THE EFFECTS OF VAGAL NERVE STIMULATION THERAPY IN REFRACTORY EPILEPSY ON THE ELECTRICAL ACTIVITY OF THE HEART

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Abstract:

Background:
Refractory epilepsy is a major problem for neurologists and epileptic patients. Vagal nerve stimulation is one of the palliative surgical therapies. Traditionally, the vagus nerve has been considered a parasympathetic efferent nerve (controlling and regulating autonomic functions, such as heart rate and gastric tone). Changes in autonomic nervous system activity affect both depolarization and repolarization phases in addition to heart rate, and thus affect QT interval.

Objective:
To evaluate the possible side effect of vagal nerve stimulation therapy on the electrical activity of the heart represented by QT, QTp, TpTe intervals and QT&QTp dispersions.

Patients and method:
This study was conducted at Neurosciences hospital in Baghdad, between September 2008 and March 2010. ECG traces were recorded for 32 pharmacoresistance epileptic patients with a mean age 21.14 ± 4.4 years, just before and after implantation of the Vagal nerve stimulation device. All QT, QTp and TpTe intervals and QT & QTp dispersion were calculated manually.

Results:
There were a differences in both QT and QTp before VNS implantation as compared to that after the implant but it did not reach a significant level. Similarly no significant differences were observed in QT and QTp dispersions. An interesting significant differences in TpTe (before and after the implant) were observed.

Conclusion:
Vagal nerve stimulation therapy may alter the cardiac conductivity in some cases.

Key words: Vagal nerve stimulation, refractory epilepsy, QT, QTp, TpTe intervals and dispersion.
Introduction

Approximately one-third of patients with epilepsy continue to have seizures on medication (1). Their seizures are referred to as refractory or drug-resistant. In those with refractory epilepsy, a combination of antiseizure medications may be tried. The combination may help to reduce the total number of seizures. However, polypharmacy often leads to an increased number of side effects. When medications are not enough to control seizures, physicians often turn to nonpharmacologic options: epilepsy surgery, ketogenic diet, and vagus nerve stimulator (VNS) therapy.

The VNS Therapy System was approved as adjunctive therapy for adults and adolescents over 12 years of age whose partial-onset seizures were refractory to antiepileptic drugs. The vagus nerve stimulator (VNS) is a battery-powered device similar to a cardiac pacemaker. Stimulating leads are surgically placed around the left vagus nerve in the carotid sheath and are connected to an infraclavicular subcutaneous programmable pacemaker.

For better understanding of the clinical use & side effect of the VNS; a brief introduction of relevant anatomy, possible mechanisms of action is required.

Anatomy

The idea of using the vagus nerve in particular stem out of its unique anatomy. It is widely distributed to both sides of the brain and brain stem structures. The majority of vagus nerve fibers 80% are afferent (sending signal towards the brain) rather than efferent 20% (sending signal away from the brain) (2).

If an electrical stimulus is placed on the vagus nerve, 80 percent of the applied stimulation travels back to the brainstem where the vagus nerve originates. The central projections of the vagus nerve (cranial nerve 10) synapse bilaterally on the nucleus of the solitary tract (NTS) in the brainstem. From the NTS, vagal afferent pathways project to many regions in the brain, including pontine and midbrain nuclei, the cerebellum, thalamus, and cortex. In
short, electrical impulses, which are applied to one of the vagus nerves, travel to both sides of the brain, and to many disparate regions.

One vagal pathway, perhaps of particular relevance to epilepsy therapy, ascends to the forebrain via the pontine parabrachial nucleus (3). This pathway transmits sensations of visceral origin to the ventroposterior parvocellular nucleus of the thalamus, which then projects to the insular cortex (4). The parabrachial nucleus also projects to other thalamic nuclei, the amygdala, and the basal forebrain. These vagal projections travel to sites that are often found to generate seizures. One way VNS may work is through connections with the seizure generating region.

Another way in which VNS may operate is through the locus coeruleus. The locus coeruleus is another pontine nucleus that receives afferents from the NTS (5,6). While receiving less dense vagal input than the parabrachial nucleus, the locus coeruleus may be essential to the antiepileptic effect of VNS, as suggested by animal studies using ablative and immunolabeling procedures.

Vagal efferent fibers originate in the dorsal motor nucleus of the vagus and the nucleus ambiguous.

These innervate the heart, vocal cords, and other laryngeal and pharyngeal muscles, and also provide parasympathetic input to the gastrointestinal viscera (2).

Because the right vagus nerve provides more innervations to the cardiac atria than the left vagus nerve (7), electrical stimulation of the left vagus nerve is generally used in clinical practice to avoid adverse cardiac effects.

**Therapeutic mechanism**

Epilepsy is defined clinically as a state of chronic recurrent seizure; the cause may be known (symptomatic epilepsy) or unknown (idiopathic or cryptogenic epilepsy). Seizure is an abnormal paroxysmal cortical cerebral activity due to hypersynchronous discharge of a group of cortical cerebral cells.
In the 1960s, studies in animals showed that repetitive vagus nerve stimulation (VNS) would either synchronize or desynchronize cortical electrical activity. The effect of stimulation on brain activity depended on the stimulus frequency and the strength of the electrical current. Because epileptic seizures are characterized by hypersynchronized cortical activity, the observation that VNS can desynchronize cortical rhythms suggested a potential antiepileptic effect of VNS (8-10).

VNS studies in a variety of animal models were then undertaken and have demonstrated that VNS has multiple antiepileptic properties (1-18):

- VNS can abort an ongoing seizure after seizure onset
- VNS is effective in acute seizure prophylaxis; ie, seizure-inducing insults (eg, strychnine administration) are less effective in inducing a seizure in the presence of VNS

- VNS is effective in chronic seizure prophylaxis, reducing seizure frequency in animal models of epilepsy
- VNS can inhibit epileptogenesis in animal models of seizure kindling

How VNS exerts its antiseizure properties exactly remains unclear.

Clinical application

In general, VNS is considered a valid treatment option for children and adults with well-documented medically-refractory seizures, who are either opposed to intracranial surgery, are not candidates, or whose medically-refractory seizures were not substantially improved by prior intracranial epilepsy surgery (19-23). Resective surgery for appropriate candidates is preferred over VNS because of the substantially greater potential for complete seizure remission

SAFETY AND TOLERABILITY

Common side effects — side effects that occurred in at least 5 percent of patients receiving high-stimulation vagus nerve stimulation (VNS) were(66):
• Hoarseness (37 percent)
• Throat pain (11 percent)
• Coughing (7 percent)
• Shortness of breath (6 percent)
• Tingling (6 percent)
• Muscle pain (6 percent)

Hoarseness was the only side effect that occurred significantly more often with high stimulation than with low stimulation.

Shortness of breath and pharyngitis, as well as voice alteration, occurred significantly more often in the high-stimulation group than in the low-stimulation group. Lowering the pulse width of stimulation can alleviate symptoms and allow for higher stimulation intensities. Lowering the frequency can also attenuate side effects related to VNS stimulation (26).

**Cardiac events** — Physiologic studies have generally found no clinically relevant effects of chronic VNS on cardiorespiratory function (28-30). However, bradycardia followed by transient asystole lasting up to 45 seconds has been reported in association with the lead test conducted during VNS implantation (the initial lead test, which is performed in the operating room when the VNS is being implanted for the first time) in approximately 0.1 percent of cases (31-33). Complete heart block due to atrioventricular nodal block was documented in three patients with no reported adverse effects (34). In some cases, a rechallenge stimulus is uneventful, and the VNS has been implanted successfully without adverse consequences. More often, the procedure is aborted. In general, baseline cardiac conduction disorders are considered a contraindication to VNS. Two case reports describe VNS-induced episodes of bradycardia and asystole occurring 2 and 9 years after device implantation (35-36).
Other adverse effects

- Surgical complications.
- Electrode failure and lead fracture (37-40).
- Infection of the subcutaneous pocket that holds the VNS generator, usually with Staphylococcus aureus (24,41-43),
- Sleep apnea is a relative contraindication for VNS (44-46). VNS is associated with more frequent apnea and hypopnea episodes in sleep, but this appears clinically relevant only in those with preexisting sleep apnea.
  - Unilateral vocal cord paralysis occurs in about 1 percent of cases, and is attributed to intraoperative manipulation of the recurrent laryngeal nerve. Most of these recover (24, 25, 27).
- Other cranial nerve palsies that can complicate VNS implant include Horner's syndrome and facial paralysis (47).
- Pneumothorax has been described in at least one patient (24).
- Some patients experience uncomfortable spasm of the left chest wall, which has been demonstrated to be due to collateral spread of stimulation to phrenic nerve, causing contraction of the left hemidiaphragm.
- Contraction of the left anterior sternocleidomastoid muscle may also occur as a result of current stimulating adjacent structures (48). These symptoms are often precipitated by assumption of certain postures or movement and are relieved by changing position.
- While gastrointestinal side effects might be expected with VNS, reports of this are infrequent.
- Forced normalization refers to a phenomenon of psychiatric disturbances that emerge in some patients with long-standing, high-frequency seizures when their seizures are dramatically reduced (49-50).
References


