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Vagus nerve stimulation

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Vagus nerve stimulation (VNS) is a key tool in the treatment of patients with medically refractory epilepsy. Although the mechanism of action of VNS remains poorly understood, this modality is now the most widely used nonpharmacological treatment for drug-resistant epilepsy. The goal of this work is to review the history of VNS and provide information on recent advances and applications of this technology. *(DOI: 10.3171/2009.6.FOCUS09126)*

Key Words • vagus nerve stimulation • epilepsy • history

Initial VNS Studies

The earliest studies documenting the effects of VNS on cerebral activity were conducted by Bailey and Bremmer[2] in 1938, and by Dell and Olson[10] in 1951. These investigators elucidated the fact that stimulating the vagus nerve causes an evoked response at the ventroposterior complex and intralaminar regions of the thalamus. This, in return, affects cortical activity via thalamocortical pathways. These authors studied the different anatomical connections of the NTS and its effects on cortical activity. The main central afferent connection of the vagus is the NTS, which projects to the LC and adjacent parabrachial nucleus, dorsal raphe, nucleus ambiguus, cerebellum, hypothalamus, thalamus, insula, medullary reticular formation, and other brainstem structures, several of which are known to modulate seizures in various models.[19,33] By stimulating the cut end of the vagus nerve, they were able to identify an evoked response at the level of intralaminar regions of the thalamus. Through a thalamic pathway this afferent connection modified neuronal activity at the level of the cerebral cortex. Zanchetti et al.[35] in 1952 demonstrated the ability of VNS to eliminate interictal epileptic events in a chemically induced seizure model in cats. In the next several decades, several experiments conducted mostly using cat models further confirmed the potential of VNS to decrease epileptic activity (Table 1). In1985, Zabara[34] reported the effects of stimulation of the vagus nerve on seizure control in animal studies. It was proposed that cervical region stimulation of the nerve might attenuate seizures by desynchronizing the cerebral cortical activity. Lockard and colleagues[16] and Woodbury and Woodbury[32] have shown that VNS can decrease seizure frequency and severity, and McLachlan[18] demonstrated changes in seizure duration and interictal spikes with VNS.

Mechanism of Action

Vagal afferent synapses use excitatory neurotransmitters (such as glutamate and aspartate), inhibitory neurotransmitter γ-aminobutyric acid, as well as acetylcholine and a variety of neuropeptides. The NTS receives the majority of vagal afferent synapses. The NTS projects to other brainstem nuclei, including the LC and raphe magnus, and thus modulates norepinephrine and serotonin release, respectively. These neurotransmitters ultimately have effects on the limbic, reticular, and autonomic centers of both cerebral hemispheres. Based on these findings by Zabara[33] and others,[19] it was postulated that afferent vagal synapses attenuate seizure activity through neurotransmitter modulation.

Further work by Naritoku and colleagues[22] examined the molecular biological effects of VNS on multiregional neuronal activities in the brainstem and cerebral cortex. This group found that intermittent VNS increases expression of neuronal fos (a marker for increased metabolic activity) in the medullary vagal complex, LC, and several thalamic and hypothalamic nuclei. Other biochemical effects of VNS include overexpression of brain-derived neurotrophic factor and fibroblast growth factor in the hippocampus and cerebral cortex, decreases in the abundance of nerve growth factor mRNA in the hippocampus, and increases in the norepinephrine concentration in

Abbreviations used in this paper: EEG = electroencephalography; LC = locus coeruleus; NTS = nucleus of tractus solitarius; VNS = vagus nerve stimulation.

TABLE 1: Anticonvulsant effects of VNS in experimental epilepsies*

Authors & Year	Model	Animal	Result
Bailey & Bremmer, 1938	none	cat	induced frontal fast activity
Zanchetti et al., 1952	strychnine	cat	blocked interictal spiking
Blum et al., 1961	none	cat	desynchronized EEG
Chase et al., 1966	none	cat	synchronized/desynchronized EEG in thalamus and cortex
O'Brien et al., 1971	none	monkey	elicited cortical-evoked potentials
Puizillout & Foutz, 1977	none	cat	induced REM sleep
Zabara, 1985	strychnine	dog	aborted seizures
Lockard et al., 1990	alumina	monkey	reduced seizure frequency
Woodbury & Woodbury, 1990	max electroshock	rat	reduced seizure severity
McLachlan, 1993	penicillin/PTZ	rat	reduced interictal spikes and seizure duration
Fernandez-Guardiola et al., 1999	amygdala kindling	cat	delayed kindling, Stage IV never reached

* PTZ = pentylenetetrazol; REM = rapid eye movement.

the prefrontal cortex.[12]

Despite basic scientific and clinical experimental work, the precise mechanism by which VNS confers antiseizure effects is still poorly understood. Although some studies have demonstrated spike reductions using VNS,[16] this reduction did not correlate with seizure reduction, and a clear EEG pattern has not been determined during VNS.[13,29] Therefore, VNS modifies cerebral electrical activity via thalamocortical pathways, but the precise mechanism of action has yet to be decoded.

Technological Development

Given the success of VNS in animal models, Dr. Jacob Zabara, a neurophysiologist from Temple University who had been the driving force behind the VNS basic science studies, collaborated with Terry Reese, an electric engineer with pacemaker technology experience, to further develop this technology. At that time, Reese was the vice president of Intermedics, a medical device company. Results of VNS testing in monkeys were equivocal and Intermedics decided not to pursue this technology. After company restructuring, Reese was no longer with Intermedics, and he and Zabara incorporated Cyberonics in December of 1987. In 1988, William Bell, a neurosurgeon working with J. Kiffen Penry, a neurologist, implanted the first VNS device in a 25-year-old man at Wake Forest Bowman Gray Medical School in North Carolina.[26] This device was a programmable stimulating device called the NeuroCybernetic Prosthesis.

Clinical Data

With the successful implantation of the device, clinical studies were performed to achieve FDA approval. Two pilot studies (E01 and E02) demonstrated the safety and efficacy of VNS in humans. Minimal adverse effects were encountered and those were limited to hoarseness and tingling in the neck. Shortly thereafter, a randomized active control study (E03) was performed in 1992, again demonstrating the efficacy of VNS in reducing seizure events.[4] In 1994, the European Community approved the use of the NeuroCybernetic Prosthesis for VNS in the treatment of refractory epilepsy. Other controlled studies followed, including the E05 trial.[14,20] In this study, 198 patients were assigned blindly to either a high-stimulation group (95 patients) or a low-stimulation group (103 patients). The mean decrease in seizure frequency at 3 months was 28% in the high-stimulation group compared with 15% in the low-stimulation group ($p = 0.039$). A reduction in seizure frequency > 75% was noted in 11% of the patients in the high-stimulation group. After completion of the initial phase of the E05 study, 195 of the patients were maintained in the research group; this time, all patients initially assigned to the low-stimulation group were crossed over to receive the high stimulation therapeutic dose.[9] Patients were followed up for at least 12 months. The median reduction of seizure frequency after the completion of the study was 45%. Of the entire group, 35% had a reduction of at least 50%, and 20% had a reduction in seizures of at least 75%. These studies proved the safety, efficacy, and tolerability of VNS in the management of refractory epilepsy. In July 1997, the US FDA approved the used of this device as an adjunct to active therapy for refractory epilepsy in adult and adolescents older than 12 years of age.

In a retrospective 12-year follow-up study, Uthman et al.[31] found a mean seizure reduction of 26% after 1 year, 30% after 5 years, and 52% after 12 years with VNS treatment. Forty-eight patients were followed up in this study group. The added benefit of prolonged stimulation includes drug reduction in this patient population with the potential gain of decreased polypharmacy and its adverse effects.[30] Overall, in terms of efficacy, VNS will offer a decrease in seizure frequency close to 50% in a third of the patients.

Stimulation Technique

The VNS Therapy System (Cyberonics) was formerly known as the NeuroCybernetic Prosthesis. The device is composed of a generator attached to a bipolar VNS lead (Fig. 1). Interrogating and programming the device is conducted using an external programming wand con-

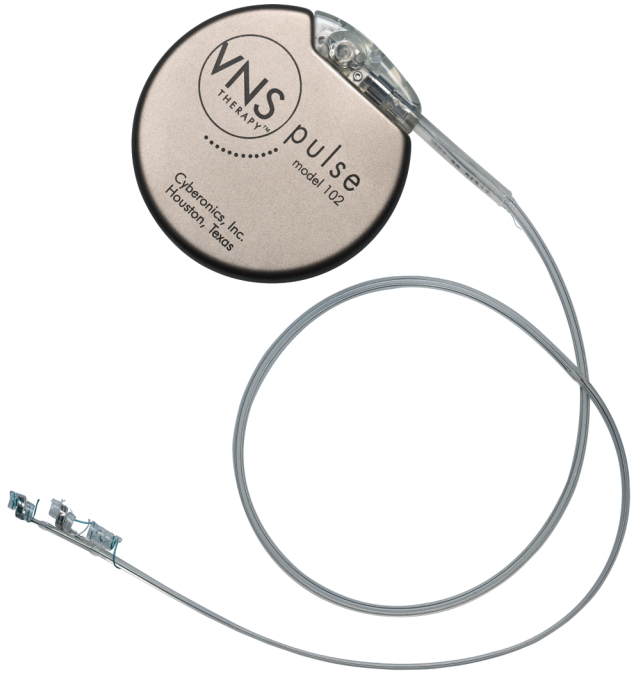

Fig. 1. Vagus nerve stimulator generator, Model 102. © Cyberonics, Inc., 2009. All rights reserved.

nected to a handheld computer. The insertion of the device is performed under general anesthesia and usually involves 2 incisions. The cervical incision is performed in a natural crease for cosmetic purposes. The platysma and subplatysmal fascia are dissected until the carotid sheath is exposed. This approach is similar to anterior cervical spine exposures. The vagus nerve is easily identified within the sheath, and at least 2.5 cm of the nerve is exposed. The lead is then attached to the vagus nerve. The cable leading to the generator is tunneled into the subcutaneous fat layer, above the clavicle, and into the left chest area. A subcutaneous pocket in the anterior chest is made for the generator (Fig. 2). The generator delivers a biphasic current that continuously cycles between on and off periods.

Fig. 2. Illustration depicting VNS generator and lead location in chest wall. © Cyberonics, Inc., 2009. All rights reserved.

The generator is turned on 10–14 days postoperatively to allow wound healing. Typically, the current output is adjusted to tolerance, using a 30-Hz signal frequency with a 500-msec pulse width for 30 seconds of "on" and 5 minutes of "off" time. These "default" settings were used in the initial double-blind studies in patients who were randomly assigned to receive high levels of stimulation. A handheld magnet is given to the patient or his/her caregiver. Stimulation can be modulated or terminated via this magnet. Several generator models have been developed with each successive model having smaller dimensions to improve cosmetic outcome (Fig. 3).

Indications for Use

The initial FDA approval for VNS use in the US in 1997 was as an "adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to antiepileptic medications." Since then, thousands of devices have been implanted in patients in the US.[1]

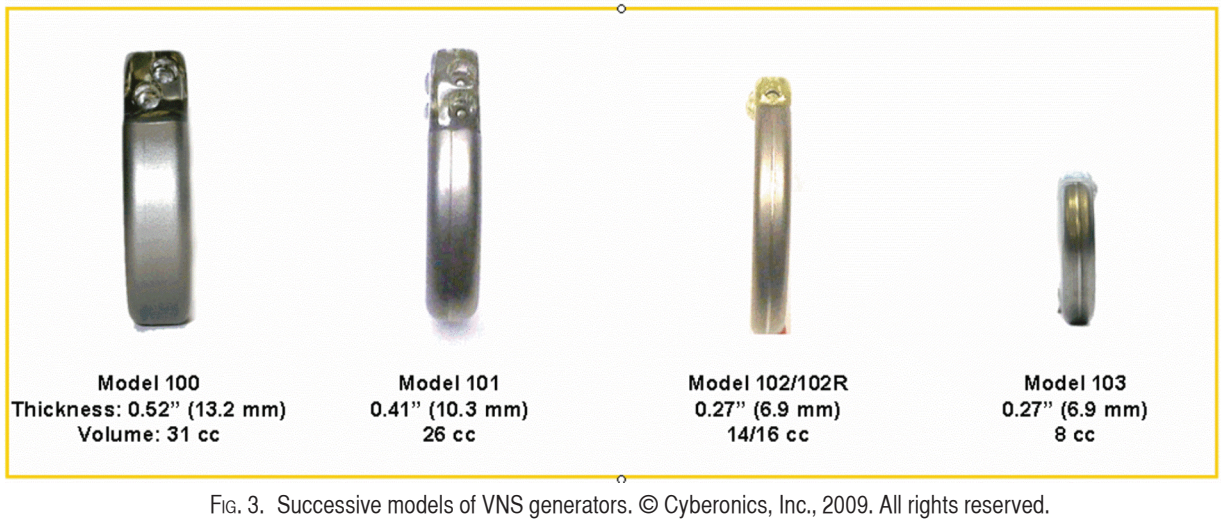

Fig. 3. Successive models of VNS generators. © Cyberonics, Inc., 2009. All rights reserved.

As is true for antiepileptic drugs, VNS was initially approved for the narrow indication of drug-resistant partial epilepsy. There is increasing evidence that VNS is effective in the symptomatic generalized epilepsies,[28] in refractory idiopathic ("primary") generalized epilepsies,[3,23] in Lennox-Gastaut epilepsy,[15] and other seizure disorders in the pediatric population.[5,17,21,25]

Another promising role for VNS is in the management of treatment-resistant depression. The idea of using VNS as a treatment for clinical depression was based on several different observations: the improved mood and cognition of patients with epilepsy after VNS therapy, as well as the fact that several anticonvulsant medications are used as mood stabilizers and antidepressants in bipolar disorder. In addition, brain regions that are critical in mood regulation (orbital cortex, limbic system) are targets of VNS. In a recent literature review, Daban et al.[8] found that open-label studies demonstrated the safety and efficacy of VNS in treatment-resistant depression. However, the only double-blinded study was associated with inconclusive results.[29] Furthermore, appropriate patient selection and optimal VNS dose have not been well established. Despite these limitations, interest in VNS for use in treatment-resistant depression is likely to continue as more clinical data are collected and evaluated.

Conclusions

Vagus nerve stimulation is a technology that has improved the quality of life of thousands of patients with medically refractory epilepsy. Successful development of VNS was predicated on decades of pioneering work by basic scientists and clinicians. Today, VNS is a key tool in the armamentarium of epilepsy clinicians. Further applications of VNS technology, including in treatment-resistant depression, are promising.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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