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SCIENTIFIC INVESTIGATIONS

A surface electrode adjacent to vagal nerve stimulator lead can aid in characterizing vagal nerve stimulator–mediated pediatric sleep-disordered breathing: a case series of 7 patients

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Study Objectives: The vagal nerve stimulator (VNS) is a nonpharmacological treatment for refractory epilepsy. A side effect of the VNS is sleep-disordered breathing. The purpose of this study was to demonstrate how a surface electrode placed over the VNS lead can help distinguish whether sleep-disordered breathing is due to VNS discharge.

Methods: Seven pediatric patients (aged 7.7 ± 2.2 years) with a VNS underwent a polysomnogram with an additional surface electrode on the left anterolateral neck to detect VNS discharge. The VNS-associated apnea-hypopnea index was calculated by determining the number of hypopneas and apneas occurring during VNS discharge. We evaluated the veracity of the VNS electrode by comparing signal duration and total number to those expected by programmed settings. We compared these findings to chin electromyogram signal change.

Results: Three patients had an obstructive pattern with VNS discharge, and 3 had an increase in respiratory rate without gas exchange abnormalities, including 1 with both patterns; 1 patient experienced no respiratory abnormalities. The mean obstructive apnea-hypopnea index was 8.2 ± 8.3 events/h. The mean VNS-associated apnea-hypopnea index was 4.8 ± 6.2 events/h and accounted for 46.9 ± 30.2% of the total obstructive apnea-hypopnea index. The additional electrode captured a statistically high percentage of expected discharges (94.7 ± 6.5%) compared to chin electromyogram (36.1 ± 35.8%; $P < .05$).

Conclusions: We demonstrated that a surface electrode on the VNS lead can temporally coregister VNS discharges and enabled us to attribute sleep-disordered breathing to VNS stimulation in 4 patients. We propose that this sensor be standard procedure in patients with VNS undergoing polysomnogram.

Keywords: vagal nerve stimulator, pediatrics, sleep-disordered breathing, obstructive sleep apnea

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Patients with medically refractory epilepsy treated with vagal nerve stimulators (VNSs) are at high risk for obstructive sleep apnea. A side effect of VNS stimulation can be sleep-disordered breathing, but there are no published methods in pediatric patients of how to accurately measure VNS-associated sleep-disordered breathing.

Study Impact: We propose that patients with VNS undergoing PSG have an additional electrode added as standard protocol to help distinguish different causes of sleep-disordered breathing. We found that a low-frequency filter of 100 Hz and a notch filter of 60 Hz placed on the left anterolateral neck surface over the VNS lead generally gave us the best signal.

INTRODUCTION

The vagal nerve stimulator (VNS) is U.S. Food & Drug Administration–approved, nonpharmacologic treatment for patients with medically refractory epilepsy. The first studies with VNS date to 1985. The surgery includes wrapping 2 electrodes around the left vagus nerve and implantation of a stimulator over the thoracic wall underneath the left clavicle and medial to the mid-axillary area.[1] The VNS device is then programmed to stimulate the left vagus nerve with specific parameters including duration (on-time), pulse width, output current, frequency, and poststimulation refractory period (off-time). Once the VNS is turned on, this programmed cycle of stimulation continues 24 hours per day. The VNS device can also be activated by either a caregiver swiping a magnet swipe across the stimulator or by the device sensing an increase in heart rate above the baseline presumably due to a seizure, which is known as autostimulation. The stimulation of afferent vagal nerve fibers by the VNS sends electrical impulses to the brain that help prevent seizures, most likely due to neuromodulation. However, the VNS device can also send anterograde signals to the recurrent laryngeal nerve, which can result in side effects such as voice alteration, hoarseness, sore throat, cough, dyspnea, nausea, vomiting, headaches, and paresthesias.[2] One of the lesser known side effects is VNS-associated sleep-disordered breathing (SDB), which has been shown to include both central and obstructive apneas and hypopneas.[3–6] In pediatric studies, > 40% of patients with medically refractory epilepsy had their seizure frequency reduced by at least 75% due to the VNS.[7]

The treatment of VNS-associated SDB can be a delicate balance between controlling SDB with positive airway pressure (PAP) and/or adjusting VNS settings while still optimizing the control of epilepsy. Discontinuation of VNS is often not considered when there is significant benefit in decreasing seizure frequency, but it may be considered if the epileptologist believes that seizure frequency did not decrease with the VNS or if the side effects outweigh the intended benefits. In a prospective consecutive study of 436 patients who were implanted with VNS, 7.3% of patients had their devices removed because of seizure worsening or nonefficacy, 7.1% had their devices removed because of MRI incompatibility, and 1.6% had their devices removed due to infection.[8]

There are multiple case reports of using PAP to overcome respiratory events attributed to VNS[5,9]; however, others have shown that PAP therapy was not efficacious.[10,11] Alternatively, titrating VNS settings can also reduce central and obstructive events. The changes to VNS settings that can potentially decrease associated SDB include decreasing stimulus frequency, decreasing output current, and increasing stimulus off-time.[3]

A challenge that sleep medicine providers face is determining to what extent SDB is caused by the VNS as opposed to the patient's baseline physiology. One method is to compare measures of SDB pre- and post-VNS changes or comparing measures with and without the VNS being inactivated.[10,12] A more direct means of determining SDB causation is to directly detect VNS discharges during a polysomnogram (PSG). Detection of VNS discharges during PSG has been previously described to variable extent,[9,13,14] but the method has not been directly described in a pediatric cohort. In some studies, the VNS can produce an artifact in the chin electromyogram (EMG) lead that can correlate with the VNS discharge time, but this artifact is not always seen and a more accurate way to assess the VNS discharge is needed.

In this study, we present a retrospective case series of 7 patients with medically refractory epilepsy who were managed with VNS. The purpose of the study was 2-fold: first, to determine whether a surface electrode placed over the implanted VNS electrode could distinguish whether SDB was time-locked with VNS discharges, and second, whether this surface electrode had greater utility in distinguishing VNS-associated SDB vs the standard chin EMG lead that may also detect VNS discharges.

METHODS

Our retrospective case series was approved by the Seattle Children's Hospital institutional review board, and records from July 1, 2019, to March 8, 2021 were reviewed. We identified patients for inclusion by flagging any patients scheduled for PSG who had a history of VNS placement. Patients had to be actively treated with their VNS to be included in the study. The medical record was reviewed for demographic information, medical history, antiepileptic medications, and VNS settings, along with prior diagnosis and/or treatment of obstructive sleep apnea (OSA). Analyzed VNS parameters included output current, frequency, pulse width, on-time, and off-time.

The PSG data (Sandman Elite Natus System, Middleton, WI) were recorded using the Sandman Elite Natus system. Parameters included a standard pediatric montage that included electroencephalograms (2 frontal, 2 central, and 2 occipital channels, referred to the contralateral mastoid), EMG (submental and anterior tibialis), electrooculograms (right and left), nasal pressure transducer, oronasal airflow (thermistor), effort signals for thorax and abdomen, oximetry, capnography, a single-lead electrocardiogram, and video and audio recording. Calibrations were performed per routine standard by technician. The Dymedix oronasal sensor (Dymedix Diagnostics, Shoreview, MN) was used if the patient did not tolerate a nasal cannula. All patients were studied on room air.

The studies were scored by sleep laboratory technicians and were reviewed and interpreted by a board-certified sleep physician (JC or JW). Scoring was per current American Academy of Sleep guidelines (*The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications,* Version 2.6).[15] Obstructive apneas were defined as a $\geq 90\%$ decrease in airflow from baseline with continued respiratory effort for a minimum of 2 breaths. Hypopneas were defined as a 30%–89% decrease in airflow from baseline with continued respiratory effort for a minimum of 2 breaths, associated with a $\geq 3\%$ desaturation, an electroencephalogram arousal, or both. Central apneas were defined as a $\geq 90\%$ decrease in airflow from baseline lasting at least the duration of 2 breaths with lack of respiratory effort, associated with a $\geq 3\%$ desaturation, an electroencephalogram arousal, or both. Central apnea can also be scored if there is a $\geq 90\%$ decrease in airflow from baseline and the duration of the event lasts more than 20 seconds. OSA severity was determined by the obstructive apnea-hypopnea index (oAHI). Mild OSA was defined by an oAHI > 1 but < 5 events/h. Moderate OSA was defined by an oAHI > 5 but < 10 events/h. Severe OSA was defined by an oAHI > 10 events/h.

VNS analysis

Two disposable deep-cup electrodes were used to detect VNS discharge (**Figure 1**). One electrode, designated VNS1, was placed on the left anterolateral neck directly over the VNS lead, which can be sometimes palpated. The second electrode, VNS2, was placed inferior to the VNS1 electrode, just above the left clavicle. If the implanted VNS lead could not be palpated, then the VNS1 electrode was placed midway up the neck dorsal to the carotid artery and the VNS2 electrode was placed directly inferior, just above the clavicle. The VNS1 electrode was then adjusted to find the cleanest signal that correlated with documented VNS settings. VNS1 was referenced to VNS2 with a low-frequency filter at 100 Hz and an additional notch filter at 60 Hz. A high-frequency filter was not used. These settings were then adjusted as needed to obtain an optimal signal. The VNS channel tracings were initially reviewed by sleep laboratory technicians followed by review by a board-certified sleep physician (JC or JW). The duration and frequency of VNS discharges found on PSG were also confirmed with the specific patient's VNS settings. For example, if the programmed VNS on-time was 30 seconds and the programmed off-time was 3 minutes, the VNS channel should show an increase in signal

Figure 1—VNS sensor placement.
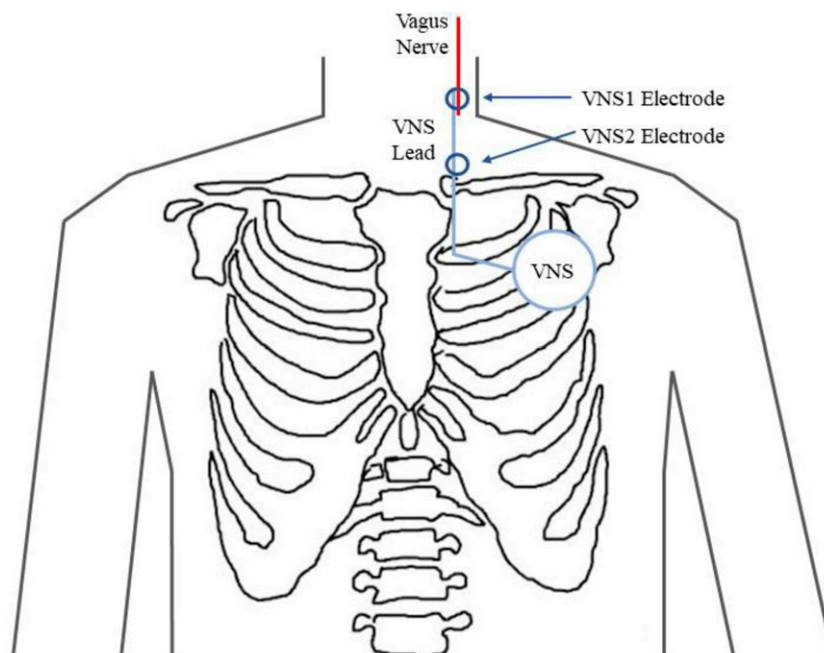
The VNS1 surface electrode (top circle) was placed on the left anterolateral neck, just over the approximate area of attachment of the VNS lead to the vagus nerve. The VNS2 electrode (bottom circle) was placed inferior to VNS1, just above the left clavicle. VNS = vagal nerve stimulator.

to full amplitude for only 30 seconds (plus any ramp-up or ramp-down time) and then should return to baseline for 3 minutes. This cycle should repeat for the entire study, with the exception of early discharges due to autostimulation mode or use of the magnet to voluntarily activate the VNS.

A VNS discharge was scored if the signal amplitude in the VNS channel was at least 2 times greater than baseline and lasted approximately the duration of the on-time (30 seconds for every patient in our study). Events were not scored if there was no clear onset and offset of the signal or if the VNS was activated by a caregiver's magnet swipe. Using these criteria, we calculated the minimum number of expected discharges that should be captured in the entire recording by dividing the total recording time of the PSG by the cycle length (on-time + off-time). We then calculated the percentage of discharges detected by our VNS electrode by dividing the total number of events scored by the expected number of discharges. Apneas and hypopneas were characterized as VNS-associated if the respiratory event occurred during the VNS discharge, regardless of when it started. Using these criteria, we calculated the VNS-associated AHI (vAHI).

Chin analysis

A senior technician (CR) scored the chin EMG lead to determine the frequency of VNS discharge events that could be detected by the chin EMG lead. The technician was blinded to the VNS electrode channel and scored events when the chin amplitude was at least 2 times greater than baseline and lasted approximately the duration of the on-time (30 seconds for every patient in our study). Events were not scored if there was no clear onset or offset of the signal. Chin lead findings were

also reviewed by a board-certified sleep physician (JC). We calculated the percentage of VNS stimulation events detected from the chin EMG lead by dividing the total number of events recorded from the chin EMG by the expected number of discharges. Apneas and hypopneas were characterized as chin-associated if the event occurred during the chin elevation regardless of when it started. Based on these criteria, we calculated the chin-associated AHI (chinAHI).

Statistical analysis

For statistical analysis, we used the SPSS statistical software (IBM SPSS Statistics, Armonk NY) to run Mann-Whitney 2-tailed U tests to determine whether there were differences between the percentage of VNS discharge detected by the chin EMG vs VNS electrode and to compare the vAHI to the chinAHI. The Spearman rank-order correlation was used for the remaining statistical analyses due to small sample size and the assumption of nonparametric variables. Although patient 5 had 2 sleep studies, only the first sleep study was included in the tables and statistical analyses because his second study was a split-titration study and did not include repeated-measure statistics.

RESULTS

Seven patients met the inclusion criteria during the study period. Three patients were referred for PSG for snoring, 2 for difficulties with sleep onset and sleep maintenance, 1 for progression of OSA, and 1 for concern for hypoventilation. Patient demographics are included in **Table 1**. All patients were male with a

mean age at study inclusion of 7.7 ± 2.2 years. Six of the 7 patients had a diagnosis of Lennox-Gastaut syndrome, and the final patient had a diagnosis of Dravet syndrome. All were on multiple antiepileptic medications and had a VNS, which was implanted at a mean age of 4.4 ± 1.8 years. VNS settings across patients can be seen in **Table 1**. VNS output current ranged from 1.25 mA to 2 mA, frequency ranged from 20 to 25 Hz, and pulse width for all patients was 250 msec. VNS on-time for all patients was 30 seconds, and off-time ranged from 30 to 180 seconds. Three patients (patients 2, 5, and 7) had a PSG before this study, with 2 patients (patients 5 and 7) having a prior diagnosis of OSA. One was presumed to have OSA given the presence of snoring and had been treated with adenotonsillectomy. The one patient 7 other patient had only mild OSA confirmed by PSG and was conservatively managed by watchful waiting.

Our PSG findings can be seen in **Table 2**. Six of the 7 patients met the criteria for OSA. The mean oAHI was 8.2 ± 8.3 events/h. Two patients had severe OSA, 2 patients had moderate OSA, 2 had mild OSA, and 1 did not have any significant OSA. No patients met the criteria for hypoventilation or central sleep apnea.

When using the VNS-dedicated electrode, we identified 3 patients (patients 1, 3, and 5) who exhibited an obstructive apneic pattern when the VNS discharged, as demonstrated in **Figure 2** and **Figure 3**. Two patients (patients 2 and 4) did not have an obstructive pattern but had an increase in respiratory rate without any change in gas exchange (**Figure 4**). Patient 6 exhibited both an obstructive pattern and an increase in respiratory rate. The mean vAHI was 4.8 ± 6.2 events/h. The vAHI accounted for 46.9 ± 30.2% of the events that were included in the total oAHI (range, 0%–78.9%).

To determine whether our VNS sensor was able to detect time-locked VNS-associated SDB better than the chin EMG lead, we compared data from the chin EMG to that of the VNS electrode. When we only used the chin EMG lead to detect VNS discharge, only 4 out of the 7 patients showed an increase in the chin tone that correlated with expected VNS discharge patterns. When using the VNS electrode, 7 out of 7 patients showed detectable VNS discharges. We were able to detect a significantly higher percentage of expected VNS discharges with the dedicated VNS electrode compared to the chin EMG (94.7 ± 6.5% vs 36.2 ± 35.8%; $P = .001$; **Table 2**). Notably, the duration of VNS discharges that we observed in the VNS electrode channel was slightly longer than the programmed on-time, 32.6 ± 0.2 seconds vs the programmed 30-second on-time, with a high precision of measurement demonstrated by our small standard deviation. **Figure 5** shows representative examples of the discharge pattern seen in the VNS electrode channel vs the chin EMG. This finding was in the setting of study methods defining the VNS signal as at least twice the baseline signal amplitude, which then includes ramp-up and ramp-down time. While there was no statistical difference between chinAHI vs vAHI in those with a usable chinAHI (1.9 ± 3.2 vs 4.8 ± 6.2; $P = .09$), there was a difference in the number of patients with a usable chin EMG signal vs a usable VNS electrode signal (4 out of 7 vs 7 out of 7).

Because we were able to determine the proportion of SDB likely attributable to VNS, we coordinated with the patients'

Table 1—VNS patient demographics and device settings.

Patient	Age (y)	Diagnosis	Antiepileptic Medications	Age at VNS Implantation (y)	BMI (kg/m²)	BMI (percentile)	VNS Output Current (mA)	VNS Frequency (Hz)	VNS Pulse Width (ms)	VNS On-Time (s)	VNS Off-Time (s)
1	8	LGS, DD, ataxic CP, obesity	BRV, CBD, CLB, LAC, OXC,	3	25.38	99	2	25	250	30	66
2	8	LGS, scoliosis, hypotonia	CBD, CLB, LTG, VPA	8	16.46	64	2	20	250	30	180
3	6	LGS	CZP, RUF,	4.5	16.6	75	1.875	20	250	30	66
4	5	Dravet syndrome	CLB, VPA, FFA	5	14.9	34	1.5	30	250	30	180
5	7	LGS, polymicrogyria, hypotonia, restrictive lung disease	CBD, GBP, LTG, VPA, ZNS	3	15.6	49	1.25	20	250	30	66
6	8	LGS, spastic CP, scoliosis	CBD, RUF	4	17	70	1.875	20	250	30	30
7	12	LGS, prematurity, ASD	BRV, CBD, CLB, GBP	3	23.3	92	1.5	20	250	30	180

ASD = autism spectrum disorder, BMI = body mass index, BRV = brivaracetam, CBD = cannabidiol, CLB = clobazam, CP = cerebral palsy, CZP = clonazepam, DD = developmental delay, FFA = fenfluramine, GBP = gabapentin, LAC = lacosamide, LGS = Lennox-Gastaut syndrome, LTG = lamotrigine, OXC = oxcarbazepine, RUF = rufinamide, VNS = vagus nerve stimulator, VPA = valproic acid, ZNS = zonisamide.

Table 2—VNS discharge detection comparing VNS electrode and chin EMG and correlation with SDB.

Patient	VNS Discharge Length (s)	Detected by VNS Electrode (%)	Detected by Chin Lead (%)	% Chin lead/% VNS Electrode	AHI (events/h)	cAHI (events/h)	oAHI (events/h)	vAHI (events/h)	chinAHI (events/h)	vAHI/ oAHI (%)
1	$32.3 \pm 4.5 \times 10^{-6}$	101.9	0	0.00	21.3	0	21.3	16.8	0	79
2	32.3 ± 0.8	99.8	0	0.00	4.5	0	4.5	1.6	0	36
3	$32.5 \pm 1.9 \times 10^{-5}$	84.3	58.6	0.70	2.6	0.7	1.9	1.3	0.7	50
4	$32.5 \pm 7.5 \times 10^{-6}$	89.2	42.9	0.48	5.0	0.7	4.3	0.7	0.7	14
5	$31.9 \pm 8.0 \times 10^{-6}$	93.7	70.9	0.76	19.0	2.4	16.6	9.5	8.8	50
6	32.7 ± 0.6	93.3	80.9	0.87	5.1	0.1	5	3.6	3.1	71
7	$34.0 \pm 2.4 \times 10^{-6}$	100.5	0	0.00	0.3	0.2	0.1	0	0	0
Average	32.6 ± 0.2	94.7	36.2	0.38*	8.3	0.6	7.7	4.8	1.9	42.9

*The overall percentage of VNS discharges detected by the VNS electrode was statistically higher than the percentage of discharges detected by the chin EMG lead ($P = .001$). The on-time for each patient was 30 seconds.
AHI = apnea-hypopnea index, cAHI = central AHI, chinAHI = chin-associated AHI, EMG = electromyogram, oAHI = obstructive AHI, SDB = sleep-disordered breathing, vAHI = VNS-associated AHI, VNS = vagal nerve stimulator.

Figure 2—A 5-minute example of VNS discharges (purple boxes) and chin EMG (green boxes) correlating with flow decrement and hypopneas (blue box with pink edges) and apneas (dark red boxes with pink edges) with desaturations (pink box with blue edges and pink box with red edges).
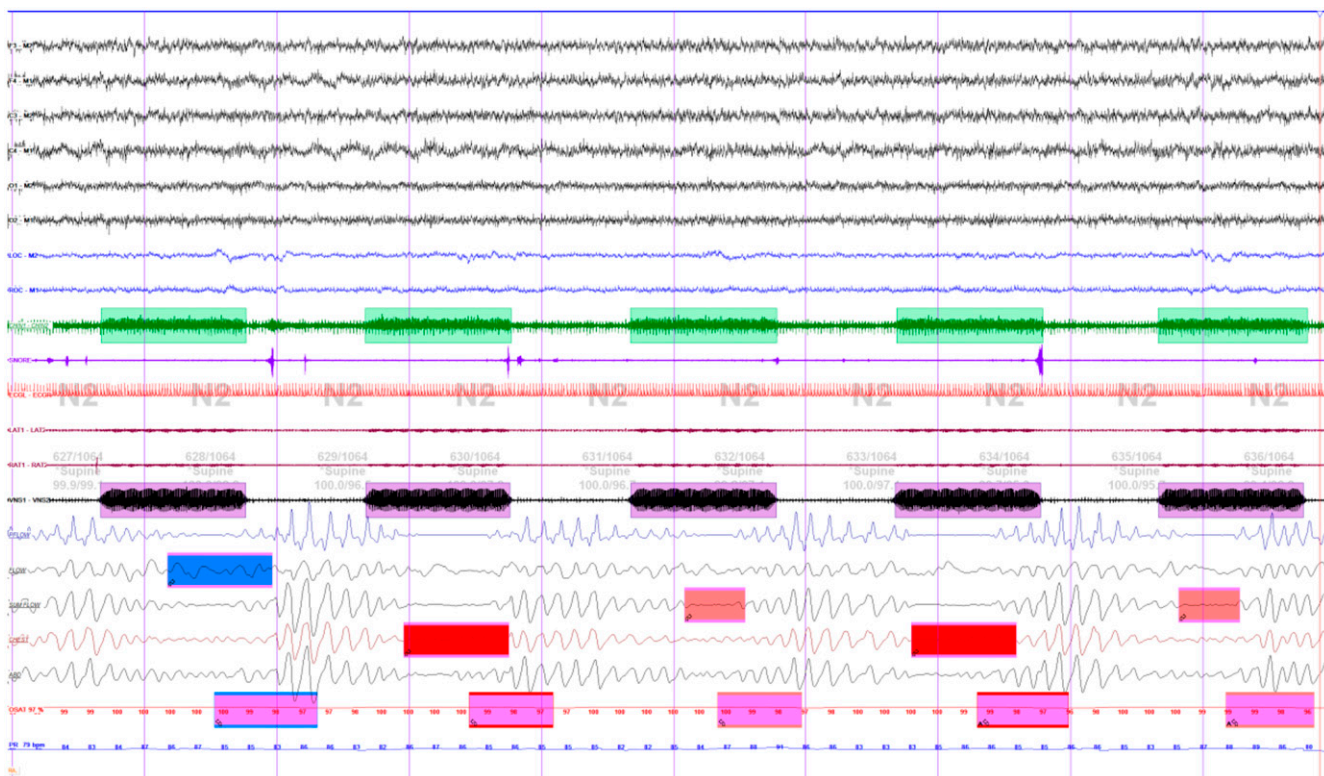
This example is from patient 6, who had an output current of 1.875 mA, frequency of 20 Hz, pulse width of 250 msec, on-time of 30 seconds, and off-time of 30 seconds. EMG = electromyogram, VNS = vagal nerve stimulator.

Figure 3—A 10-minute example of VNS discharges (purple box) and chin EMG (green boxes) correlating with flow decrement and hypopnea (blue box with pink edges) and desaturation (pink box with blue edge).
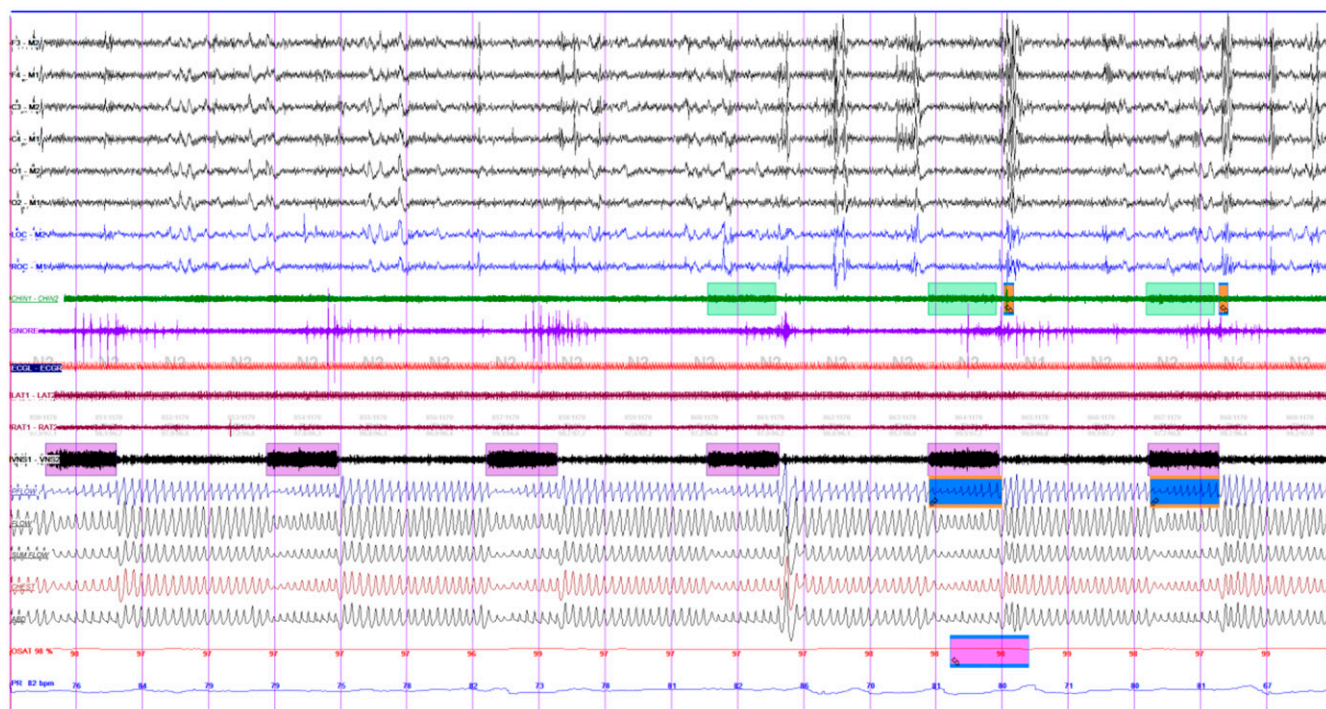
Note the lack of signal change in chin EMG for the first 3 discharges. This example is from patient 3, who had an output current of 1.875 mA, frequency of 20 Hz, pulse width of 250 msec, on-time of 30 seconds, and off-time of 66 seconds. EMG = electromyogram, VNS = vagal nerve stimulator.

epileptologists to titrate the VNS settings for the 4 patients who experienced an obstructive pattern during VNS discharge. Patient 1 (initial vAHI: 16.8 events/h) had the VNS off-time increased from 66 seconds to 180 seconds. Unfortunately, soon after these changes were made, the patient's apneic seizures worsened and we reverted the VNS settings to the prior settings. Patient 3 (initial vAHI, 1.3 events/h) had the VNS turned off without any changes in seizure frequency. Patient 5's output current was decreased from 1.25 mA to 1 mA, and the frequency was decreased from 20 Hz to 10 Hz. Subsequent split-night PSG showed resolution of VNS-associated SDB with a baseline AHI of 4.3 events/h and a vAHI of 0 events/h. Patient 6 had the VNS frequency decreased from 20 Hz to 10 Hz, with the outcome still yet to be determined.

There was no correlation with VNS output current and total AHI (r_s = 0.11013; P = .81), but there was a weak positive correlation with VNS output current and arousal index (r_s = 0.20191; P = .66) and a moderate positive correlation with VNS output current and vAHI (r_s = 0.3637; P = .42) and VNS output current and saturation nadir (r_s = 0.45889; P = .30). None of these correlations reached statistical significance.

DISCUSSION

Our study showed that adding an extra electrode over the VNS lead can be helpful in determining the extent to which SDB is

associated with VNS discharges in pediatric patients. With this electrode, we were able to detect on average $94.7 \pm 6.5\%$ of the expected VNS discharges compared to only $36.1 \pm 35.8\%$ when exclusively using the chin lead. Interestingly, 2 patients had more discharges detected by the VNS electrode than the minimum expected discharges. This finding was likely due to the autostimulation function of the VNS, which discharges when the VNS detects that the patient's heart rate has increased by some relative amount to the baseline. Consequently, the VNS discharges earlier than expected. In these patients, we observed that the expected cycle length resumed after each early discharge. We also demonstrated that the measured duration of the VNS discharge as detected by the VNS-dedicated sensor was very precise and was, on average, approximately 2 to 3 seconds longer than the programmed on-time. This result was most likely due to our scoring method, which started the VNS discharge when the signal amplitude was twice the background and thus included the ramp-up and ramp-down discharge tails observed at the beginning and end of VNS discharge. If measured only when the signal reached maximal amplitude, the discharge length would be closer to the programmed 30-second on-time.

In this case series, 6 of the 7 patients had changes in their respiratory pattern when their VNS discharged. Three patients (patients 1, 3, and 5) displayed an obstructive pattern of sleep apnea; 2 patients (patients 2 and 4) experienced an increase in their respiratory rate without any change in gas exchange. Patient 6 displayed both OSA and increased respiratory rate,

Figure 4—A 10-minute example of VNS discharges (purple box) and chin EMG (green box) correlating with increase in respiratory rate without hypopnea.
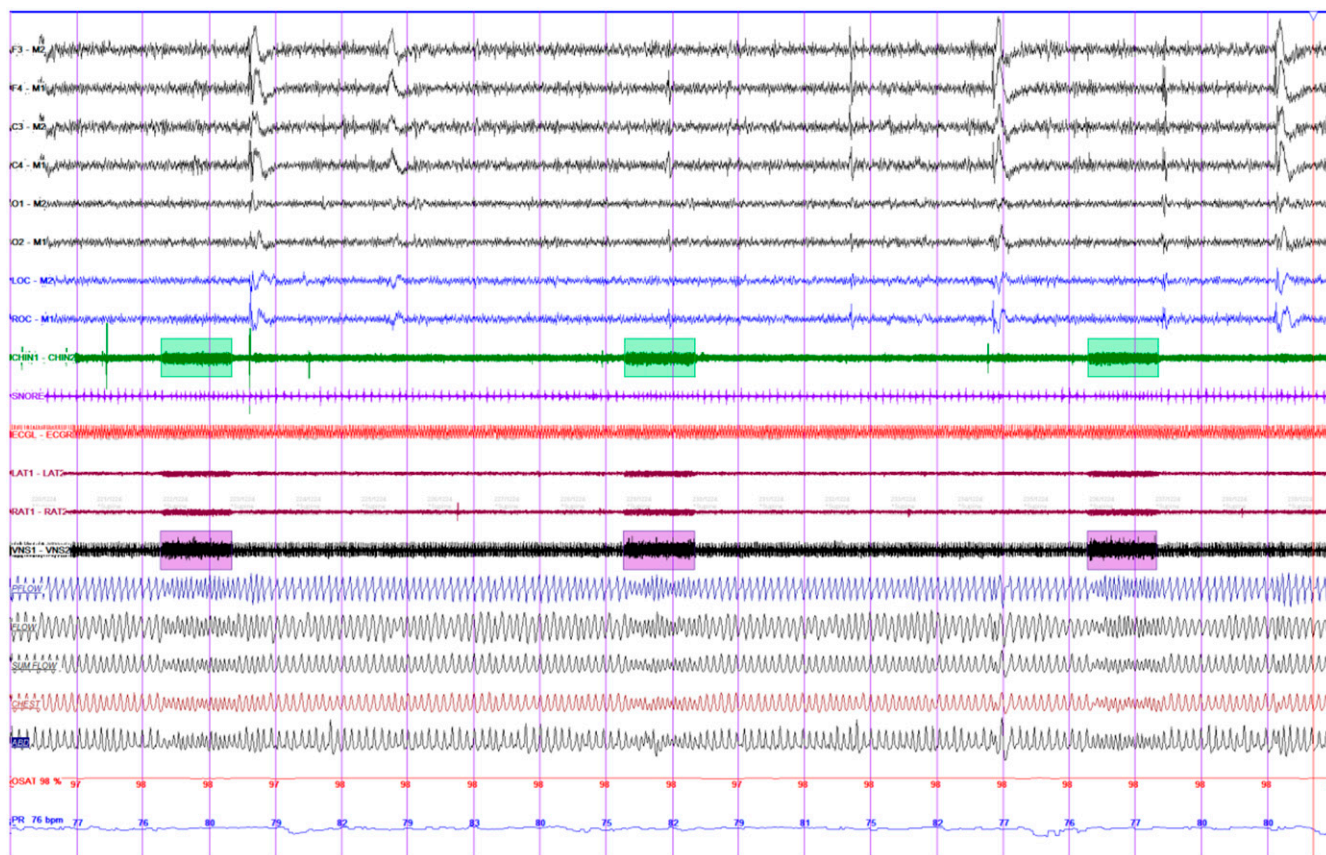
This example is from patient 4, who had an output current of 1.5 mA, frequency of 30 Hz, pulse width of 250 msec, on-time of 30 seconds, and off-time of 180 seconds. EMG = electromyogram, VNS = vagal nerve stimulator.

while patient 7 experienced no changes in respiratory parameters during VNS discharge. With this information, we were then able to coordinate with the patients' epileptologists to make changes to their VNS settings in hopes of decreasing their SDB. If we had only relied on the chin EMG to detect the VNS discharge, then we would have missed a significant cause of SDB in patient 1 because only the VNS electrode was able to capture the VNS discharge. Although chinAHI and vAHI were not significantly different, there was a trend toward significance even with the small sample size. Interestingly, there was a positive moderate correlation between output current and vAHI and saturation nadir that did not meet statistical significance, likely because of the small sample size.

Based on our results, we believe that identification of the proportion of OSA associated with VNS discharges can help dictate different treatment courses. When the majority of OSA is caused by VNS discharges, and if the patient can tolerate it, changing the patient's VNS settings rather than treating with PAP may be the preferred SDB treatment. In our study, we were able to change VNS settings in 4 of our patients with at least 1 of our patients showing full resolution of VNS-associated SDB. The cause of SDB may partially explain why some studies have shown that PAP therapy fails to effectively treat VNS-associated SDB.[10,11] One theory for why VNS-associated SDB is sometimes refractory to PAP therapy is that VNS discharge can cause a fixed airway obstruction due to unilateral or even bilateral vocal cord adduction.[16] In the setting of fixed obstruction caused by VNS discharge, it is unlikely that PAP alone would be able to alleviate the flow limitation and may thus require changing VNS settings to reduce the amount of VNS-associated SDB, or potentially a combination of PAP therapy and VNS setting titration.

Despite not having significant associated flow limitation, 3 of our patients experienced increased respiratory rates with VNS discharge, which has been previously reported.[17,18] VNS discharges in these patients did not cause any abnormalities in gas exchange, but Holmes et al[17] showed that intermittent hypocapnia can be caused by VNS discharge due to the increase in respiratory rate. If the hypocapnia is severe enough, then CO_2 levels can drop below the apneic threshold and cause a posthyperventilation central apnea, which was shown in a 13-year-old female with refractory epilepsy.[19] Furthermore, if the VNS off-time is also short enough, then the resulting posthyperventilation central apnea could be confused for a periodic breathing pattern with a cycle length as short as 60 seconds. If the VNS is not suspected to be the culprit, then further diagnostic studies and/or treatments could be performed.

Figure 5—Two examples of the signal change seen on the dedicated VNS electrode (VNS1-VNS2, purple box) and chin EMG lead (CHIN1-CHIN2, green box) when VNS was discharging in patient 6.
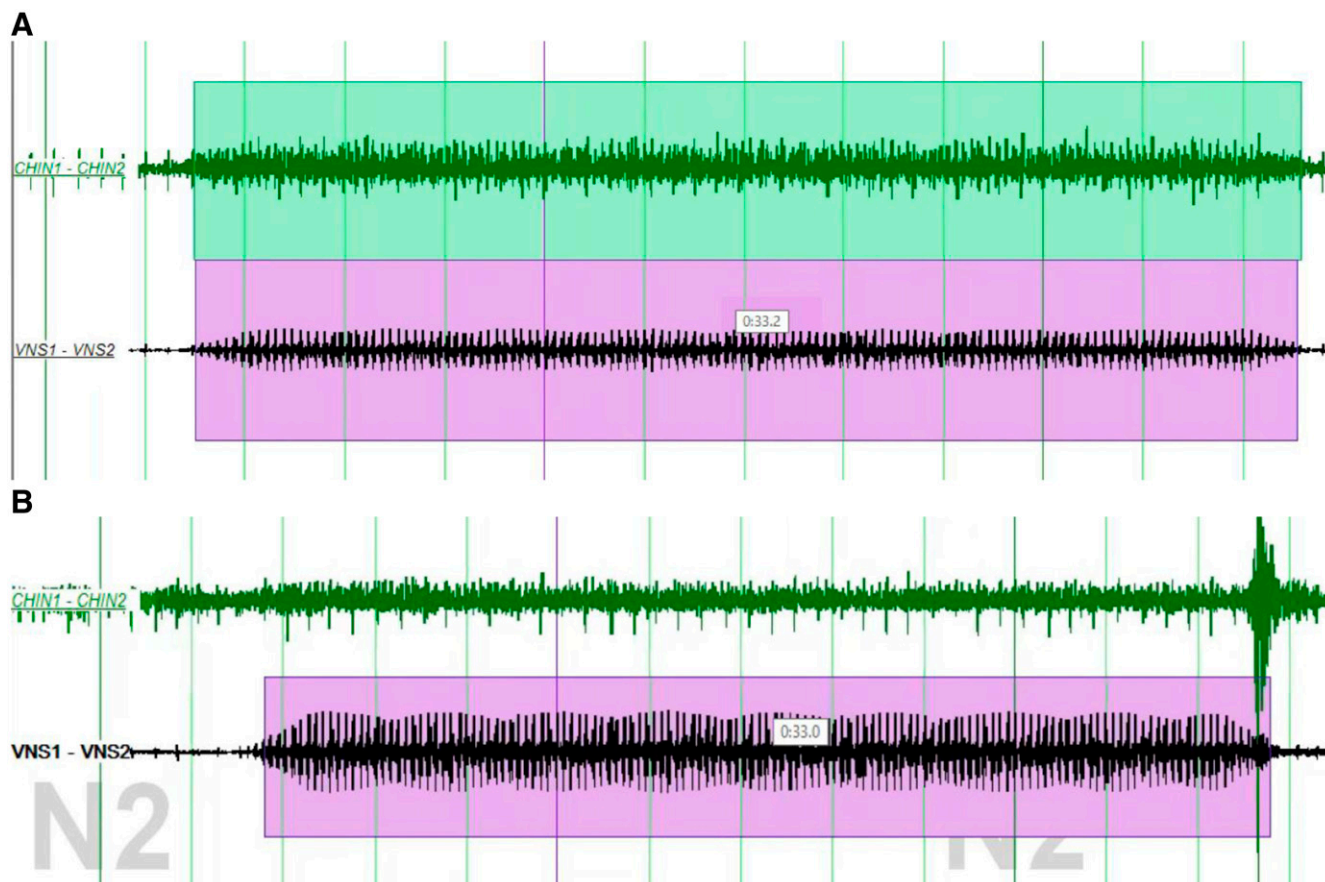
The first example **(A)** shows that the VNS signal lasted for 33.2 seconds when including time to ramp up to full signal and ramp back down, while the programmed on-time for this patient was 30 seconds with a concomitant increase in the chin lead. The second example **(B)** shows an increase in the VNS signal that lasted for 33.0 seconds without a change in the EMG lead. EMG = electromyogram, VNS = vagal nerve stimulator.

The limitations of our study include the small cohort size and the associated inability to exhaustively evaluate the full spectrum of potential VNS-associated changes that could be captured during PSG. Future studies with larger cohort sizes should be conducted because they can capture a wider variety of SDB events and may also more accurately assess the percentage of patients with VNS devices who experience changes in breathing patterns attributable to VNS discharge. It could also be helpful to evaluate whether or how SDB events may correlate with specific VNS settings. In addition, due to the retrospective nature of our study, we do not have long-term follow-up data for our patients. Ideally, future studies would follow patients long-term to assess any persistent change in seizure frequency or oAHI following VNS setting changes.

CONCLUSIONS

As the number of patients receiving VNS as a treatment for medically refractory epilepsy continues to increase, it is becoming more important to recognize and address the physiologic changes that can occur as a result of VNS stimulation. The ability to time-lock VNS discharges with changes in respiratory flow trace and respiratory rate, as demonstrated in our study, is critically important for nuanced PSG interpretation and appropriately informed treatment for VNS-associated sleep disruption. An extra sensor on the lateral left neck placed superficially over the VNS lead can aid in this endeavor. In our institution, we found that a low-frequency filter of 100 Hz and a notch filter of 60 Hz generally gave us the best signal. We suggest that the use of an external VNS electrode should be standard practice collection and scoring technique when performing PSG on patients with a VNS.

ABBREVIATIONS

AHI, apnea-hypopnea index
chinAHI, chin apnea-hypopnea index
EMG, electromyogram
oAHI, obstructive apnea-hypopnea index
OSA, obstructive sleep apnea

PAP, positive airway pressure
PSG, polysomnogram
SDB, sleep-disordered breathing
VNS, vagal nerve stimulator
vAHI, VNS-associated apnea-hypopnea index

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors report no conflicts of interest.