Epilepsia, **44**(7):930–935, 2003
Blackwell Publishing, Inc.

Effects of Vagus Nerve Stimulation on Sleep-related Breathing in Epilepsy Patients

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Summary: *Purpose:* To describe the effects of vagus nerve stimulation (VNS) on sleep-related breathing in a sample of 16 epilepsy patients.

Methods: Sixteen adults with medically refractory epilepsy (nine men, seven women, ages 21–58 years) underwent baseline polysomnograms (PSGs). Three months after VNS therapy was initiated, PSGs were repeated. In addition, patient 7 had a study with esophageal pressure monitoring, and patient 1 had a continuous positive airway pressure (CPAP) trial.

Results: Baseline PSGs: One of 16 patients had an apnea–hypopnea index (AHI) >5 (6.8). Treatment PSGs: Five of 16 patients had treatment AHIs >5. Respiratory events were more frequent during periods with VNS activation (on-time) than without VNS activation (off-time; $p = 0.016$). Follow-up studies: Esophageal pressure monitoring in patient 7 showed crescendos in esophageal pressure during VNS activation, supporting an obstructive pattern. The CPAP trial of patient 1 showed that all respiratory events were associated with VNS stimulation at low CPAP levels. They were resolved at higher CPAP levels.

Conclusions: Treatment with VNS affects respiration during sleep and should be used with care, particularly in patients with preexisting obstructive sleep apnea. The AHI after VNS treatment remained <5 in the majority of patients and was only mildly elevated (<12) in five patients. In one patient, CPAP resolved VNS-related respiratory events. **Key Words:** Epilepsy—Vagus nerve stimulator—Obstructive sleep apnea.

Vagus nerve stimulation (VNS), delivered by a surgically implanted nerve stimulator (Cyberonics, Houston, TX, U.S.A.), has proven effective in treating medically refractory epilepsy. Although the exact mechanism by which VNS reduces seizure frequency is unknown, it is believed to modulate electrical stimuli to the nucleus tractus solitarius and the brainstem reticular formation. In this way, VNS may interrupt the synchronous electrical activity characteristic of seizures (1). Common side effects include laryngeal irritation, hoarseness, and dyspnea.

We previously reported in a pilot study of four patients that VNS is associated with decreased respiratory airflow and effort during sleep (2). Others have confirmed our observations. One group reviewed polysomnograms (PSGs) of six patients with VNS and reported VNS-related tachypnea in all six. They also reported VNS-related apnea in two PSGs (3). Another group, which reported on seven patients treated with VNS, found more events of increased upper airway resistance during VNS activation (4). A third group found mild respiratory impairment during sleep associated with VNS activation in four children treated with VNS (5). We now extend our findings to include PSGs of 16 patients treated with VNS. We also report on follow-up PSGs with esophageal pressure monitoring (Pes) and continuous positive airway pressure (CPAP) therapy to better define the characteristics of VNS-related respiratory events.

Accepted March 1, 2003.
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METHODS

Patients

This protocol was approved by the University of Michigan Institutional Review Board, and informed consent was obtained. Patients were recruited from patients 18 years or older with medically refractory epilepsy who underwent evaluation for placement of the VNS device in the University of Michigan Epilepsy Clinic between January 1999 and March 2000. All patients had complex partial seizures with or without secondary generalization, except for subject 5, who had juvenile myoclonic epilepsy. Two patients eligible for the protocol chose not to participate. One subject who underwent a baseline PSG did not undergo a treatment PSG because he was never implanted with the device because of insurance disapproval. Sixteen adults (nine men, seven women), ranging in age from 21 to

58 years (mean age, 33.6 ± 11.1, standard deviation), underwent baseline PSGs and Multiple Sleep Latency Tests (MSLTs) according to standard procedure in the Michael S. Aldrich Sleep Disorders Laboratory at the University of Michigan. Three months after VNS was initiated, PSGs and MSLTs were repeated. Patients were asked to keep accurate seizure logs during the period between baseline and treatment PSGs. The primary objective of this protocol was to assess the effect of VNS on daytime sleepiness, results that have been reported previously (6). The effects of VNS on respiration during sleep (decreased airflow and effort) were unanticipated findings in the first four patients recorded, and were the subject of an expedited publication (2). Respiratory data from these four previously presented patients (patients 1, 7, 8, and 10) are included in this report for completeness.

Patients were excluded if they had cognitive impairment severe enough to interfere with their ability to provide informed consent or to participate in the study. Because sleep disorders can result in daytime sleepiness, patients reporting a history of any sleep disorder other than treated obstructive sleep apnea were excluded from the protocol. Referring physicians were asked to keep patients on stable doses of antiepileptic medications (AEDs) during the 3 months between baseline and treatment studies, unless changes were necessary because of escalating seizure frequency or medication toxicity. (See Table 1 for medication changes that occurred between baseline and VNS treatment studies in patients 9, 11, and 14).

Vagus nerve stimulator device

The Vagus Nerve Stimulator device (Cyberonics, Houston, TX, U.S.A.) consists of a spiral bipolar electrode wrapped around the left vagus nerve and connected to a pulse generator (1). The generator is implanted in the infraclavicular region on the left side. Intraoperative impedance testing is performed to ensure electrical continuity of the VNS system. The device is activated at the patient's first postoperative outpatient visit with a wand placed over the generator.

In each patient, the parameters of the electrical output were programmed on postsurgical activation of the device. Electrical stimulus intensities were set according to established guidelines regarding seizure frequency and patient tolerance (7). The stimulus intensities ranged among patients from 0.75 to 2.75 mA, at 30-Hz frequency and 250 or 500 μs pulse width. Fifteen of the 16 patients received stimulation for 30 s, with intervening 5-min off-periods. In patient 3, the VNS device was activated for 30 s, with intervening 3-min off-periods (more rapid cycling). Each patient's VNS device was programmed at the postoperative visit, and no changes in the VNS parameters were made during the 3-month period between baseline and treatment study.

TABLE 1. *Patient characteristics*

Patient no.—age/gender	Baseline sz/mo	Sz freq. after 3 mo VNS therapy	B-AHI (REM AHI)	T-AHI (REM AHI)	B-min. O_2	T-min. O_2	Stimulus intensity	AEDs in mg/day
1—35/m	4	Reduced 100%	4.0 (14)	11.3[a] (15.7)	91	84	1.0	LTG, 600; PHT, 400; CZP, 1.0
2—27m	6–10	Unchanged	2.0 (1.5)	10.1[a](8.6)	90	90	1.25	PHT, 200; FBM, 5,400
3—46/f[b]	>20	Reduced 45%	0.9 (4.4)	9.9[a] (2.3)	93	90	0.75	CBZ, 1,400; LTG, 450
4—57/f	6–10	Unchanged	4.9 (0)	8.2[a] (20.6)	89	88	1.25	PHT, 400; LTG, 200; levothyroxine, 0.2
5—34/m	5	Reduced 20%	1.4 (2)	5.9[a] (1.8)	93	93	0.75	PHT, 400; TGB, 48
6—33/m	4–5	Reduced 100%	1.3 (0.9)	2.9 (9.5)	96	94	1.75	PHT, 325; sertraline, 100
7—58/f	3	Unchanged	6.8[a] (22)	4.5 (7.3)	87	81	2.0	PHT, 300; TGB, 28
8—20/m	5	Reduced 40%	0.6 (2.1)	2.6 (4.3)	90	91	1.5	CBZ, 3,200; LTG, 700
9—26/ml	11–20	Unchanged	1.1 (3.1)	2.4 (2.1)	94	88	1.0	LEV,[c] 3,000; LTG[c], 350; risperidone, 5
10—31/f	6–10	Unchanged	0.8 (8.8)	2.1 (0)	90	91	1.75	PHT, 425; TPM, 500
11—27/m	60	Reduced 50%	1.4 (17.8)	1.8 (2.1)	94	88	1.5	CBZ, 1,000; VPA, 3,000; PB, 100; sertraline, 200
12—31/m	6–10	Reduced 50%	0.3 (0.5)	1.5 (0.7)	94	95	0.75	PHT, 400; TPM, 100
13—22/f	>20	Unchanged	0.3 (0)	1.3 (2.6)	95	95	1.25	CBZ, 1,600; TPM, 300
14—25/f	6–10	Unchanged	3.0 (15)	1.3 (4)	93	88	2.75	VPA, 2,250[c]; CBZ, 1,400; sertraline, 50
15—29/m	>20	Unchanged	1.1 (1.4)	1.0 (4.2)	94	90	1.25	LTG, 500; VPA, 1,125; PHT, 430; LZP, 6; GBP, 4,800
16—36/f	>20	Unchanged	0 (0)	0.1 (0)	94	94	0.75	CBZ, 2,000[c]; PB, 120; levothyroxine, 0.075

All patients were stimulated with 250- or 500-μs pulse width and 30-Hz frequency.

AHI, apnea–hypopnea index; B, baseline; T, treatment; min. O_2, minimum oxygen saturation; AED, antiepileptic drug; CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; TPM, topiramate; TGB, tiagabine; LTG, lamotrigine; CZP, clonazepam; LEV, levetiracetam; FBM, felbamate; VPA, valproic acid; LZP, lorazepam; GBP, gabapentin.

[a] Clinically significant AHI (>5).

[b] VNS set at a more rapid cycling rate (30-s stimulation every 3 min).

[c] Patient 9: LEV increased to 3,500, and LTG increased to 600; Patient 14, VPA decreased to 2,000; Patient 16, CBZ increased to 2,400 between baseline and treatment studies.

Polysomnography

Polysomnograms were recorded on 32-channel computerized EEG systems (Grass Telefactor Corp., West Conshohocken, PA, U.S.A.) and included EEG, electrooculogram, submental electromyogram (EMG), nasal–oral airflow, thoracic and abdominal effort as measured by belts containing piezo crystals, pulse oximetry, and anterior tibialis EMG. EEG was recorded with a 0.3-Hz low-frequency filter and 70-Hz high-frequency filter. The sampling rate used was 200 Hz. For VNS treatment PSGs, a surface electrode was placed over the site of the VNS lead and referenced to a second surface electrode placed laterally to record when the VNS was activated ("activation-time").

Studies were staged and scored for respiratory events by the first author, a registered technologist (M.M.), blinded to the VNS signal. The senior author (B.A.M.) confirmed accuracy of scoring. Respiratory analysis was done according to the protocol of our laboratory. According to these standards, an obstructive apnea is defined as an 80% decrease in airflow from baseline amplitude for $\geq$10 s. A hypopnea is defined as a 10-s, 50–80% decrease in airflow or effort of baseline amplitude associated with an EEG arousal (8), or an oxygen desaturation of $\geq$4%. In our laboratory, obstructive versus central hypopneas are not distinguished. However, if effort is preserved during a hypopnea, we tend to characterize it as obstructive.

The apnea–hypopnea indices (AHIs) for each study were calculated by dividing the number of apneas and hypopneas per hour of sleep. An AHI of $\geq$5 was chosen to define clinically significant obstructive sleep apnea (OSA) (9). For patients with clinically significant OSA on studies with VNS, separate AHIs were calculated for VNS activation and nonactivation periods of sleep to relate respiratory events to VNS activations. Activation AHIs were calculated by using the number of respiratory events per hour that occurred during VNS activation. Nonactivation AHIs were calculated in the same manner by using respiratory events and sleep time that occurred during VNS off-time. Calculating AHIs separately for VNS activation and nonactivation periods compensated for differences in overall AHIs between baseline and treatment studies that may have been owing to night-to-night variability of sleep and of apnea in the same patient. VNS activation and nonactivation occurred in an alternating pattern periodically throughout all stages and positions of sleep. We calculated separate AHIs for stimulus on and off periods only for those patients with clinically significant AHIs, because we thought this to be the most meaningful group to study.

Follow-up studies

Two patients returned to the sleep laboratory for further testing for clinical indications after completing the protocol. Patient 1 (treatment AHI, 11.3) underwent a CPAP titration in the laboratory. Patient 7 underwent one PSG with esophageal pressure monitoring (Pes) and nasal pressure in addition to the standard nasal–oral thermistor. This follow-up PSG was performed because several arousals were associated with snoring, which indicated possible upper airway resistance syndrome on the treatment PSG. This clinical symptom was not present on the baseline PSG for this patient. Therefore, more information was necessary to diagnose her sleep-disordered breathing syndrome.

Statistical analysis

Statistical tests were performed by using the SPSS statistical analysis package (SPSS Inc., Chicago, IL, U.S.A.). For all statistical tests, the level of significance was set at $\alpha = 0.05$. Two-sample paired t tests were used to determine differences in AHI between the baseline and treatment studies and also between VNS activation periods and nonactivation periods in treatment studies. Two-sample independent t tests were used to examine whether age or body mass index (BMI) differed between patients with AHIs <5 and those with AHIs $\geq$5. χ^2 tests were used to examine whether gender differed between patients with AHIs <5 and those with clinically significant AHIs ($\geq$5).

RESULTS

Baseline sleep studies

Only patient 7 of the 16 had a baseline AHI >5 (6.8; Table 1). Patient 12, who initially had an AHI of 37, was treated with CPAP and was entered in the protocol with an AHI of 0.3.

VNS treatment sleep studies

Fourteen of the 16 patients had increased AHIs on treatment PSGs. In the 16 patients overall, the treatment AHI was higher than the baseline AHI ($p = 0.008$). The respiratory patterns in all 16 patients were identical to those reported in our prior publication and consisted of consistent decreases in airflow with diminished but relatively preserved effort, often associated with tachypnea, which occurred during VNS activation. They sometimes met scoring criteria for apneas or hypopneas. We did not see any central apneas in association with VNS.

AHIs increased to clinically significant levels (AHI > 5) in five patients. Patients 1 and 2 had $\geq$10 events per hour. We analyzed the activation and nonactivation AHIs in treatment PSGs in those patients with treatment AHIs > 5 and found a higher activation AHI ($p = 0.016$; Table 2). Patient 7, with a 6.8 baseline AHI, had a lower treatment AHI of 4.5, which was not owing to decreases in rapid eye movement (REM) sleep, supine, or REM–supine sleep and may reflect night-to-night variability.

Patients with an elevated AHI (>5) did not differ in age, gender, or BMI ($p > 0.10$). The effects of VNS therapy on seizure control in patients with an elevated AHI were comparable to those without an elevated AHI. Those

TABLE 2. *Separate AHI on VNS treatment PSGs for patients with clinically significant AHIs*

Patient no.	AHI	Activation AHI	Nonactivation AHI
1	11.3	26.2	6.9
2	10.1	11.9	7.6
3	9.9	20.2	6.9
4	8.2	16.2	3.1
5	5.9	10.7	5.2
7-np/Pes study	12.9	40.9	5.9

Activation AHI was significantly higher than nonactivation AHI (two-tailed paired *t* test; $p = 0.016$).

AHI, apnea–hypopnea index; Activation AHI, AHI for periods when vagus nerve stimulator (VNS) was activated; Nonactivation AHI, for periods when VNS was not activated; np, nasal pressure; Pes, esophageal pressure.

with an elevated AHI had a mean seizure reduction of $33 \pm 42\%$, and those without an elevated AHI had a mean seizure reduction of $22 \pm 34\%$ ($p > 0.10$). Two of the five patients with elevated AHIs had evidence of preexisting sleep apnea. After completion of our study, the caregiver of patient 1 reported witnessed apneic episodes and snoring. Patient 2 had previously undergone a tonsillectomy to treat OSA. As mentioned earlier, patient 3's VNS cycled more rapidly than the others. Therefore, the amount of VNS activation time during sleep was higher for that patient than for the others. Other factors associated with an increased AHI could not be identified in the other two patients with treatment AHIs >5. Patient 12, who had preexisting OSA treated with CPAP, did not have worsening of his OSA with VNS treatment.

Follow-up sleep studies

Patient 1 had an AHI of 3.8 for the follow-up PSG with CPAP titration. At lower pressures of CPAP (5 and 7 cm), all apneas and hypopneas were VNS related and resembled the patterns previously described in the VNS treatment sleep studies. The events were resolved at 9 cm of CPAP pressure. Patient 7's follow-up study was done with Pes and nasal pressure. The AHI based on the nasal–oral thermistor was 12.9. Analysis of this study showed crescendo patterns in the Pes channel during VNS activation, supporting an obstructive pattern (Fig. 1). At times, a lag occurred between the onset of VNS activation and the PES crescendo seen. Recordings from the nasal pressure channel also supported an obstructive pattern, as effort was diminished but observable throughout the events. The higher AHI for this follow-up study, as compared with the VNS treatment study, may have been the result of having nasal pressure monitoring and esophageal pressure monitoring, which allowed detection of respiratory events that did not meet scoring criteria that applied to previous studies with only the nasal–oral thermistor. This patient was then offered a CPAP titration but declined CPAP therapy.

DISCUSSION

In this study, we extended our prior observations on the effects of VNS on sleep-related breathing to a total of 16 patients. In comparing AHIs for baseline and treatment studies, respiratory events increased to clinically significant levels in five (31%) of our 16 patients. To determine what portion of these AHIs could be attributed to the VNS activation, we calculated separate AHIs for VNS activation sleep time and nonactivation sleep time and found that AHIs were significantly higher during VNS activation.

In all subjects, we observed decreases in airflow and effort coinciding with VNS activations. The effort was

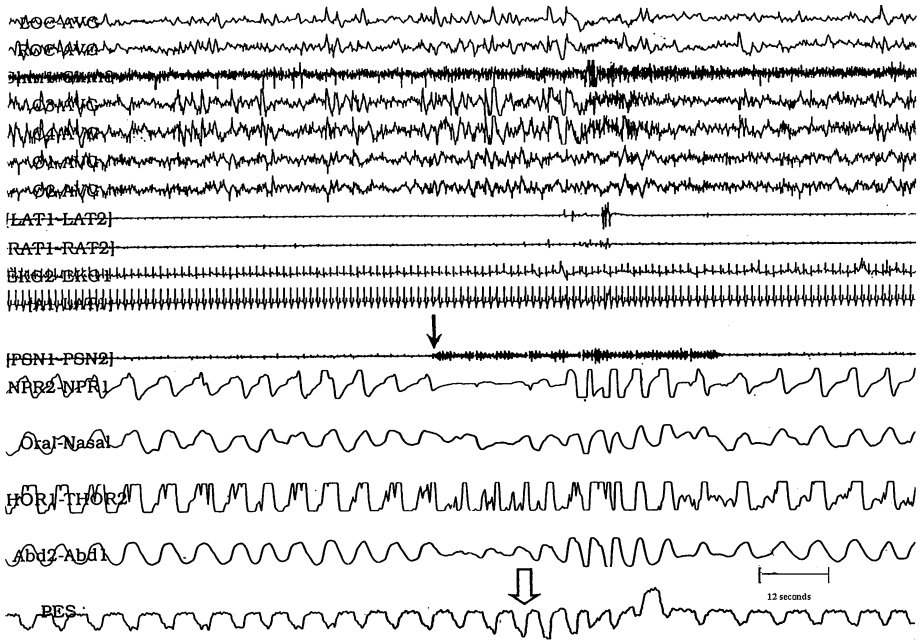

FIG. 1. Two-minute epoch of polysomnography with nasal pressure, esophageal pressure, and vagus nerve stimulation (VNS). *Black arrow*, VNS activation (on-time) and corresponding decrease in nasal pressure and airflow and EEG arousal from sleep. *Open arrow*, crescendo increase (i.e., progressive increase over several breaths) in esophageal pressure associated with respiratory event. LOC, left outer canthus; ROC, right outer canthus; chin, chin electromyogram; C3-AVG *and* C4-AVG, central EEG channels; O1-AVG *and* O2-AVG, occipital EEG channels; LAT, left anterior tibialis; RAT, right anterior tibialis; PSN, vagal nerve signal; NPR, nasal pressure; *oral-nasal*, oral–nasal thermistor; *thor*, thoracic effort; *abd*, abdominal effort; PES, esophageal pressure monitor.

generally preserved compared with decreases in airflow, suggesting that airway patency was compromised. This compromise in airway patency was further supported by nasal and esophageal pressure monitoring in one patient and the resolution of respiratory events during a CPAP titration study in another patient. The nasal and esophageal monitoring study showed that airflow decreased and pressure increased, whereas effort was sustained through the events (Fig. 1). In addition, one patient with preexisting OSA (patient 12) treated with CPAP showed no worsening of OSA with VNS treatment.

In our previously published pilot work, we discussed the various mechanisms whereby VNS may affect respiration during sleep (2). These include both peripheral effects on upper airway musculature innervated by the vagus nerve and more central mechanisms influencing upper airway patency and respiratory effort. VNS activation of C-fibers, or other mechanisms related to VNS activation, may explain the tachypnea associated with respiratory changes during sleep (3). Of relevance to and consistent with our work is the recently reported finding that atrial overdrive pacing reduced obstructive and central apneas in patients with sinus-node dysfunction and coexisting sleep apnea. The authors of this report postulated that the reduction in vagal tone caused by cardiac pacing might exert its beneficial effect on sleep-disordered breathing via a reduction in vagal tone (10). VNS increases vagal tone, whereas cardiac pacing reduces vagal tone—these opposing effects may explain why VNS caused reduced airflow and effort during sleep, and cardiac pacing ameliorated sleep-disordered breathing.

The clinical impact of VNS on sleep-related breathing remains uncertain. In our sample, the effects of VNS on breathing during sleep are mild in most cases. Seizure improvements in the five patients with increased AHIs were similar to those of the other 11 patients, indicating that in this population, the effects of mild OSA are not a barrier to seizure improvement. Only two patients of the 16 had an AHI >10 with VNS (patients 1 and 2), and both had prior evidence of OSA (although not known in patient 1 at time of inclusion in our study). Patient 1 was treated with CPAP, and patient 2 received positional therapy, as the majority of respiratory events occurred in the supine position. The other three patients with AHIs >5 were treated with positional therapy, given that the majority of respiratory events occurred in supine position in these cases as well. A limitation of our study is that we were not able to bring these patients back for follow-up studies to determine whether OSA associated with VNS activation was improved by the positional therapy.

As this protocol was designed to investigate the effects of VNS on daytime sleepiness, not sleep-related breathing, some limitations occurred in our study. One of the limitations is that patients with untreated OSA were excluded; therefore the effects of VNS on sleep-related breathing in patients with untreated or unrecognized OSA are unknown. In addition, only one patient had nasal pressure and esophageal pressure monitoring. Further controlled studies of VNS patients with monitoring of nasal pressure, esophageal pressure, or both are necessary to quantify definitely the central or obstructive nature of the effects of VNS. We observed that crescendos in esophageal pressure were not consistently time-locked to the start of VNS activation, suggesting that VNS effects on respiration during sleep are complex and will require further quantification in future studies. We also observed mild elevations in the nonactivation AHIs, although not to the same extent as during activation. This may reflect night-to-night variability or effects of VNS on upper airway patency, although this latter possibility must be investigated in follow-up studies. Finally, AEDs also may affect respiration through weight gain or changes in upper airway tone (11,12). Such AED effects may interact with the VNS treatment to affect respiration during sleep. Further studies with larger numbers of patients will be necessary to address this issue.

As a result of our preliminary report on the effects of VNS on sleep-related breathing (2), Cyberonics issued a caution in their product labeling to read ''Patients with obstructive sleep apnea (OSA) may have increased apneic events during stimulation. Cyberonics recommends care when treating patients with preexisting OSA. Lower stimulating frequencies or prolonging off-time may prevent exacerbation of OSA.'' At the University of Michigan, we now approach the concern of OSA being related to VNS by taking a careful sleep history, exploring symptoms of sleep-related breathing. If OSA is likely, a PSG is performed, and clinically significant OSA is treated before VNS is implanted. In addition to minimizing the potential risk of VNS worsening sleep-disordered breathing, treating OSA may reduce seizures and improve patient tolerance of AEDs (13–15). Although the mechanisms whereby VNS affects sleep-related respiration remain unclear and warrant further study, CPAP appears to be an effective treatment in patients in whom OSA develops during VNS.

VNS is an effective and useful treatment for epilepsy. Its effect on sleep-related breathing warrants further investigation and care in treating patients. Further directions for this work include performance of follow-up PSGs in patients treated with VNS to determine whether the effects on sleep-related breathing diminish over time.

Acknowledgment: Mr. Kevin Weatherwax assisted with collection of data and figure preparation. Dr. Ralph Lydic and Dr. David Mendelowitz provided valuable discussion regarding the neurophysiology of VNS. This study was supported by: Cyberonics and NINDS KO2 NS02099.

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