Case Report

The therapeutic dilemma of vagus nerve stimulator-induced sleep disordered breathing

Hinesh Upadhyay[1], Sushanth Bhat[1], Divya Gupta[1], Martha Mulvey[2], Sue Ming[1,2]

[1]Sleep Disorder Center, Neuroscience Institute, JFK Medical Center, Edison, [2]Department of Neurosciences and Neurology, Rutgers University - New Jersey Medical School, Newark, New Jersey, USA

Address for correspondence:
Dr. Hinesh Upadhyay, JFK Medical Center, 65 James Street, Edison, New Jersey, USA.
E-mail: drhinesh@gmail.com

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Abstract:

Intermittent vagus nerve stimulation (VNS) can reduce the frequency of seizures in patients with refractory epilepsy, but can affect respiration in sleep. Untreated obstructive sleep apnea (OSA) can worsen seizure frequency. Unfortunately, OSA and VNS-induced sleep disordered breathing (SDB) may occur in the same patient, leading to a therapeutic dilemma. We report a pediatric patient in whom OSA improved after tonsillectomy, but coexistent VNS-induced SDB persisted. With decrease in VNS output current, patient's SDB improved, but seizure activity exacerbated, which required a return to the original settings. Continuous positive airway pressure titration was attempted, which showed only a partial improvement in apnea–hypopnea index. This case illustrates the need for clinicians to balance seizure control and SDB in patients with VNS.

Key words:

Epilepsy, obstructive sleep apnea, seizure, vagus nerve stimulator

Vagus nerve stimulation (VNS) is a effective adjuvant therapy for refractory epilepsy and reduces the frequency of multiple seizure types.[1,2] However, there are several reports in the literature of VNS implantation causing disturbances of breathing in sleep.[3-9] We present a clinically challenging case of a 14-year-old female with VNS-induced sleep disordered breathing (SDB) in whom adjustment of VNS parameters (decreasing VNS output current) was effective in reducing the apnea–hypopnea index (AHI), but worsened seizure frequency. There was only partial improvement of VNS-induced SDB with continuous positive airway pressure (CPAP). Therapeutic options in VNS-induced SDB are briefly discussed.

Case Report

A 14-year-old female with a history of perinatal left middle cerebral artery stroke and intractable seizures since infancy requiring VNS implantation at the age of 8 years presented to the outpatient sleep clinic with an 8-month history of snoring, choking in sleep, and witnessed apneas. On examination, the patient was alert and oriented, overweight (body mass index 37 kg/m^2), and had a neck circumference of 15 inches. She had normal nasal turbinates with a nondeviated nasal septum, bilateral grade 3+ tonsils without inflammation, and a crowded oropharynx (Mallampati grade 3). Neurological examination revealed right upper and lower extremity weakness with spasticity and hyperreflexia, as well as right-sided dysmetria and dysdiadochokinesia. For symptoms suspicious for obstructive sleep apnea (OSA), she underwent an initial standard digital polysomnogram (PSG), including channels for electrooculography, chin and limb electromyography, flow channels (oral thermocouple and nasal pressure transducer), piezoelectric effort belts (thoracic and abdominal), and a SaO_2 channel. An extended electroencephalography montage (in bipolar and referential arrangements according to the international 10–20 system) was used, and VNS stimulations were recorded with an additional VNS channel (active electrode placed over the lead in the left neck and a reference electrode placed a short distance away). Her VNS settings were output current 2.25 mA, frequency 30 Hz, pulse width 250 μs, on-time 30 s, and off-time 3 min. The PSG was staged and scored according to the standard 2012 American Academy of Sleep Medicine guidelines for scoring respiratory

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events. Since her body habitus resembled that of an adult, adult scoring criteria were used.[9] An AHI of <5/h was considered normal, 5–15/h mildly elevated, 15–30/h moderately elevated, and >30/h severely elevated. Her initial PSG showed moderate OSA, with an AHI of 19/h and SaO_2 nadir of 90%, mainly due to obstructive-type apnea/hypopnea events predominantly clustering in supine sleep. In addition, there were airflow limitation events correlating with VNS stimulations, as noted by the signal in the VNS channel [Figure 1], accompanied by a mild tachypnea. Some, but not all of these VNS-induced events were associated with SaO_2 desaturations of 3%. However, the majority of her respiratory events were not associated with VNS stimulations. Due to the above findings, she underwent a tonsillectomy/adenoidectomy and also lost weight (around 9 kg over the next year). A repeat diagnostic PSG was performed 1 year after surgery to confirm the resolution of symptoms. It showed interval improvement of OSA to the mild range (AHI 12/h). However, now the vast majority of her obstructive respiratory events occurred in a periodic pattern synchronized with VNS stimulations in onset and duration, suggestive of VNS-induced SDB. Most of these events were now accompanied by 3% SaO_2 desaturations. These VNS-induced respiratory events occurred in both non-rapid eye movement and rapid eye movement (REM) sleep. In REM sleep, most of these VNS-induced events caused arousals and body movements at their termination. These VNS-induced events also occurred in wakefulness, although with a much lower degree of airflow reduction and without SaO_2 desaturations. To study the effects of the adjustment of VNS parameters on her SDB, the patient underwent another PSG, during which the VNS output current was serially decreased (from the baseline of 2.25 mA to 1.75 mA and then to 1.25 mA). The degree of flow limitation events improved with each reduction in output current, and at setting lower than 2.25 mA, the VNS-induced events were no longer accompanied by arousals or SaO_2 desaturations [Figure 2]. Eventually, VNS was switched off and all respiratory events resolved. To prevent breakthrough seizures, VNS was switched back on, but at a lower VNS output current setting (1.75 mA) since neither arousals nor SaO_2 desaturations occurred at that setting. However, this had to be increased back to 2.25 mA at a subsequent outpatient clinic visit because of breakthrough seizures. The patient presented to the sleep laboratory again 4 months later with worsening of excessive daytime sleepiness. Since VNS adjustment was not considered viable due to the risk of breakthrough seizures, CPAP titration was attempted. During the CPAP titration study, there was re-demonstration of persistent airflow limitation coinciding with VNS stimulation, causing SaO_2 desaturations and arousals in supine sleep that could not be eliminated by increasing CPAP pressures [Figure 3]. The residual AHI at the highest pressure of 8 cm H_2O, thus remained mildly elevated (5.3/h). The patient was given a trial of CPAP of 8 cm H_2O home, but compliance remains poor due to inability to tolerate CPAP pressure.

Discussion

Our case illustrates the complex decisions that are involved in the management of patients with an implanted VNS, who have concomitant OSA. While VNS is clearly beneficial in the treatment of pharmacoresistant epilepsy, it has the potential to worsen SDB, leading to a therapeutic dilemma. Adjustment of VNS settings often improves VNS-induced SDB, but may lead to breakthrough seizures, and CPAP treatment has not been uniformly shown to be beneficial in treating VNS-induced SDB. VNS was described as an effective means to control refractory epilepsy as early as in 1990,[10] and the US Food and Drug Administration approved these devices for that indication in 1997. VNS devices are also currently approved for the treatment of refractory depression, and their efficacy in a number of other medical, psychiatric, and neurological disorders is currently under review.[11] The VNS generator is subcutaneously implanted into the anterior chest wall and has a lead in contact with the left vagus nerve. Stimulation occurs at set intervals, with several adjustable parameters, such as stimulation on-time and off-time (duty cycle), output current, frequency, and pulse width. The means by which VNS exerts its beneficial effect remain unclear; it is thought that reduction in seizure frequency

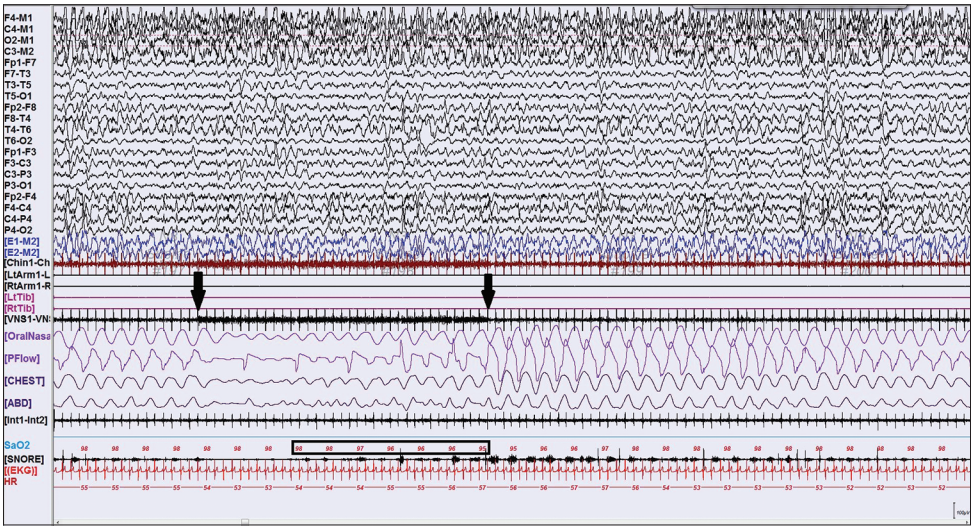

Figure 1: A 120 s epoch of polysomnography tracing in N3 showing the occurrence of vagus nerve stimulation-induced flow limitation corresponding to vagus nerve stimulation (artifact in the vagus nerve stimulation channel [vagus nerve stimulation 1]; between the arrows). At the patient's original vagus nerve stimulation settings (output current 2.25 mA), some of these flow limitations were accompanied by SaO_2 desaturations of 3% (SaO_2 falls from 98% to 95%; box)

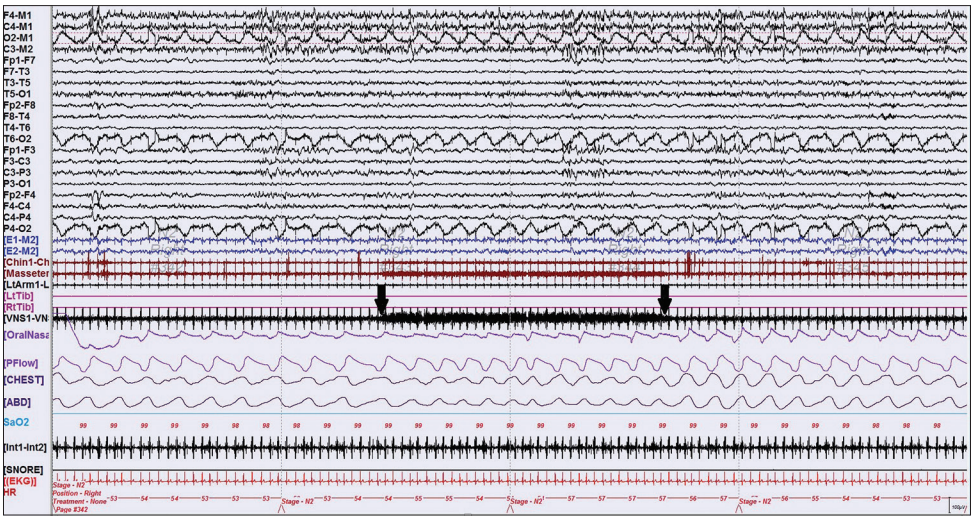

Figure 2: A 120 s epoch of polysomnography tracing in N2 sleep. Note that at a reduced vagus nerve stimulation output current of 1.25 mA, the degree of vagus nerve stimulation-induced airflow limitation was much improved, and no SaO_2 desaturations or arousals occurred with any of these events

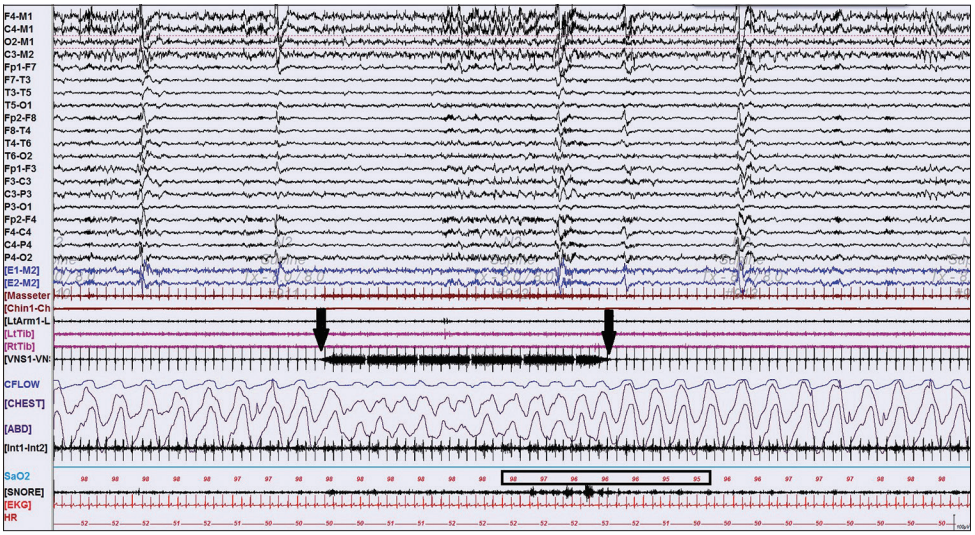

Figure 3: A 120 s epoch of N2 sleep from our patient's continuous positive airway pressure titration study. At the highest tested pressure of 8 cm H_2O, vagus nerve stimulation-induced flow limitation events continue to occur, accompanied in supine by SaO_2 desaturations of 3% (in this example, SaO_2 falls from 98% to 95%; box), suggesting only partial response of vagus nerve stimulation-induced sleep disordered breathing to continuous positive airway pressure

is due to the relay of vagal afferents to the thalamus causing desynchronization of cortical rhythms. The most common adverse effects of VNS therapy are dyspnea, coughing, and hoarseness of voice.[12] There have been several case reports of VNS adversely affecting breathing. VNS stimulations have been shown to change respiratory patterns during both wakefulness and sleep; the most commonly described changes included increased respiratory rate, decreased respiratory amplitude, and slightly decreased oxygen saturation during sleep,[3,4] similar to what we observed in our patient. VNS-induced SDB has been described to be severe enough as to cause OSA in both children and adults.[5,6] Previous studies have shown that the respiratory events associated with VNS are mostly obstructive, but rarely can be central in nature.[8] The possible underlying mechanism for the obstructive respiratory event is related to laryngeal motility alteration with upper airway narrowing due to the stimulation of upper airway muscles supplied by the vagus nerve.[13] Treatment for VNS-induced SDB is yet to be standardized, but the two main current therapeutic options are discontinuing the VNS device or changing the VNS parameters, on the one hand, or CPAP therapy, on the other hand. Several different VNS operational parameters, such as stimulation frequency and on- and off-times (duty cycle), have been noted to affect the severity of airflow obstruction and can be adjusted in patients with VNS-induced SDB. Furthermore, changing the output current with duty cycle can be an effective approach[14] and it has been recommended by the manufacturer.[8,15] In our patient, decreasing VNS output current improved the sleep disruption and SaO_2 desaturations associated with VNS-induced SDB, as well as improved the degree of flow limitation. Other options include deactivating the VNS only during sleep in refractory cases, although it is unclear what effect this might have on seizure control.[16] In our patient, VNS-induced SaO_2 desaturations tended to occur most often in supine sleep; positional therapy could be used as an adjunct in such cases. There have been contradictory

reports in the literature about whether CPAP is effective in treating VNS-induced SDB;[7,17] our patient did not have complete resolution of VNS-induced SaO_2 desaturations with CPAP titration. Ultimately, the question may come down to whether VNS-induced SDB is severe enough to even warrant intervention. This is often an individualized decision. Our patient experienced excessive daytime sleepiness as a consequence of VNS-induced SDB severe enough to necessitate repeat PSG and a trial of CPAP titration, but many patients with VNS-induced SDB are asymptomatic. It is well-known that in addition to improving cardiovascular status and daytime sleepiness, treatment of OSA improves seizure frequency in patients with epilepsy, presumably by decreasing sleep fragmentation and improving oxygenation.[18] However, it is unclear what long-term consequences VNS-induced SDB causes either to overall health or to seizure control, especially when the VNS-induced events merely cause flow limitation or are accompanied by only mild SaO_2 desaturations or intermittent arousals, as in our patient. Nevertheless, given the high prevalence of OSA in the epilepsy population,[19] screening VNS candidates for OSA seems reasonable. Preimplantation OSA should be treated aggressively, and patients with sleep complaints after VNS implantation (daytime sleepiness, insomnia, frequent arousals, choking/gasping in sleep, and witnessed apneas) should undergo PSG evaluation, preferably with a VNS lead.

Conclusion

For VNS-induced SDB, management decisions should be made with the overall clinical picture in mind, including weighing the patient's complaints, the severity of the impact on breathing in sleep, and theoretical (and as yet unproven) possibility of worsening of seizure frequency due to sleep fragmentation against the consequences of decreasing the strength of VNS stimulation or turning it off, i.e., established risk of worsening seizure frequency. As discussed, CPAP titration may represent a means to treat VNS-induced SDB without forgoing the benefit of VNS, but it is not uniformly effective in this regard. While both sleep specialists and epileptologists need to be aware of the potential impact of VNS on breathing in sleep, we await larger studies to determine the long-term impact and best treatment strategies for VNS-induced SDB.

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Conflicts of interest

There are no conflicts of interest.

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