The development of vagus nerve stimulation (VNS) began in the 19th century. Although it did not work well initially, it introduced the idea that led to many VNS-related animal studies for seizure control. In the 1990s, with the success of several early clinical trials, VNS was approved for the treatment of refractory epilepsy, and later for the refractory depression. To date, several novel electrical stimulating devices are being developed. New invasive devices are designed to automate the seizure control and for use in heart failure. Non-invasive transcutaneous devices, which stimulate auricular VN or carotid VN, are also undergoing clinical trials for treatment of epilepsy, pain, headache, and others. Noninvasive VNS (nVNS) exhibits greater safety profiles and seems similarly effective to their invasive counterpart. In this review, we discuss the history and development of VNS, as well as recent progress in invasive and nVNS.

Key words: vagus nerve, vagus nerve stimulation

HISTORY OF VAGUS NERVE STIMULATION

In the late 19th century, American neurologist James Corning was the first to use vagus nerve stimulation (VNS) to treat epilepsy, then thought to be due to excessive cerebral blood flow (CBF). He applied a “carotid fork” for partial bilateral carotid artery compression and attached it to direct current electrodes for crude transcutaneous stimulation of the vagus nerve (VN) and sympathetic nerves in an attempt to reduce the CBF and slow the heart rate (Fig. 1).1 Though it did not work well, Corning introduced the idea of VNS into the world.

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Half a century later, several animal studies started to shed some light on the mechanism of VNS. Bailey and Bremer developed the “encéphale isolé” procedure on vagotimized cats. They observed an increased electrical potential on the contralateral orbitofrontal cortex during Faradic stimulation (24-50 Hz) of the afferent VN.3 In 1952, using “encéphale isolé” cats with strychnine-induced seizures, Zanchetti et al found global cortical desynchronization and sleep spindle blockage during VNS (2 volts, 50 Hz, 0.5 ms pulse).4 Magnes et al stimulated the nucleus of the solitary tract at low (1-16 Hz) or high (>30 Hz) frequencies, producing EEG synchronization or desynchronization.

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respectively. Chase et al stimulated the afferent VN and discovered that EEG synchronization and desynchronization were likely due to the stimulation of fast and slow conducting fibers (<15 m/s), respectively. In the strychnine dog model of status epilepsy, Zabara et al reported that VNS (20-30 Hz, 0.2 ms pulse) interrupted the seizure and induced an extended seizure inhibitory period. Other animal models also demonstrated potential antiepileptic properties of VNS. While C-fibers were thought to be the primary nerve type involved in seizure control in animal models, A- and B-fibers were later found to play the major role in antiseizure efficacy in humans.

DEVELOPMENT OF CLINICAL VNS

With the success in animal studies, human studies ensued in the early 1990s. Uthman et al and Penry et al reported 2 pilot studies showing significant seizure reduction following VNS in patients with intractable epilepsy. In 1994, a randomized, multicenter, double-blind study on 67 patients with refractory partial seizures showed significant reduction in seizure frequency after 14 weeks of VNS. The US Food and Drug administration (FDA) later approved an implanted left cervical VNS device for managing treatment-refractory epilepsy (TRE) in 1997, and for chronic treatment-resistant depression (TRD) in 2005 (NeuroCybernetic Prosthesis System, Cyberonics, Inc, Houston, TX, USA). Novel implantable devices are currently being engineered. An investigational closed-loop technology, which senses the increased heart rate at the onset or during a seizure, automates the delivery of additional stimulation for improved seizure control (AspireSR, Cyberonics). A recent phase II study suggests the potential role of right cervical unidirectional VNS for managing chronic heart failure (CardioFit System, BioControl Medical Ltd, Yehud, Israel). Further, a miniaturized implant is undergoing trials for rheumatoid arthritis and inflammatory bowel disease (SetPoint Medical, CA, USA). Noninvasive VNS (nVNS) devices have also been developed. A noninvasive transauricular VNS (taVNS) device, which stimulates the auricular branch of the VN, was approved in Europe for the treatment of epilepsy and depression in 2010, and pain in 2012 (NEMOS; Cerbomed GmbH, Erlangen, Germany). A similar auricular VNS, neuro-electric therapy (NET; Auri-Stim Medical Inc., Denver, CO, USA), is
not widely available and currently marketed as a microcurrent/music therapy device. A customized taVNS also demonstrated its potential in seizure frequency reduction. In addition, a non-invasive transcervical VNS (tcVNS) device, which stimulates the cervical branch of the VN (gammaCore; electroCore LLC, Basking Ridge, NJ, USA), has received European clearance for the acute and prophylactic treatment of primary headaches (cluster headache, migraine, hemicrania continua), medication overuse headache, and reactive airway disease (asthma, exercise-induced bronchospasm, COPD), as well as adjunctive therapy for epilepsy prevention and reducing the symptoms of certain anxiety/depression conditions (eg, panic disorder, posttraumatic stress disorder, major depressive disorder, obsessive-compulsive disorder), gastric mobility disorders, and irritable bowel syndrome.

To date, VNS is also being investigated for bipolar disorder, Alzheimer’s disease, obesity, impaired glucose tolerance, gastroparesis, asthma, fibromyalgia, traumatic brain injury, stroke (neuroprotection, neurogenesis), hemostasis, cerebellar tremor, and involuntary movement disorders.

RECENT PROGRESS IN INVASIVE VNS

Left cervical VNS received FDA approval for TRE and TRD. By August 2013, more than 100,000 VNS devices had been implanted in more than 70,000 patients worldwide. The NCP system received FDA approval for use in conjunction with drugs or surgery as an adjunctive treatment for adults and adolescents over 12 years of age with medically refractory partial onset seizures, and for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments. The American Academy of Neurology guideline states that VNS is possibly associated with an increase in the number of patients achieving a \( \geq 50\% \) reduction in seizures (Level C). While VNS may be considered for seizures in children, for LGS-associated seizures, and for improving mood in adults with epilepsy, more information is needed on the treatment of primary generalized epilepsy in adults.

Right cervical VNS, which has received European clearance, is undergoing a phase III clinical trial for the treatment of heart failure. The rationale was to increase the parasympathetic outflow (B-fiber) to lower heart rate, reduce arrhythmia, and exert positive effects on LV function. Anti-apoptotic, anti-inflammatory, and antiadrenergic effects of VNS may induce remodeling and improve left ventricle ejection fraction. The CardioFit System is designed to sense the heart rate via an intracardiac implanted electrode, and deliver stimulation at preset delays from the R wave, as well as interrupt stimulation when the heart rate reaches the bradycardia limit (eg, 55/min). The stimulation lead is an asymmetric, bipolar, multicontact cuff electrode specifically designed for cathodic induction of action potentials in the VN while simultaneously applying asymmetrical anodal blocks. These anodal blocks minimize activation of A-fibers (60% reduction in A-fiber compound action potential to reduce side effects) but preferentially activate parasympathetic efferent B-fibers. Compared with other stimulation electrodes that activate nerves bidirectionally, this new design allows for unidirectional activation directed to the heart. Schwartz et al first reported this experience using right VNS for treating heart failure. In an open-labeled, phase II study using the CardioFit System in CHF patients with severe systolic dysfunction, the investigators showed an improved quality of life and left ventricle ejection fraction after 1 year of use. A similar unidirectional VNS system (FitNeS System) was designed for epilepsy to preferentially activate the afferent VN with minimal efferent stimulation-associated side effects.

VNS DEVICE IMPLANTATION AND COMPLICATIONS

NCP implantation is performed under general anesthesia in an outpatient setting. The electrodes (3 spiral coils: anode, cathode, and anchor tether) are attached to the left VN below where the superior and inferior cervical cardiac branches come off (Fig. 2). Stimulation of these 2 cardiac branches
may cause bradycardia and/or rarely asystole. Lead misplacement can usually be identified intraoperatively by the lead test. Stimulation parameters are adjusted by a programming wand placed over the device. Stimulation is turned on or off by a magnet. The NCP device operates on a wide variety of stimulation parameters (output current, signal frequency, pulse width, signal ON time, signal OFF time). Approved stimulation parameters are 0.25-3.5 mA (0.25 mA steps), 20-30 Hz (<10 Hz ineffective, >50 Hz might induce nerve damage), 0.25-0.5 ms pulse, signal ON for 30-60 seconds, and signal OFF for 5 minutes. A rapid stimulation of signal ON for 7 seconds and OFF for 14-21 seconds is also available. The optimal VNS stimulation settings, however, remain unknown. Based on clinical effect and tolerability, it is recommended to start low (0.25-0.75 mA) and gradually increase the amplitude to compensate the tissue resistance. The device can be activated by a magnet to provide on-demand stimulation to prevent or shorten a seizure. The magnet can also be used to temporarily inhibit stimulation.

NCP implantation is associated with certain complications. Intraoperatively, bradycardia and asystole can occur, albeit rarely, during lead impedance testing. This could be due to either collateral current spread or inadvertent placement of electrodes on VN cardiac branches. In animal studies, right VNS resulted in more bradycardia than left VNS. In human series, right VNS was as effective as left VNS without observable cardiac side effects. Although rare, delayed arrhythmias and syncope have been reported after long-term use. Surgical trauma may result in peritracheal hematoma or VN trauma, with unilateral vocal cord dysfunction and dyspnea. Voice alteration can occur in up to 62% of subjects during the preceding months after surgery. Cough, dyspnea, paresthesia, and pain occurred in about 20-25%. After 5 years, voice alteration occurred in fewer than 20% and other AEs were fewer than 5%. VNS-associated airway obstruction causing sleep apnea was not uncommon, but can depend on the stimulation settings. The overall mortality rate was similar to non-VNS patients with refractory epilepsy. Longer VNS use was associated with lower epilepsy mortality. Exposure of the NCP System to any radiofrequency (RF) transmitter coil must be avoided. RF energy (eg, ECT, MRI, electrocautery, shock wave lithography, defibrillation) induces heat on the

Fig. 2.—(A) The VN anatomy and placement of the electrical lead. (B) The schematic of the 3 electrodes. (Adapted with permission from Cyberonics. VNS Therapy System Physician’s Manual. Houston, TX: Cyberonics, Inc.; 2015.)
implant and may cause thermal injury to the VN and adjacent structures. For MRI imaging, only a local receiver coil under 1.5-3 Tesla is allowed.

RECENT PROGRESS IN NONINVASIVE VNS

To avoid surgical implant-related complications, researchers developed 2 types of nVNS: transauricular and transcervical. The transauricular VNS (taVNS) stimulates the auricular branch of the VN (ABVN), which innervates the cavity of conchae and cymba conchae. ABVN has been associated with ear-cough reflex, ear-vomiting reflex, and auriculo-cardiac reflex. The transcervical VNS (tcVNS) most likely stimulates both efferent and afferent VN fibers in the carotid sheath. So far, there are no Phase III studies on nVNS showing efficacy in reducing seizures in epilepsy patients.

**taVNS Device.**—NEMOS (Fig. 3), which delivers biphasic pulses (25 Volts, 10 Hz, 0.3 ms pulse), received European clearance in 2010 for the indication of epilepsy. It is applied through a patient-controlled stimulation session that usually last for 1 hour, 3-4 times per day. Stefan et al observed reduced seizure frequency in TRE patients using taVNS for 9 months. Busch et al found that 1 hour taVNS influences the central pain processing in healthy human and increases mechanical and pressure pain thresholds. The NEMOS device is generally well tolerated. In subjects with no known pre-existing cardiac pathology, preliminary data do not indicate arrhythmic effects of taVNS. To activate the myelinated afferent VN fibers, the stimulus intensity is adjusted to a level between patients’ detection threshold (first perceptible or tingling sensation) and pain threshold (first pricking or unpleasant sensation). Typically, the detection threshold is around 0.8 mA on the cymba conchae. Because the tingling sensation is similar to tactile sensation, Ellrich et al suggested that such nonpainful peripheral nerve stimulation preferentially activates Aβ-fibers but not Aδ-nociceptive fibers. The actual fibers being stimulated remains to be confirmed but can depend on stimulation settings.

In a functional brain imaging study (fMRI) of 16 patients, Kraus et al studied BOLD signal following transcutaneous stimulation on the left auditory canal (anterior, posterior) and center of the ear lobe (sham control). Comparing anterior with posterior stimulation, they found an increased signal in many regions but decreased signals in the left parahippocampal gyrus, left posterior cingulate cortex,
and right thalamus pulvinar. Comparing anterior with sham stimulation, in addition to above regions, they found signal decreases in the LC and the area of the solitary tract. Comparing posterior with sham stimulation, decreased signals were found in left uncus, medial frontal gyrus, insula, anterior cingulate cortex, subgenual cingulate cortex, right superior frontal gyrus, and medial frontal gyrus. Brain activation patterns from tVNS were similar to those observed in invasive VNS (eg, diminished activity in thalamus, hippocampus, amygdala, cingulate).

**tcVNS Device.**—The gammaCore device (Fig. 3) is a handheld tcVNS device that stimulates the cervical VN with a 1 ms pulse (of 5 kHz sine waves) repeated at 25 Hz. The pulse waveform was designed to penetrate the biological barrier (eg, skin, tissue, nerve sheath) to stimulate the cervical VN. The stimulation intensity is self-controlled (up to 24 V and 60 mA) and lasts 2 minutes. It can be repeated multiple times safely; multiple stimulations (doses) have been administered up to 6-12 times per day in clinical studies. By adjusting the intensity of stimulation, one gets mild facial twitching through the stimulation of A- but not C-fibers. The optimal stimulation settings (number of stimulations per day, total stimulation duration) to reach a satisfactory response for each disorder remain to be determined. At the moment, the gammaCore device has been studied for the treatment of cluster headache, migraine, and hemicrania continua, and may also improve gastroparesis and asthma. In all of these studies, tcVNS was well tolerated without any major cardiac AEs.

**REFERENCES**


