Increasing off-time improves sleep-disordered breathing induced by vagal nerve stimulation

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ABSTRACT – Vagal nerve stimulation (VNS) has been reported to adversely impact breathing in sleep. While continuous positive airway pressure is often employed to treat these patients, little data exist on the effects of adjusting various settings on VNS-induced sleep-disordered breathing. We describe a patient in whom increasing off-time caused resolution of VNS-induced arterial oxygen desaturations in sleep, which we believe is a novel observation.

Key words: sleep apnea, vagal nerve stimulation, epilepsy, polysomnography, nocturnal desaturation, VNS-induced OSA, VNS off-time

Vagal nerve stimulation (VNS) has been widely reported to adversely affect breathing in sleep. However, there have not been many studies investigating the effects of modifying various device settings on such VNS-induced sleep-disordered breathing (SDB). We describe a patient in whom increasing off-time caused resolution of VNS-induced arterial oxygen (SaO₂) desaturations, resulting in improvement of the VNS-induced apnoea-hypopnoea index (AHI).

Case Study

A 22-year-old autistic man suffering from epilepsy since childhood underwent VNS implantation for refractory seizures. VNS significantly reduced his seizure frequency and improved daytime alertness and interaction with family. Video electroencephalography (EEG) monitoring showed rare left temporal sharp waves; brain magnetic resonance imaging was normal. He tolerated increases in VNS intensity and decreases in off-time well. However, he gained weight and started snoring, and was therefore sent to the sleep laboratory to rule out obstructive sleep apnoea (OSA).

After a night of sleep deprivation, the patient underwent daytime polysomnography (PSG) at our institution. A standard digital PSG was performed, including channels for...
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electrooculography (EOG), chin and limb electromyography (EMG), flow channels (oral thermocouple and nasal pressure transducer), and piezoelectric effort belts (thoracic and abdominal). In addition, we employed an extended EEG montage (in bipolar and referential arrangements according to the international 10-20 system) and included a VNS channel by placing an active electrode over the lead in the left neck and a reference electrode a short distance away to capture VNS stimulations. We used the 2007 American Academy of Sleep Medicine (AASM) guidelines for scoring respiratory events; apnoeas were defined as events lasting at least 10 seconds and accompanied by a 90% or greater reduction in airflow (if respiratory effort persisted, the event was described as an obstructive apnoea, and if effort was absent the event was described as a central apnoea). A hypopnoea was defined as a reduction in airflow of at least 50% lasting at least 10 seconds and accompanied by an SaO₂ desaturation of at least 3% or an arousal (Iber et al., 2007). When an event met amplitude criteria for a hypopnoea but was not accompanied by a significant SaO₂ desaturation or an arousal, we scored a flow limitation. AHIs of less than 5/hr were considered normal, 5-15/hr mildly elevated, 15-30/hr moderately elevated, and greater than 30/hr severely elevated.

His baseline VNS settings were: an intensity of 2 mAmps, frequency of 30 Hz, pulse width of 500 microseconds, on-time of 30 seconds and off-time of 3 minutes. No epileptiform activity was recorded on the EEG channels. At baseline settings, the patient had cyclical hypopnoeas consisting of episodes of decreased airflow (with fairly uniform signal amplitude drops of 66% from baseline) and SaO₂ desaturations of 3 to 5%, occurring with every event. These hypopnoeas directly corresponded to VNS stimulation and persisted for the duration of the stimulation, as noted on the VNS channel (figure 1). As per AASM guidelines, an SaO₂ desaturation was only scored if there was a drop of at least 3%. These events resulted in an SaO₂ nadir of 92%. During these events, a mild tachypnoea was noted. There was also a reduction in amplitude of the effort belts, suggesting that these events were possibly central hypopnoeas, although oesophageal manometry was not performed to confirm this. These events did not cause arousals or sleep fragmentation. There were no recorded apnoeas. His baseline apnoea-hypopnoea index (AHI) was 17/hr, in the moderate range.

Figure 1. A 120-second epoch of PSG tracing showing an example of VNS-induced SDB. The patient was in stage N2 sleep. Respiratory events corresponded to VNS stimulation (as noted by artefact in the VNS channel; between the arrows). At the patient’s original VNS settings (intensity: 2 mAmps; frequency: 30 Hz; pulse width: 500 microseconds; on-time: 30 seconds; off-time: 3 minutes), the flow limitations were accompanied by SaO₂ desaturations of up to 5% (in this example, SaO₂ falls from 97% to 93%; box). Also noted was a mild tachypnoea during the event. The first 20 channels correspond to extended EEG channels in referential and bipolar montage (international 10-20 electrode nomenclature), followed by: left and right EOG (E1-M2, E2-M1); Masseter EMG (Masseter1-Masseter2); chin EMG (Chin 1-Chin 2); EMGs of right biceps brachii, left and right Tibialis anterior (Rt Arm1-Rt Arm2, Lt Tib; Rt Tib); VNS channel (VNS1-VNS2); respiratory air flow (OroNasal and PFlow) and effort (Chest and Abd); EKG (electrocardiogram); and HR (heart rate). Also included were arterial pulse oximetry (SaO₂) and snore channels.
VNS settings were then adjusted in real time during PSG recording. Decreasing the frequency to 25 Hz resulted in VNS-induced respiratory events with airflow signal amplitude drops of 84%; SaO$_2$ desaturations occurred with 85% of events. Further reduction of the frequency to 20 Hz resulted in VNS-induced airflow amplitude drops of 78%; SaO$_2$ desaturations occurred with 69% of events. Thus, decreasing the frequency improved the AHI by decreasing the number of events with which there was SaO$_2$ desaturation, but hypopnoeas persisted. We then increased the off-time to five minutes, which completely eliminated the SaO$_2$ desaturations (there were falls in SaO$_2$ values of less than 3%, which do not meet AASM criteria for desaturation events), although VNS-induced cyclical flow limitations continued with 74% drops in amplitude. None of these events, however, met standard criteria for hypopnoeas (figure 2). Maintaining these settings and subsequently decreasing intensity, first to 1.75 mAmps and then to 1.5 mAmps, did not significantly ameliorate the flow limitations, but again, SaO$_2$ desaturations, and therefore hypopnoeas, did not occur. Also, of note, the events did not appear to be influenced by sleep stage or body position, although we were unable to capture all stages and positions at every setting (see table 1). Finally, we restored all original settings except off-time, which remained at five minutes. At these settings, he continued to have VNS-induced flow limitations (drops of 84% from baseline) but only 27% of these events had associated SaO$_2$ desaturations. Therefore, his final AHI on these settings was now normal at 2.7/hr. Thus, changing VNS off-time from three to five minutes improved AHI from the moderately elevated range to the normal range.

Table 1 lists the changes in the nature of the respiratory events as VNS settings were altered.

**Discussion**

VNS is a Food and Drug Administration (FDA)-approved treatment modality for pharmacoresistant epilepsy. It has also recently been approved for treatment-resistant depression (Groves and Brown, 2005). The VNS device consists of a generator that is subcutaneously implanted into the anterior chest wall with a lead that wraps around, and intermittently stimulates the left vagus nerve. The mechanisms underlying VNS efficacy in seizure reduction are unclear, but may be related to modulation of vagal afferents to the nucleus tractus solitarius and thence to the thalamus, causing desynchronisation of cortical rhythms. Studies have suggested that as many as 65% of patients experience at least a 50% reduction in seizure frequency, with efficacy gradually improving.
Table 1. Effect of adjusting varying parameters on VNS-induced respiratory events.

<table>
<thead>
<tr>
<th>VNS settings</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
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<tbody>
<tr>
<td>intensity (mAmps)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1.75</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>frequency (Hz)</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>30</td>
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<tr>
<td>pulse width (microsecs)</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
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<tr>
<td>on time (secs)</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
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<tr>
<td>off time (mins)</td>
<td>3</td>
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<td>3</td>
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<tr>
<td>Decrease in airflow signal amplitude (from baseline) with VNS activation (%)</td>
<td>66</td>
<td>84</td>
<td>78</td>
<td>74</td>
<td>78</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>Number of hypopnoeas (events associated with greater than or equal to 3% O₂ desaturations)</td>
<td>12</td>
<td>6</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Number of flow limitation events (events associated with less than 3% O₂ desaturation)</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Apnoea-hypopnoea index (per hour)</td>
<td>17.1/hr</td>
<td>15.7/hr</td>
<td>10.6/hr</td>
<td>0/hr</td>
<td>0/hr</td>
<td>0/hr</td>
<td>2.7/hr</td>
</tr>
<tr>
<td>Flow limitation index (per hour)</td>
<td>0/hr</td>
<td>2.6/hr</td>
<td>4.7/hr</td>
<td>15/hr</td>
<td>9.5/hr</td>
<td>6.0/hr</td>
<td>7.2/hr</td>
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<tr>
<td>Sleep stages</td>
<td></td>
<td></td>
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<tr>
<td>NREM (both supine and non-supine)</td>
<td>42 mins</td>
<td>23 mins</td>
<td>51 mins</td>
<td>24 mins</td>
<td>13 mins</td>
<td>46.5 mins</td>
<td>83.5 mins</td>
</tr>
<tr>
<td>REM (all non-supine)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>16.5 mins</td>
<td>none</td>
<td>12.5 mins</td>
<td>25 mins</td>
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<td></td>
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<td></td>
<td>(all non-supine)</td>
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<td>(all non-supine)</td>
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with time after VNS placement (Cersósimo et al., 2011). This reduction in seizure frequency occurs in several seizure subtypes and across all age groups (Khurana et al., 2007). VNS has been shown to improve overall quality of life (Mikati et al., 2009).

While the commonly reported side effects of VNS therapy include dyspnoea, coughing and hoarseness of voice, there have been several reports of VNS adversely affecting breathing in sleep. VNS devices have several adjustable settings, including intensity, frequency, pulse width, and duty cycle (on and off-times). Malow et al. (2000) found VNS-induced SDB in four patients and studied the effects of device settings on the PSGs in two of them. They found cyclical respiratory events (mainly obstructive apnoeas and hypopnoeas with reduction in airflow and relative preservation of effort) corresponding to VNS output; only reduction in frequency from 30 Hz to 20 Hz (and not changes in pulse width or on-times) consistently improved SDB, with more marked improvement at 10 Hz. The results of decreasing intensity were inconsistent. They did not adjust VNS off-times and did not specifically comment on the effects of adjustment of settings on SaO\textsubscript{2} levels. Zaaimi et al. (2005), however, found that thoracoabdominal signal excursions worsened with increasing VNS intensities. In another report, Marzec et al. (2003) found that VNS-induced SDB was associated with increasing oesophageal pressures on manometry (proving their obstructive nature), and that these respiratory events could be eliminated with higher levels of continuous positive airway pressure (CPAP).

In published literature, the traditional treatment of VNS-induced SDB has been CPAP. However, in our patient, increasing the off-time from three to five minutes resulted in the most marked improvement of VNS-induced SaO\textsubscript{2} desaturations, although it did not significantly alter the degree of flow limitation. While decreasing VNS frequency from 30 Hz to 20 Hz (maintaining the off-time at the original setting of three minutes) reduced the number of events with SaO\textsubscript{2} desaturation, the majority of such events were still hypopnoeas. The combination of a lower frequency and increased off-time completely eliminated VNS-associated SaO\textsubscript{2} desaturations, but returning the frequency to the higher baseline setting while maintaining the longer off-time still resulted in improved SaO\textsubscript{2} desaturations over the baseline. In contrast to earlier reports (Malow et al., 2000; Nagarajan et al., 2003), reducing VNS frequency and intensity did not significantly affect the degree of flow limitation in our patient. In an interesting report, Gschliesser et al. (2009) studied the effect of VNS duty cycle on SDB in two patients. A rapid cycle mode (on-time: 7 seconds; off-time: 12 seconds) was compared to a standard mode (on-time: 30 seconds; off-time: 5 minutes), with all other settings kept constant. They found that while the rapid cycle mode induced a greater number of respiratory event-related arousals (defined as increases in respiratory effort or flattening of the nasal waveform lasting at least 10 seconds and causing an arousal from sleep) and flow limitations, there was no difference in the AHI or in the index of SaO\textsubscript{2} desaturations, both of which improved in our patient with the increase in off-time. To our knowledge, this is the first description of off-time affecting VNS-induced SDB and SaO\textsubscript{2} desaturations, and further suggests that adjusting VNS settings may be a viable alternative to CPAP therapy in such patients. However, the development of a protocol describing the exact VNS settings that alleviate SDB await larger systematic trials.

The mechanism by which VNS causes SDB remains unclear. Afferents from the peripheral chemoreceptors travel through the vagus nerve, which may suggest a peripheral aetiology. The occurrence of central apnoeas associated with VNS (Papacostas et al., 2007) may be secondary to this process. It may also explain the phenomenon of increased respiratory rate during VNS-related breathing events seen in our patient and in those reported earlier (Malow et al., 2000; Nagarajan et al., 2003; Hsieh et al., 2008), an effect that has been noted to be more pronounced at higher VNS intensities (Zaaimi et al., 2005). Conversely, VNS may stimulate the motor efferents to laryngeal and pharyngeal musculature arising in the nucleus ambiguus and travelling in the vagus nerve, causing possible upper airway obstruction. Reports of VNS-induced vocal cord adduction and laryngeal hemispasm, including nocturnal stridor, improved by reducing intensity, seem to support this theory (Zumsteg et al., 2000; St Louis and Faber, 2010).

The overall impact of VNS-induced SDB remains to be elucidated. Many investigators have suggested that VNS-induced SDB is mild, with minimal clinical consequence to the patient (Nagarajan et al., 2003) and does not adversely impact the beneficial effects of VNS on seizure control (Marzec et al., 2003). On the other hand, there have been reports of VNS causing severely elevated AHI, eliminated by switching off the device (Hsieh et al., 2008). Even patients with mild VNS-induced SDB have reported symptoms significant enough to cause discontinuation of VNS therapy (Holmes et al., 2003). Similarly, while a decrease in daytime sleepiness has been demonstrated in patients after VNS placement, independent of seizure control (Malow et al., 2001), our patient was more alert and interactive with family and at his day program after VNS implantation four years prior to this study, despite induction of OSA by the device. VNS-induced OSA may thus have variable clinical presentation. Whether the resolution of SaO\textsubscript{2} desaturations by increasing off-time without completely eliminating...
flow limitation, as noted in our patient, has any clinical implication cannot be determined without further study using a larger number of patients and longer follow-up period. However, our case adds to the existing literature on the impact of device settings on VNS-induced SDB and strengthens the recommendation that all patients who are candidates for VNS placement undergo a detailed sleep evaluation and appropriate PSG testing.

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Authors have no conflict of interest to declare.

References