



# Vagus Nerve Stimulation for Epilepsy La Stimulation du Nerf vague dans l'épilepsie



Ali Turkmani, Marwan Najjar  
Surgery Department, Division of Neurosurgery,  
American University of Beirut, Lebanon.  
Email: mwnajjar@yahoo.com  
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## **Abstract**

Vagus nerve stimulation (VNS) is now a well established therapeutic modality for patients with intractable epilepsy who are not candidates for epilepsy surgery. It consists of placement of a battery and lead device that stimulates the left vagus nerve to reduce seizures. There are several possible mechanisms of action, although the exact mechanism is not well defined. Its efficacy in both the pediatric and adult populations has been established in many studies. Unlike anti-epileptic medications, the response to treatment improves with time and the procedure is generally well tolerated and has minimal side effects. In this paper, authors shed light on and review these various aspects relating to vagus nerve stimulation for drug-resistant epilepsy.

**Keywords:** Epilepsy- Vagus nerve stimulation- Anti-epileptic drugs.

## **Résumé:**

La stimulation du nerf vagal (VNS) est devenue une thérapie efficace pour les patients avec épilepsie pharmacorésistante, et qui ne sont pas candidats pour la chirurgie. Elle consiste à placer une batterie et un appareil câblé pour stimuler le nerf vagal du côté gauche pour réduire la fréquence des crises. Il y a plusieurs mécanismes d'action, mais il n'y a pas un seul mécanisme qui est bien défini. Son efficacité chez les adultes et enfants a été établi grâce à plusieurs recherches. Contrairement aux médicaments anti-épileptiques, ce mode de thérapie donne une réponse qui s'améliore avec le temps. En plus, cette thérapie est mieux tolérée par les patients, avec peu d'effets secondaires. Dans cet article, les auteurs expliquent et passent en revue les aspects liés à la stimulation du nerf vagal pour l'épilepsie résistante aux médicaments.

**Mots-clés :** Stimulation du nerf vagal- Médicaments anti-épileptiques- Epilepsie.

## **Introduction**

Epilepsy is chronic brain disease characterized by paroxysmal excess in neuronal electric discharge [1]. It is the second most common neurologic disorder involving all age groups [2]. Despite the introduction of several new anti-epileptic drugs, many patients continue to have intractable epilepsy (up to 30% of all epilepsy cases, 50% of whom do not greatly benefit from epilepsy surgery) [3]. Those patients, usually on multiple drugs at high doses, can suffer from various cognitive and behavioral

side effects beside the devastating effect of uncontrolled seizures on mental function and its development. Innovative modalities were proposed for treatment of this subgroup of patients with intractable epilepsy not amenable to surgical treatment. One such modality was vagus nerve stimulation (VNS). It is based on using somatic stimulation to inhibit epileptic discharge in the brain. In 1997, VNS was approved by the FDA (US Food and Drug Administration) as an adjunct modality to pharmacotherapy in children older than 12 years of age with intractable seizures when surgical treatment either fails or is not considered. This approval was the result of five clinical trials conducted in the U.S. and internationally with more than 450 human subjects participating in the studies [4].

## **History**

Stimulation of the vagus nerve to treat seizures was first brought into interest by Corning in 1883 [5]. He thought that seizures are caused by cerebral hyperemia. Thus, he tried to control seizures by reducing cerebral blood flow through reduction of heart rate. In 1938, Bailey and Bremer reported on the central nervous system (CNS) effect of vagus nerve stimulation as opposed to the indirect physiologic effects thought of earlier [6]. Dell and Olson, in their experimental studies, noticed that vagus nerve stimulation causes slowing of the wave activity in the anterior rhinal sulcus [7]. In 1985, Zabara suggested that the hypersynchronous electrical activity in the brain which is at the basis of seizures could be disrupted or altered by VNS [8]. In 1988, Penry and Dean implanted the first VNS battery in humans [9].

## **Indications for VNS**

VNS is not a first line therapy for intractable epilepsy. It is considered only in pharmaco-resistant epilepsy where patients do not fit the criteria for surgical resection of an epilepsy focus or when patients are not willing to go through a major surgery [10]. Several factors should be observed when taking the decision to implant the VNS device [2]. First, is inadequate seizure control after at least 3 treatment trials. Second, the quality of life is usually markedly compromised. Lastly, the patient may suffer pronounced side-effects of the medications or the patient may be non-compliant with drug therapy. VNS has been used in children younger than 12 years of age [11]. There is growing evidence that suggests that early seizure control would improve many of the neurocognitive

parameters (behavior, school, performance and mood) in children and this has lead to increasing use of VNS in this population. This is in addition to the fact that it would limit the complications resulting from pharmacotherapy side effects [12].

### **Mechanism of Action**

The exact mechanism of action of VNS is not well established. Recent neurophysiologic and neuro-imaging studies have pointed out some of the neural pathways activated by VNS and have given some proof that the alteration of the afferent fibers of the vagus nerve leads to an increase in seizure threshold [2]. 80% of the vagus nerve fibers are afferent fibers, somatic and visceral, which transmit input from the head, thorax and abdomen into nucleus tractus solitarius. The nucleus solitarius has 3 major outputs: Autonomic feed up loop, direct projection to the reticular formation of the medulla, and the Ascending Projections into the parabrachial (PB) nucleus and Locus ceruleus (LC) [13].

The LC is a major Norepinephrine (NE) nucleus in the CNS. The NE released upon VNS stimulation increases seizure threshold by releasing  $\gamma$ -aminobutyric acid [14]. It also inhibits glutamate secretion in the regions that project afferent fibers into the LC. Rat studies have shown that destroying the LC makes VNS ineffective in seizure control [15]. In addition, both PB and LC nuclei project efferent fibers into the amygdala and the stria terminalis. This is possibly the reason for the antidepressant and mood alteration effect observed with VNS.

Another suggested mechanism is that VNS, by altering heart rate and contractility, alters cerebral blood flow (CBF) to specific areas in the brain leading to a higher seizure threshold [16]. Certain studies have shown some evidence on this: Vonck et al., using single photon emission computed tomography scans showed that there was acute limbic hyperperfusion and chronic thalamic hypo-perfusion concomitant with VNS stimulation [17]. These correlated with positive clinical efficacy.

Recent studies have concentrated on the cortical neurophysiology [18]. Initially, it was widely thought that C-fiber activation with high current is needed to achieve an anti-epileptic effect. However, Krahel et al reported that destroying the C-fibers in rat models didn't affect VNS efficacy [19]. Other investigators interestingly showed that low current intensities, which cause stimulation purely of the myelinated A or B fibers, achieve a longer lasting seizure control effect than high currents, which are also associated with more side-effects [18].

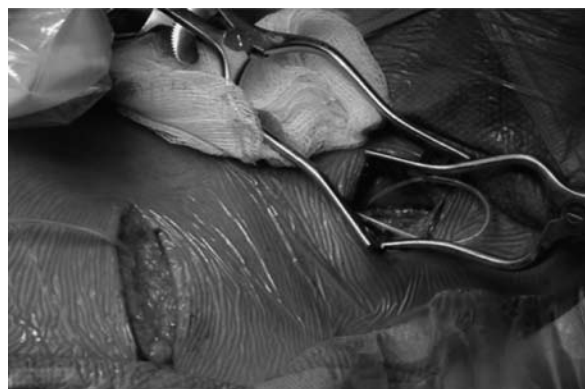
### **The VNS Device**

Unlike Cardiac pacemakers, which are on-demand devices that interfere in case of abnormal cardiac currents, VNS batteries usually work inter-ictally in a continuous fashion causing long term changes in the brain and increasing the seizure threshold, and thus, decreasing the seizure frequency. VNS devices are produced by Cyberonics Incorporation in Houston, Texas. Each device has three parts: a current pulse generator composed of lithium

cadmium battery, a lead wire that is placed subcutaneously, and a silicone rubber embedded platinum electrode. Each electrode has three helical coils, and each has three loops to ensure maximum contact when wrapped around the left vagus nerve. The first and the distal coils are the positive and negative leads. The middle helix is only for anchoring. Each patient is given a hand-held magnet to activate the neural stimulation when an aura occurs, thus, aborting or minimizing a seizure activity.

### **Surgical Placement of VNS**

Under General anesthesia, a skin incision is made on the left at the anterior border of the sternocleidomastoid muscle at the level of the cricothyroid membrane. The platysma is opened and careful dissection anterior to the sternocleidomastoid is then done to expose and then open the carotid sheath which contains the internal jugular vein, the carotid artery and the left vagus nerve. We need to expose at least 3 cm of the vagus nerve for proper electrode attachment. After isolating the vagus nerve, a subcutaneous pocket to hide the generator is made above the pectoralis fascia through a left chest skin incision. Some authors perform the surgery through a single incision at a midpoint between the two usual incisions. A tunneler is used to pass the connection lead from the neck to the chest incision (figure1). Following this, the electrodes are wrapped around the exposed part of the vagus nerve, and the lead connected to the generator which is placed in the chest pocket. Before closure, a programmer is used to interrogate the generator and to verify that there is good lead impedance, and all connections are verified. The current practice is to put on the system at 2 weeks after implantation.



**Figure 1: Typical incisions in VNS placement, where the lead wire has been passed between the two incisions and the helical coils wrapped around the vagus nerve.**

It is worth to note that the mid-cervical portion of the vagus nerve is usually devoid of branches except for the recurrent laryngeal nerve. Hoarseness due to activation of the recurrent laryngeal nerve is a common side-effect. In addition, the superior laryngeal nerve can be stimulated via a retrograde current resulting in a feeling of throat pain and tightness. Since the right vagus nerve has much more effect in regulating the heart rate and inducing bradycardia than the left vagus nerve, the current practice is to position VNS electrodes on the mid-cervical part of

the left vagus nerve distal to the take-off of the cardiac branches.

### **Clinical Efficacy and Safety**

In 1999, VNS was labeled effective and safe by the therapeutics S technology assessment subcommittee of the American Academy of neurology [20]. This was based on a review that found a large availability of class I evidence. The efficacy was measured with the median 50% reduction in seizure frequency. In his prospective study on long-term efficacy, DeGeorgio found a 34% reduction of seizure frequency at 3 months and 45% at 12 months [21]. Tatum et al in their prospective study of 21 patients, found that they could successfully reduce either the number or dosage of anti-epileptic drugs in 15 patients [22]. This was done without losing seizure control and with good patient satisfaction. Sirven et al reported on 45 adults who had VNS device for intractable epilepsy [23]. They reported more than 50% reduction of seizure frequency in 12 patients within 3 months and in 21 of 31 patients by 12 months. This clearly suggests cumulative effect with time in seizure control.

The cumulative effect is further demonstrated by long term studies. In a 12 year observational study, Uthman et al noted decreased mean seizure frequency by 26% after 1 year, 30 % after 5 years, and 52% after 12 years of VNS treatment [24]. In another review of 65 patients treated with VNS and followed up to 10 years, mean seizure reduction was 35% at 6 months, 52% at 1 year, 60% at 4 years, and 75% at 10 years [25].

As for the pediatric population, there have been numerous recent reports indicating efficacy and safety. In a study of 34 children with drug-resistant epilepsy treated with VNS with a mean follow up of 30 months, the mean reduction of seizures was 38% at 6 months, 49% at 12 months, 61% at 24 months, and 71% at 36 months [26]. Side effects were mild and transient as seen in the adult population group. We have reported earlier on successful VNS surgery for a small infant with myoclonic encephalopathy [27].

In 2001, Cyberonics recommended to avoid use of short-wave diathermy, microwave diathermy and therapeutic ultrasound diathermy in patients with VNS because of the risk that the generator or the lead wire could cause thermal soft tissue injury. Diagnostic ultrasound was not included in the warning.

### **Tolerability**

A recent study evaluated the quality of life in 132 patients before VNS is initiated and 3 months after treatment is started [28]. Responders reported improvement in several aspects of daily life including energy, memory, mental performance, social performance and seizure frequency. The improvement of quality of life was beyond the extent that could be caused by reduction of seizure frequency alone. We have also reported on improvement of quality of life in patients with intractable epilepsy who had VNS [29]. 16 patients had VNS at our center (11 children and 5 adults) at the time of the study. The quality of life was compared pre and post VNS. There was a significant improvement in

the social domain and in total quality of life at a mean of 1.26 years post VNS.

### **Side effects and complications**

The side effects are usually mild and transient. These may be divided into acute and chronic. Among the acute complications are: wound infection (3-6%), left vocal cord palsy (1%), lower facial palsy (related to surgical incision placement), and very rarely bradycardia/asystole when the VNS device was turned on immediately after implantation [30]. Currently, it is advised to turn it on 2 weeks after implantation.

As for the chronic side effects, these are usually mild and related to the activation of the pharynx and larynx [30]. Hoarseness, hypophonia, and coughing due to activation of recurrent laryngeal nerve and superior laryngeal nerve are commonly seen and usually abate with time and may be reduced by adjusting the settings. There are other rare and reported complications such as laryngo-pharyngeal dysfunction due to vocal cord palsy, jaw pain, headache, abdominal pain, and even chronic diarrhea [31,32]. The hypoglossal nerve and the phrenic nerve are in close vicinity to the mid-cervical part of the vagus. High current output can lead to diaphragm left hemiparalysis or paresis and hemiparetic tongue. Horner syndrome may also be caused by injury to the sympathetic trunk located deep and posterior to the vagus nerve.

### **Conclusion**

Vagus nerve stimulation is a palliative but proven surgery for patients with intractable epilepsy who are not candidates for epilepsy surgery. It affords an acceptable mean seizure reduction that improves with time, with minimal side effects. It is well tolerated for both the pediatric and adult population, and has become an important part of our armamentarium in the treatment of drug-resistant epilepsy.

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