Vagus Nerve Stimulation Therapy for Seizures

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Abstract: Of the 3 million patients with seizures in North America approximately 70% have effective seizure control with medications. In the group refractory to medical treatment only a minority fit the criteria for surgical therapy. Vagus nerve stimulation therapy seems to be a suitable nonpharmacologic therapy for reducing seizure frequency in these cases. It is a simple device with 2 electrodes and an anchor loop implanted on the midcervical portion of left vagus nerve and the impulse generator is implanted subcutaneously in the left infracavicular region. The left vagus is the preferred site as the right vagus innervates the sinoatrial node and influences the heart rate. Data from laboratory studies suggest that it most probably works by increasing the release of norepinephrine in the locus ceruleus, which in turn increases the seizure threshold. More than 32,000 devices have been implanted since it was approved in 1997. There is class I evidence that vagus nerve stimulator reduces the frequency of seizures. In addition it also elevates the patients’ mood—indeed independent of seizure control. In one of the studies 50% reduction in seizure frequency was 37% in the first year and 44% in the second and third year. The side effects commonly reported are constriction in the throat, change in voice, and throat pain which most patients are able to tolerate and continue the use of the device. In conclusion VNS seems to be an effective nonpharmacologic therapy for medically refractory partial onset seizures.

Key Words: vagus nerve stimulator, VNS therapy, brain stimulation, seizure therapy, locus ceruleus

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The word “epilepsy” is derived from the Greek word epilepsia—which means “seizure” (attack). It is a chronic disorder characterized by paroxysmal brain dysfunction due to excessive neuronal discharge.1 There are ≈3 million patients with epilepsy in North America.2 It is the second most common neurologic disorder (after stroke) and is the most prevalent neurologic disorder involving all age groups. Despite the advances in neuropharmacology and the advent of new antiepileptic drugs, seizure control is ineffective in ≈30% of epilepsy cases.3,4 Roughly half of these are partial onset seizures.5,6 Partial onset seizures are those in which the first clinical and electroencephalogram (EEG) changes indicate initial activation of a system of neurons limited to part of one cerebral hemisphere.7 Only a minority of these patients benefit from surgical treatment. Antiepileptic drugs also have cognitive, psychologic, and behavioral side effects. Thus, the present day pharmacologic management of epilepsy is far from satisfactory and this underscores the importance of effective nonpharmacologic treatment measures for epilepsy.

In 1997, the United States Food and Drug Administration (FDA) approved the vagus nerve stimulator (VNS) therapy (manufactured by Cyberonics Inc, Houston, TX) as an adjunct therapy for reducing seizure frequency in patients over 12 years of age with partial onset seizures refractory to antiepileptic medications. The VNS device intermittently stimulates the vagus nerve and transmits afferent stimuli to the central nervous system (CNS) and increases the seizure threshold in the patient. The VNS device is the first such device for seizure control approved by the FDA and is a significant departure from the conventional manner in which seizure is treated (somatic activation for a CNS disease). This review will address the neuroanatomy, physiologic basis of VNS, its mechanism of action and its anesthetic implications.

TREATMENT OPTIONS FOR EPILEPSY

Presently the treatment options available for a patient with seizure disorder are medical treatment first followed by surgical resection, if the patient is refractory to medical treatment. With antiepileptic medications seizure control is effective in ≈70% of the cases.3 Most patients who do not respond to 3 antiepileptic drugs (given separately or in combination) do not ultimately respond to pharmacotherapy.3 In the group refractory to medical management (≈30% of patients with seizure disorder) 50% have partial onset seizures.5,6 These are the patients suitable for seizure surgery workup. However, only 10% to 30% of these partial onset seizure patients refractory to medical management are appropriate candidates for seizure surgery and eventually only 1% undergo the procedure.9 Surgical options include focal cortical resection, temporal lobectomy, corpus callosumotomy, subpial resection, and hemispherectomy. In the temporal lobe amygdalo-hippocampectomy is one of the most common surgical procedures carried out.10 The outcome after surgery depends on the degree of sclerosis in the amygdala and the hippocampus—in patients with severe sclerosis 88.7% are seizure free and when sclerosis is mild 59.6% are seizure free after surgery.10,11 In a

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29
comparison between surgery and medical management in temporal lobe epilepsy, after 4.8 years of follow-up 44.6% in the surgical group and 4.3% in the medical management group were seizure free. However, for those patients where surgery is not indicated (or the patient is unwilling to undergo surgery) and those who do not respond to surgical resection, there is a big void in treatment option. In addition there are patients in the medical management group who are noncompliant with medication because of the intolerable side effects to antiepileptic drugs. VNS is a therapeutic option when medical and surgical treatments of epilepsy either fail or are not feasible.

**VAGUS NERVE STIMULATION**

**History**

VNS is an example of treating neuro-psychiatric diseases by somatic stimulation. Other techniques include electroconvulsive therapy for depression and deep brain stimulation for Parkinson disease and essential tremor. Corning, back in 1883, was the first to propose the idea of VNS for seizures—based on his theory that seizure activity is caused by venous hyperemia in the brain and that vagus nerve activation will treat seizures by decreasing the heart rate and the cerebral blood flow (CBF), thereby correcting the cerebral hyperemia. However, Bailey and Bremer in 1938 recognized the direct CNS effects of vagus nerve activation (in contrast to the cardiovascular effects as proposed by Corning). Dell and Olson in their study on awake cats with high cervical lesion, observed a slow wave activity in the anterior rhinal sulcus with vagus nerve activation. Consolidating all this basic information, Zabara created experimental seizures in dogs and demonstrated the antiepileptic effect of VNS therapy. He hypothesized that VNS therapy can “control/prevent the motor, autonomic and conscious components of epilepsy.” He also observed that the inhibitory effect on seizures outlasts the period of VNS activation (at least 4 times longer in the acute experimental epilepsy models and much longer in the chronic models). The first VNS was implanted in 1988 by Penry and Dean.

**Indications for VNS**

VNS therapy is recommended in patients over 12 years of age with partial onset seizures refractory to antiepileptic medications. In the earlier studies where efficacy of the VNS was evaluated the defining criteria for medically refractory seizure was 6 seizures or more per month and seizure-free interval of no more than 2 to 3 weeks despite therapy with multiple medications. However, now multiple factors are taken into account before advising the VNS therapy such as—uncontrolled seizures despite 2 drug trials, compromised quality of life, noncompliance with antiepileptic medication, intolerable side effects to antiepileptic medications, and patients not suitable for surgery or not willing to undergo surgery. Decision to implant VNS is made on a case-by-case basis. Off label use of VNS has been reported in children as young as 3 years of age and in patients with generalized seizures.

**Anatomy of Vagus Nerve**

Vagus nerve gets its name from the Latin word “vagus” which means “wandering.” This refers to the extensive distribution of the vagus nerve to the head, neck, thoracic, and abdominal viscera. In the vagus nerve, 80% of the fibers are afferent carrying both somatic and visceral afferents. The vagus nerve carries afferent fibers from the head, neck, thoracic, and abdominal viscera and parasympathetic efferents to the heart, lung, and major part of the gastrointestinal tract. The motor efferents to the pharynx and larynx also arise from the vagus. The cell bodies of the afferent sensory component of vagus are located in the nodose ganglion. The nodose ganglion...
relays the afferent input to the nucleus tractus solitarius (NTS). From the NTS there are 3 major outflows:

(1) Autonomic feed back loop.
(2) Direct projection to the reticular formation in the medulla.
(3) Ascending projection to the parabrachial nucleus (PB) and locus ceruleus (LC).

LC is one of the primary norepinephrine (NE) secreting nuclei in the CNS. The release of NE in response to VNS seems to determine the antiepileptic action of VNS. The PB and LC also have efferent connections to the amygdala and the stria terminalis. The antidepres-

sant and mood elevation effect observed with the VNS (which may or may not be associated with seizure control) could be related to the effect of the vagus nerve activation on the amygdala. The amygdala controls emotional behavior and mood.

The midcervical portion of the vagus nerve is devoid of any branches. In the neck, the superior and inferior cardiac branches arise rostral to the midcervical part of the vagus nerve. Branches from the right vagus supply the sinoatrial node whereas the branches from left vagus innervate the atrioventricular node. Hence the right vagus influences the heart rate much more than the left vagus. Because of this reason the VNS electrodes are almost always placed on the left vagus in its midcervical portion (caudal to the origin of the cardiac branches). Despite this, occasionally because of retrograde stimulation there can be bradycardia with the activation of the left vagus nerve. The branches to the pharynx, carotid sinus, and the superior laryngeal nerve also arise rostral to the midcervical portion of the vagus nerve. The recurrent laryngeal nerve is the only branch caudal to the midcervical part of the vagus. Hence with the midcervical placement of the VNS, the recurrent laryngeal nerve does get activated and hoarseness of voice is a common occurrence. Retro-

grade activation of the superior laryngeal nerve can cause a feeling of tightness and pain in the throat.

**Theoretical Basis of VNS Therapy**

Although the mechanism of the antiepileptic efficacy of the VNS therapy remains to be elucidated in humans, there is compelling evidence that the modulation of afferent vagal nerve activity increases the seizure threshold. The vagal afferents from the viscera relay impulses to multiple regions in the CNS many of which are potential sites for epileptogenesis. This includes the hippocampus, amygdala, cerebellum, diencephalon (includes the thalassa-

mus and hypothalamus), and insular cortex. As described in the section on anatomy, the vagal afferents project to the NTS and from NTS sensory afferents are relayed to the PB and LC. The hippocampus and the amygdala also get afferent input from the LC. LC is one of the major NE secreting regions of the CNS. Activation of the LC has been implicated as one of the possible mechanisms by which the VNS works. As a proof, in laboratory seizure models (rats) if the LC is destroyed then VNS is no longer effective in controlling seizure activity. Infusion of 6-hydroxydopamine can deplete NE level in the LC and this has been shown to neutralize the efficacy of VNS. It has been suggested that the LC activation releases NE and serotonin which in turn modulates the seizure threshold by releasing γ-amino butyric acid or by inhibiting the release of glutamate in the regions with afferent connectivity to the LC. Injection of γ-amino butyric acid or glutamate antagonist in the NTS (which is connected to the LC) blocks seizure activity. Yet another mechanism suggested is the change in heart rate and cardiac contractility associated with the VNS therapy, which alters the CBF in specific regions of the CNS resulting in a rise in seizure threshold. However, the argument against this theory is the VNS is not associated with any primary change in cardiovascular function and the changes in CBF observed are more likely to be secondary to the alteration in neuronal activity induced by the VNS.

**VNS Device**

The VNS device is manufactured by Cyberonics Inc (Houston, TX). The device primarily consists of a pulse generator (Fig. 1) and implantable leads. The patient end of the lead has 3 discrete helical coils (Fig. 2), which wrap around the left vagus nerve. The proximal and distal coils are the positive and negative leads whereas the middle coil is an anchor. This anchor ensures that undue tension is not exerted on the vagus nerve with movements of the neck. It is meant to snugly fit around the nerve. Each helix has 3 coils and the middle turn is a platinum ribbon coil, which is welded to the lead wire. This shape ensures optimum contact with the nerve. This open helical design prevents damage to the nerve. Although snugly fitting around the nerve, the electrode is meant to move with the nerve thus minimizing shear on the nerve. Model 102 is the generator currently available. It is powered by a lithium cadmium battery and is hermetically sealed in a titanium module. It has a projected battery life of 6 years. The actual life is dependent upon the stimulus intensity and frequency.

The pulse generator is placed in a subcutaneous pocket in the left infraclavicular region. The leads are placed on the midcervical portion of the left vagus nerve and the leads are tunneled to the generator pocket. There is an interrogating device for checking the device before implantation and after it is implanted. The output current, frequency, pulse width, and signal on and off time have to be set on the generator. Activation is initiated with 0.25 mA current and increased gradually to 1.25 to 2 mA over several weeks. The other settings are pulse width of 250 to 500 μs, 20 to 30 Hz frequency, and signal on for 30 seconds and off for 3 to 5 minutes. Settings are altered as per the patient’s requirement. The baseline signal output from the generator is continuously on. Each patient is given a hand held magnet. When the magnet is run briefly over the generator it manually triggers a train of stimuli superimposed on the baseline activation. If a patient has an aura then manual triggering can be initiated to abort or minimize a seizure activity. Alternatively if a patient wants to stop the device (in case
of malfunction) placing the magnet on the generator continuously, terminates the baseline activation. The magnet is also used for testing the device. Patients are advised to check the device periodically by manually inducing activation. Patients perceive the activation as a mild tingling in the throat.

Clinical Efficacy (http://www.vnstherapy.com/epilepsy/hcp)

On the basis of a randomized control trial, in 1999 the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology noted that "sufficient evidence exists to rank VNS for epilepsy as effective and safe on the basis of a preponderance of class I evidence." More than 32,000 VNS devices have been implanted worldwide with 94,000 patient years of follow-up. The efficacy of the device is measured in terms of the median (50%) reduction in seizure frequency. In a multicenter trial, 113 patients were studied to determine the optimum stimulation parameters. All patients satisfied the criteria for medically refractory seizures and were implanted the device. Half the patients were stimulated every 5 minutes for 30 seconds and the other half every 90 minutes for 30 seconds. The rest of the stimulation parameters were the same—30 Hz frequency, 3.5 mA current, and pulse width of 500 µs. At 3 months, 31% in the high stimulation group had a 50% reduction in seizure frequency compared with 13% in the low stimulation group.

Studies reveal that 50% reduction in seizure frequency (a benchmark for assessing the efficacy of the VNS therapy) is achieved in 37% of the subjects in the first year and 43% in the second and third year. A 12-year follow-up was reported by Uthman et al in 48 patients. With longer follow-up the efficacy of the VNS tends to improve. Twenty-nine out of the forty-eight patients (60%) had a 50% reduction in seizure frequency over 12 years whereas 42% of the subjects had a 75% reduction in seizure frequency. Three patients were seizure free. In addition to the decrease in seizure frequency patients also reported a significant improvement in quality of life. They were more alert, daytime sleeping was less, they were less depressed, and memory also improved. Patients on VNS are less likely to discontinue this therapy compared with those on medical therapy.

Side Effects/Complications

Side effects/complications with the VNS placement could be acute or chronic. Acute side effects reported are wound infection, left vocal cord palsy, lower facial palsy, and very rarely severe bradycardia/asytole. The incidence of wound infection reported is in the range of 3% to 6% and in one of the studies infection led to removal of the device in 3 out of 198 cases. Left vocal cord palsy was reported in 2 out of 198 cases in the EOS study. It resolved spontaneously. Left facial nerve palsy was related to surgical incision placement—with change in surgical technique it is no longer observed. Severe bradycardia leading to asystole (reversible) was related to the immediate testing of the device on implantation. Reported incidence was 0.1%. The current practice is not to test the device immediately after implantation. The device is activated 2 weeks after the implantation. With this approach patients have been able to use the device without any risk of bradycardia. It is advisable to have continuous electrocardiogram monitoring and resuscitation equipment when the device is activated for the first time.

Both the sensory and the motor innervations of the pharynx and the larynx are supplied by the vagus nerve. Hence most of the chronic side effects of the VNS therapy are related to the activation of the pharynx and the larynx. Hoarseness of voice (37.2%), hypophonia (37.2%), and coughing (45%) have been reported—because of the activation of the recurrent laryngeal nerve and the superior laryngeal nerve. Many patients report a constriction in throat and change in voice—which may persist for a long time. Laryngo-pharyngeal dysfunction because of the vocal cord palsy leading to aspiration of pharyngeal secretions has been reported in some subjects. Vocal cord palsy and evidence of aspiration was seen on doing an endoscopic evaluation during the stimulation interval. This implies that patients on chronic VNS therapy may be at risk of aspiration and standard aspiration precautions may be required in these cases. Occasionally pain in the jaw, headache, and pain in the abdomen has been reported. There is a case report of chronic diarrhea with VNS therapy. In a follow-up it was observed that most of the side effects resolve within the first year. Some of the side effects (like throat pain, cough, and dyspnea) subside with alteration in the stimulation parameters. It may reappear with generator change (if the stimulation gap is more than 3 wk).

In the neck, vagus nerve lies between the carotid artery and the internal jugular vein, within the carotid sheath. Hypoglossal nerve is proximal to the midcervical part of vagus whereas the phrenic nerve lies beneath the carotid sheath. High current output can infrequently cause hemiparalysis of the diaphragm and weakness of one-half of the tongue. The sympathetic trunk is deep and posterior to the vagus nerve. Horner syndrome has also been reported after VNS therapy.

Implications for Anesthesiologist

As anesthesiologist, we should be cognizant of the fact that as the mechanism of the VNS device is understood and cumulative data regarding its efficacy comes up, more and more of these devices are likely to be implanted. Even more so now, with the expansion of its indications for major depressive disorders. As of now there is no report of any electrical interference with the VNS device. Anesthetic management may be required in the following situations:

1. Seizure patients coming for VNS implantation.
2. Patients coming for generator change.
3. Patients with VNS coming for incidental surgery.

The VNS implantation procedure is usually done under general anesthesia. During surgery the head is turned to the right, as the middle segment of the left side vagus nerve has to be exposed. Hence general
endotracheal anesthesia is preferred. Generator change can be carried out under local anesthesia. The important anesthetic implications in a patient coming for VNS implantation are

1. Optimum seizure control in the perioperative period: antiepileptic medication should be continued till the morning of surgery and resumed as soon as possible in the postoperative period. Plasma level of the antiepileptic medication should be checked to ensure that the level is therapeutic.

2. Augmented metabolism of drugs: Because the patients with refractory seizures are likely to be on multiple antiepileptic medications as a side effect there is an augmented hepatic metabolism of drugs resulting in enhanced requirement for muscle relaxants, narcotics, and benzodiazepines. This is observed only with phenytoin and carbamazepine. It is not seen with newer antiepileptic medications. Intermediate acting neuromuscular blockers vecuronium and rocuronium are predominantly metabolized in the liver and their requirement is likely to be higher. Cisatracurium has a nonorgan-dependent metabolism and its dosage requirement may not be influenced by chronic antiepileptic medication. Up-regulation of acetylcholine receptors would also contribute to the altered dose requirement of muscle relaxants.38

3. Proconvulsant drugs to be avoided: Because of the propensity for seizures, anesthetic agents and adjuvant drugs, which potentially cause seizures or decrease seizure threshold are preferably avoided. Induction dose of sevoflurane has been shown to cause epileptic EEG activity in children and adults.39 This has also been demonstrated to occur at surgical level of anesthesia in epileptic and nonepileptic subjects.40 This is because of the structural similarity between sevoflurane and enflurane (enflurane can cause seizures at normocapnea and hypocapnea). So it would be prudent to avoid sevoflurane and enflurane in these cases. High doses of opioids can also cause epileptic EEG activity. This has been demonstrated in laboratory models and in humans. In humans, fentanyl dose of 25 to 100 μg/kg and sufentanil dose of 2.5 to 10 μg/kg was shown to cause epileptic EEG activity in patients without history of seizure undergoing cardiac surgery.41 In clinical practice for a 1 to 2-hour surgical procedure it is highly unlikely that such a high dose of opioids will be required. However, because of the enhanced metabolism, opioid dose requirement could be higher than normal.

4. Physiologic factors that can decrease seizure threshold should be avoided. This would include hypoxia, hypotension, hypocarbia, and hyponatremia.

When a patient with a VNS comes for an incidental surgery issues related to anesthesia/anesthetic management are:

1. We have to ensure that the VNS device is working effectively and seizures are being managed as effectively as is medically feasible. VNS patients are generally under the medical supervision of a neurologist. Hence it is advisable to contact the concerned neurologist to ensure that the device is interrogated before and after the surgical procedure, carry out the appropriate device adjustment if required and optimize the medical management of seizure.

2. Anesthesiologist must be cognizant of the side effects associated with a VNS, such as hoarseness of voice, mild throat constriction, and hypophonia. At all times we have to be aware that any medication/biochemical alteration (hyponatremia, acidosis, and hypoxia) which decreases the seizure threshold can make a patient more prone to get seizure.

3. As discussed above, some patients may be at a higher risk for aspiration because of laryngo-pharyngeal dysfunction. Standard aspiration precautions should be followed if there is an evidence of aspiration risk.

4. Use of electrocautery, external defibrillator: these devices could potentially damage the VNS generator and/or the electrodes. As of now there are no reports in literature about electrical interference with a VNS device. However, it would be prudent to avoid the use of electrocautery and external defibrillator within the vicinity of the device and the electrodes. If electrocautery is required a bipolar cautery is preferable. As followed for a permanent pacemaker, monopolar cautery grounding pad should be placed away from the VNS generator and closer to the operative site. The defibrillator paddles also should be placed away from the VNS generator. As far as possible lower current energy level should be used. Current vector in both the electrocautery and defibrillator should be perpendicular to the direction of the VNS leads.

5. Airway obstruction: in patients with obstructive sleep apnea during VNS activation airway obstruction has been reported and confirmed by polysomnography studies. The incidence of obstructive sleep apnea in medically refractory seizure patients is somewhere in the range of ≈33%. Considering this, combined effects of the residual effects of anesthesia, opioids, and VNS stimulation could increase the chances of postoperative airway obstruction in patients with obstructive sleep apnea.42 Institution of constant positive alveolar pressure can relieve the obstruction. VNS stimulation may have to be turned down or turned off temporarily.

6. Placement of a central intravenous access on the side of the VNS placement should be avoided. The neck should be in neutral position to avoid any stretching or displacement of the electrodes implanted on the vagus nerve.

7. Though the VNS device is magnetic resonance imaging compatible, radiofrequency current can generate heat in the vicinity of the vagus nerve, which could potentially damage the nerve. Settings of the device could be altered by the magnetic resonance imaging magnet. As a general rule after any possible potential electrical interference with the VNS device, the device should be interrogated and reset if required.
Non epileptic indications for VNS

In addition to epilepsy other potential indications for the VNS therapy are depression and anxiety disorders (e.g., panic disorder, irritable bowel syndrome). In July 2005, FDA approved the VNS therapy for patients over 18 years of age with major recurrent depressive disorder, with inadequate response to 4 or more antidepressant medications. This implies that in the future we are likely to see more patients with the VNS device.

CONCLUSIONS

The VNS therapy is a promising nonpharmacologic alternative for decreasing the seizure frequency in partial onset medically refractory seizures. There is class I evidence to justify its use in epilepsy. Device is well tolerated by most subjects. In addition to seizure control it also improves the quality of life.

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