3	13	2.0/30/500/30, 5	Lt frontocentral	No
23	20	F	25.4	26.7	12	7	CPS, 2GTC	Heterotopia	0/0/10/0	0/0/9/0	3	14	2.75/30/500/30, 5	Rt, Lt frontotemporal	No
24	26	M	28.4	28.7	2	23	CPS, 2GTC	WNL	0/0/15/2	0/0/9/0	3	9	2.0/30/500/30, 5	Bilat. frontal	No
Mean± SD	30.6± 9.6		26.1± 4.2	26.6± 4.5	9.9± 7.3	20.2± 11.2	-	-	-	-	4.4± 1.2	13.7± 5.6	-	-	-

AEDs, antiepileptic drugs; bilat, bilateral; BMI, body mass index; CL, calcified lesions; CPS, complex partial seizure; EEG, electroencephalography; ENC, encephalomalacia; F, female; FC, fronto-central; FL: frontal lobe; GTC, generalized tonic–clonic seizure; HS, hippocampal sclerosis; HSI, high signal intensity; HTL, hypothalamic lesion; Lt, left; M, male; MRI, magnetic resonance imaging; MSPS, motor simple partial seizure; OC, output current; OL, occipital lobe; Pt, patient; PW, pulse width; Rt, right; SD, standard deviation; SF, signal frequency; SOFT, signal on/off times; TL, temporal lobe; VNS, vagus nerve stimulation; WNL, within normal limits; 2GTC, secondary GTC.

AHI (<5) in 17. Among 20 patients who showed increased AHI after VNS, this increase was within the normal range in 11 of them (mean AHI: 0.64/hr to 1.76/hr). After implanting the VNS device, four out of seven patients with pre-existing mild (*n*=5) and moderate (*n*=2) OSA worsened to moderate OSA (*n*=3) and severe OSA (*n*=1), respectively, and five patients with normal AHI developed mild OSA. The findings are summarized in Tables 2 and 3. Compared with those without an AHI increase, patients exhibiting an AHI increase showed higher body mass index (BMI) (*p*=0.008), AHI (*p*=0.016), ODI (*p*=0.022), RAI (*p*=0.029), ISI (*p*=0.043), and lower stage-3 sleep (*p*=0.019). There was no significant change in ESS (7.2 to 6.1, *p*=0.484), ISI (8.3 to 6.5, *p*=0.261), or PSQI (7.0 to 5.9, *p*=0.354) between before and after VNS treatment (Refer Table 4).

The results of multiple regression analyses are presented in Table 5. The predictor of larger increases in AHI and RDI was being older at baseline, and the predictor of a larger increase in apnea index was a longer epilepsy duration at baseline. The strongest predictor of a larger increase in ODI was a higher frequency of aura episodes at baseline, followed by a longer epilepsy duration at baseline. The strongest predictor of a larger decrease in SaO_2 nadir was a higher frequency of aura episodes at baseline, followed by a longer epilepsy duration.

After long-term VNS treatment, the number of aura or seizure episodes per month was remarkably reduced (aura: 4.77 to 1.83, *p*=0.059; CPS: 6.98 to 3.38, *p*<0.001; 2GTCS: 0.67 to 0.04, *p*=0.006). The percentage seizure reductions in aura, CPS, and 2GTCS were 65.9%, 51.6%, and 93.8%, respectively. Seven of 14 patients reported that using the VNS magnet could stop seizure progression.

DISCUSSION

This prospective study has provided further evidence that long-term VNS treatment is associated with an increase in OSA in patients with DRE. Furthermore, changes in AHI, apnea index, RDI, and SaO_2 nadir were significantly associated with age, epilepsy duration, and frequency of aura episodes

Table 2. Apnea-hypopnea index (AHI) before (pre) and after (post) VNS treatment

Pt no.	Supine position (%)		AHI (/hr)		Supine AHI (/hr)		Lateral AHI (/hr)		REM-sleep AHI (/hr)		NREM-sleep AHI (/hr)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	85.1	100.0	0.0	0.3*	0.0	0.3	0.0	-	0.0	1.5	0.0	0.0
2	74.0	72.0	0.7	2.0*	0.7	2.8	0.7	0.0	3.3	3.8	0.4	1.7
3	75.3	66.0	0.6	0.0†	0.9	0.0	0.0	0.0	1.6	0.0	0.4	0.0
4	29.8	44.5	6.6	17.5*	22.1	38.9	0.0	0.3	0.0	0.0	7.5	20.6
5	73.2	100.0	0.0	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0	0.0
6	100.0	84.6	8.7	14.8*	8.7	13.6	-	21.4	28.0	29.2	6.0	12.4
7	100.0	100.0	0.8	1.9*	0.8	1.9	-	-	3.8	4.1	0.2	1.0
8	76.5	84.9	1.4	3.2*	1.8	3.4	0.0	1.8	6.0	12.1	0.4	0.7
9	99.6	100.0	9.6	0.6†	9.7	0.6	0.0	-	1.4	0.0	10.7	0.7
10	98.5	100.0	28.3	19.8†	28.7	19.8	0.0	-	60.5	60.0	22.4	16.8
11	84.4	37.9	1.8	14.4*	2.0	19.8	1.1	10.7	0.0	11.5	2.2	15.1
12	100.0	100.0	25.7	42.5*	25.7	42.5	-	-	0.0	0.0	25.7	42.5
13	90.4	69.9	0.7	3.2*	0.7	4.0	0.0	1.5	0.0	0.0	0.7	3.8
14	57.7	84.9	0.0	0.7*	0.0	0.9	0.0	0.0	0.0	2.7	0.0	0.0
15	62.3	84.7	7.2	26.1*	11.0	29.9	0.9	4.9	5.7	34.3	7.5	25.2
16	86.7	69.4	0.4	0.6*	0.2	0.7	1.5	0.5	0.0	1.0	0.4	0.5
17	86.3	69.3	1.6	8.6*	1.9	11.5	0.0	1.8	2.4	3.0	1.4	10.3
18	100.0	100.0	0.3	0.4*	0.3	0.4	-	-	1.7	1.5	0.0	0.2
19	76.6	76.7	2.9	12.4*	3.8	14.1	0.0	6.7	9.1	30.4	1.0	4.6
20	100.0	78.7	3.7	8.8*	3.7	9.9	-	4.8	0.0	0.0	3.7	10.2
21	54.1	81.9	1.2	2.6*	1.9	3.0	0.3	0.8	0.0	6.7	1.3	1.9
22	35.5	100.0	10.3	15.5*	25.7	15.5	1.8	-	3.0	30.0	12.5	14.3
23	100.0	96.0	1.5	3.6*	1.5	3.3	-	10.3	0.0	17.1	1.7	1.9
24	74.5	100.0	3.3	9.3*	4.5	9.3	0.0	-	10.4	18.7	1.9	8.3
Mean±SD	80.0±20.3	83.4±17.8	4.9±7.5	8.7±10.4	6.5±9.3	10.3±12.3	0.3±0.5	2.7±5.1	5.7±13.1	11.2±15.4	4.5±7.0	8.0±10.5

*Increased AHI in follow-up polysomnography (PSG); †Decreased AHI in follow-up PSG.
NREM, non-REM; Pt, patient; REM, rapid eye movement; SD, standard deviation; VNS, vagus nerve stimulation.

at baseline.

The mean AHI in patients with DRE increased significantly after VNS treatment. About 83.0% of our patients showed an increase in AHI after VNS treatment. Our findings for the AHI changes induced by VNS are partly consistent with the results of previous studies.[6,7,9-12,18,24-26] Applying VNS treatment to PWE has been shown to induce mild OSA or increase the severity of pre-existing OSA, accompanied by not only increases in the respiratory rate and AHI, but also decreases in the respiratory amplitude, tidal volume, and oxygen saturation.[9-11,24] A recent study of 18 PWE who underwent awake endoscopic laryngoscopy after VNS treatment for 4 years showed left-vocal-cord adduction in 11 patients with new-onset or worsened OSA during VNS.[26] This suggests that reduction of the glottal space or lack of laryngeal–respiratory coordination

Table 3. Polysomnography findings

Sleep parameter	Baseline	Follow-up	*p*
Total sleep time (min)	361.9±76.6	392.1±78.1	0.043*
Time in bed (min)	417.4±36.2	456.3±37.8	<0.001*
Sleep latency (min)	8.5±11.0	9.0±15.5	0.883
REM sleep latency (min)	115.1±69.9	119.8±62.1	0.759
Arousal index (/hr)	9.7±6.0	12.2±7.8	0.086
Sleep efficiency (%)	87.4±16.9	86.5±16.5	0.913
Stage 1 (% of total sleep time)	9.8±6.6	11.6±7.8	0.204
Stage 2 (% of total sleep time)	64.6±10.9	63.3±12.3	0.668
Stage 3 (% of total sleep time)	11.9±12.0	8.8±8.3	0.240
Non-REM sleep (% of total sleep time)	85.7±7.2	84.7±7.4	0.502
REM sleep (% of total sleep time)	13.9±7.1	15.0±7.4	0.498
Apnea (/hr)	0.4±0.8	1.0±1.8	0.021*
Hypopnea (/hr)	4.5±6.9	7.7±8.8	0.015*
AHI (/hr)	4.9±7.5	8.7±10.4	0.009*
RDI (/hr)	6.0±7.6	10.0±11.0	0.013*
SaO_2 nadir (%)	90.6±4.7	88.0±6.8	0.004*
ODI	4.3±6.2	8.3±10.4	0.018*
WASO (min)	45.8±72.3	53.4±71.1	0.802
WASO (%)	12.0±17.1	12.1±15.7	0.978
Snoring, number of episodes	1.8±3.2	3.6±5.9	0.104

Data are mean±standard deviation values.
*Statistically significant at $p<0.05$.
AHI, apnea-hypopnea index; hr, hour; ODI, oxygen desaturation index; RDI, respiratory disturbance index (apnea+hypopnea+respiratory-effort-related arousals); REM, rapid eye movement; SaO_2 nadir, lowest arterial oxygen saturation; WASO, wake time after sleep onset.

Table 4. Insomnia severity index (ISI), Epworth sleepiness scale (ESS) score, and Pittsburg sleep quality (PSQI) of all participants

Patient no.	ISI		ESS score		PSQI	
	Pre	Post	Pre	Post	Pre	Post
1	11	11	10	17	11	10
2	5	15	6	5	10	16
3	9	2	9	7	7	3
4	13	1	6	0	8	7
5	19	3	4	1	11	3
6	4	11	6	2	6	7
7	5	4	24	13	5	6
8	2	7	13	6	8	6
9	15	6	8	11	3	6
10	8	5	5	11	8	3
11	2	15	11	17	4	9
12	13	8	3	2	2	2
13	6	4	9	9	7	9
14	10	21	7	8	8	14
15	1	11	3	4	8	9
16	6	6	9	1	7	3
17	3	1	7	6	3	2
18	10	4	2	2	9	10
19	5	8	3	6	5	8
20	21	4	19	9	10	4
21	16	4	0	5	13	1
22	0	1	2	0	6	3
23	9	1	6	4	4	1
24	5	2	0	0	6	0
Mean±SD	8.3±5.7	6.5±5.2	7.2±5.6	6.1±5.0	7.0±2.8	5.9±4.1

Post, after VNS treatment; Pre, before VNS treatment; SD, standard deviation; VNS, vagus nerve stimulation.

Table 5. Results from multiple regression analyses of predictors associated with worsening obstructive sleep apnea (OSA), as well as new onset of OSA

Dependent variable	Predictor	Standardized coefficient	*p*	R^2
Change in AHI	Age at baseline	0.429	0.038*	0.287
Change in apnea	Epilepsy duration	0.280	0.012*	0.794
Change in RDI	Age at baseline	0.440	0.020*	0.366
Change in ODI	Frequency of aura episodes at baseline	0.371	0.013*	0.618
	Epilepsy duration	0.311	0.039*	
Change in SaO_2 nadir	Frequency of aura episodes at baseline	-0.399	0.031*	0.350
	Epilepsy duration	-0.386	0.037*	

*Statistically significant at $p<0.05$ in a multiple regression analysis after adjusting for the effects of the reduction in seizure frequency (aura, CPS, and 2GTC) on the changes in AHI, apnea, RDI, ODI, and SaO_2 nadir after VNS treatment.
AHI, apnea-hypopnea index; CPS, complex partial seizure; ODI, oxygen desaturation index; RDI, respiratory disturbance index (apnea+hypopnea+respiratory-effort-related arousals); SaO_2 nadir, lowest arterial oxygen saturation; VNS, vagus nerve stimulation; 2GTC, secondary GTC.

influence the exacerbation of OSA after VNS. Another study of 16 adult patients with DRE found that 5 patients with normal AHI values worsened to mild OSA after VNS treatment for 3 months.[10] Based on these previous VNS studies, OSA might be induced by VNS not only via the airway obstruction secondary to the stimulation effects of VNS on respiratory centers of central nervous system, but also by the morphological alteration of neuromuscular transmission to laryngeal and pharyngeal muscles induced by the peripheral stimulation of vagus nerve afferents.[9,26,27]

The multiple regression analyses performed in this study revealed that older patients with a higher frequency of aura episodes and a longer epilepsy duration have a higher risk of worsening OSA after a VNS device is implanted. There have been no reports of risk factors affecting the worsening of respiratory variables after VNS. Although not directly related to our findings, a previous study found that the risk factors for OSA included a wide range of clinical and sleep-related variables, such as being older, being male, and having obesity, larger neck circumference, loud snoring, EDS, depression, hypertension, and diabetes.[28] One Canadian study found age to be an independent risk factor for OSA.[29] Those authors suggested that the decrease in the muscle tone with aging and the consequent reduction in the dimensions of upper airway lumen are pathogenic mechanisms for OSA. Another study of 60 adult PWE demonstrated that older patients and those with a longer epilepsy duration tend to have a higher AHI.[30] Those authors suggested that age and the duration of epilepsy play a role in the pathogenesis of worsened OSA, because the BMI was not higher in PWE with a higher AHI than in nonapneic patients. DRE patients who participated in this study were taking a mean of 4.4 AEDs (range: 3–7 AEDs) at baseline, and taking multiple AEDs is associated with weight gain, which potentially exacerbates or increases the risk of OSA.[31] The risk of obesity in patients with DRE might be higher in those receiving AED polytherapy than in those receiving monotherapy. These results support our finding that the patients with increased AHI showed higher BMI compared with the patients without an increased AHI.

Benzodiazepines, such as clobazam and clonazepam, are often used to treat DRE.[32] The use of these drugs is associated with reduced upper airway muscle tone and respiratory responses to hypoxia.[33] Two studies have shown that administering benzodiazepines for OSA may be associated with an increase in and prolongation of apnea episodes.[34,35] Respiration can be affected by the input from limbic regions to the respiratory center located in the brainstem. Stimulating multiple cortical areas including the amygdala, hippocampus, ventral and medial temporal pole, and anterior insular and anterior limbic gyrus due to frequent seizures induces respiratory inhibition.[36,37] However, focal seizures that do not spread to these areas can also cause respiratory disturbances. These findings might be consistent with the results of the present study.

This study found that daytime sleepiness symptoms decreased slightly after VNS treatment (mean ESS score: 7.2 to 6.1), although the change was not statistically significant. This is partially consistent with the results of the previous two studies showing that VNS with a low stimulation intensity of ≤1.5 mA improved daytime sleepiness symptoms.[17,18] The vagus nerve projects via the nucleus tractus solitarius into many brainstem regions, including the parabrachial nucleus (PBN) and locus coeruleus. The PBN connects to the thalamus, basal forebrain, hypothalamus, and cerebral cortex. Low-intensity VNS is transmitted to the PBN via afferent nerves, which in turn stimulates orexin (hypocretin) neurons that promote awakening, and consequently reduced daytime sleepiness.[17]

In conclusion, the present study showed that VNS reduces the seizure frequency in PWE, but increases OSA. Furthermore, the increase in OSA is correlated with being older and a longer duration of epilepsy. Therefore, careful monitoring of OSA is recommended in patients implanted with a VNS device, with OSA being treated if it occurs.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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