Vagal Nerve Stimulation for Nonneurological Diseases: An Overview

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Abstract

Vagal nerve stimulation (VNS) is US Food and Drug Administration approved treatment for drug refractory epilepsy and major depression. In vivo research showed that VNS has anti-inflammatory properties and has a role in inflammatory conditions such as inflammatory bowel disease, rheumatoid arthritis, sepsis, lung and bowel injuries, and in patients with head injury. It is also shown that VNS can restore the homeostasis between the sympathetic and parasympathetic systems. This property is made use of in heart failure, angina, and peripheral arterial disease. Cluster headache and migraine are the other conditions. In this review, we describe the indications along with the mechanisms in various clinical conditions other than epilepsy and the associated outcomes.

Keywords

- angina
- heart failure
- inflammatory bowel disease
- peripheral arterial disease
- rheumatoid arthritis
- sepsis

Introduction

The vagal nerve plays a key role as an interface between the central nervous system and the autonomic centers in the brain stem. It provides an extensive network of input and output for major viscera such as cardiovascular system, lungs, and gut and modulates their autonomic functions. The role of vagal nerve stimulation (VNS) in the treatment of drug refractory epilepsy (DRE) has been extensively studied and has received US Food and Drug Administration (FDA) approval for the same.[1,2] Recent studies have shown that VNS has anti-inflammatory properties.[3-5] VNS has also shown to have various other effects such as improvement in alertness, consciousness, and psychomotor activity. VNS has been approved for treatment-resistant depression in patients of ≥ 18 years of age.[6] Stimulation of vagal nerve demonstrated anti-inflammatory properties and VNS is being explored in various chronic inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, lung injury, and fibromyalgia.[3-5]

In the current article, we enumerated the mechanisms of VNS, its use in various conditions other than epilepsy, and their outcomes.

Background

James L. Corning (1880s) for the first time stimulated the vagus nerve to abort a seizure attack.[7] Consequently, in 1949, MacLean stimulated vagus nerve in monkeys and elucidated slow waves from frontal lobes. It was only after Zabara (1985), who showed anticonvulsive effects of VNS in dogs, that the use of VNS gained momentum. First human pilot study was conducted by Penry and Dean (1988) in four patients. The study reported complete resolution of

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seizure in two patients, 40% reduction in seizure frequency, and no change in each of the remaining patients. The FDA approved VNS for epilepsy in humans in 1997 for patients above 12 years of age and in 2017 it is extended to children of 4 years of age and above. More than 1,00,000 VNS devices have been implanted worldwide by 2018.

Mechanism of Action of Vagal Nerve Stimulation

Vagal nerve is the longest cranial nerve, has complex functions, and consists of ~80% afferent and ~20% efferent fibers. The vagus nerve fibers are categorized into four types on the basis of function and tracts: special visceral efferent, general visceral afferent, general somatic afferent, and general visceral afferent fibers. The special visceral efferent fibers supply muscle of palate, pharynx, larynx, and upper esophagus. General visceral efferent fibers originate from dorsal median nucleus and end in synapse in end organs such as lungs, heart, and gut and are implicated in VNS-mediated effects in inflammatory bowel disease, heart failure, diabetes mellitus, etc. The somatic afferent fibers from pharynx, posterior fossa meninges, and external auditory meatus synapse in spinal trigeminal nucleus and these afferent fibers are stimulated in noninvasive VNS (nVNS) to treat headache and migraine. General visceral afferent fibers carry information from chemo- and baro-receptors of aortic arch and general visceral information from heart, lungs, and digestive system. These fibers project to nucleus of the tractus solitarius (NTS) and influence central functions through brain stem. The mechanisms of action of VNS in various indications are illustrated in ►**Fig. 1**.

1. **Depression:** Anecdotal observation of mood elevation in patients with DRE following VNS led to prospective study on the effects of VNS in these epileptic patients. VNS can induce synchronization of fronto-orbital activity on electroencephalography and also induce frontal slow waves (a marker of electroconvulsive therapy [ECT]). Recent neurochemical studies suggested that chronic VNS is associated with elevation of serotonin metabolite 5-hydroxyindolacetic acid and gamma aminobutyric acid (GABA) levels. These two effects of VNS are thought to have a role in the treatment of treatment-resistant depression.
2. **Chronic pain:** Various local anesthetic studies concluded that NTS, raphe nucleus, locus coeruleus, and periaqueductal gray matter may play a role in VNS-related pain modulation. VNS seems to affect "pain network" that includes thalamus and hypothalamus. Elevated brain neurotransmitters such as serotonin, opioids, and GABA play a role in mood and pain modulation. In additions to this, *indirect* activation of paraventricular nucleus through vagal afferents results in increased release of adrenaline and corticosteroid from adrenals and mediate antinociceptive and anti-inflammatory effects.
3. **Headache:** The occurrence of headaches is hypothesized to be arising as a result of two mechanisms. The peripheral mechanisms include vascular theory, histamine theory, and trigeminal nerve activation. However, these theories failed to explain the associated autonomic features as well as the cyclical occurrence of cluster headaches. The central mechanisms have been implicated in the causation of the headaches, based on the neurochemical and imaging studies. Cyclical and seasonal occurrence of cluster headaches along with the associated autonomic features have paved the way to consider hypothalamus as a central generator. This has been demonstrated with functional magnetic resonance imaging and positron emission tomography studies, especially of the posterior hypothalamus and the trigeminal system. Reduction in glutamate levels and direct inhibition of caudal trigeminal nucleus by vagal afferent fibers cause modulation of hypothalamic activity, resulting in long-lasting alleviation of pain associated with headache syndromes.
4. **Rheumatoid arthritis, sepsis, and inflammatory bowel disease:** VNS produces anti-inflammatory effect through two pathways: hypothalamic-pituitary-adrenal (HPA) axis pathway and vagal anti-inflammatory pathway. Vagal stimulation increases serum adrenocorticotropic hormone and cortisol levels through the HPA axis thereby inhibiting the production of proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α). The other pathway involves activation of splanchnic nerves that produce norepinephrine in the vicinity of choline acetyltransferase positive T-cells. The acetyl choline thus produced is inhibitory to the macrophages with consequent reduction in the cytokine production, contributing to reduction in the systemic and synovial inflammation.
5. **Heart failure:** Multiple mechanisms are likely to be involved in the beneficial effects of VNS in heart failure: first, the antiadrenergic effects by decreasing the sympathetic efferents; secondly, by increasing intracellular cyclic adenosine monophosphate levels through muscarinic M2 and M3 receptors; and lastly, by decreasing the renin-angiotensin system. The end result is release of nitric oxide (NO) at cardiac level.
6. **Consciousness:** Altered consciousness following traumatic brain injury (TBI) is caused by impaired forebrain arousal inputs from thalamus and brain stem. VNS alters

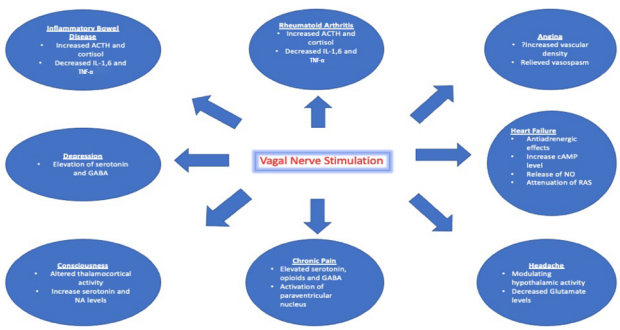

Fig. 1 Mechanisms of actions of vagal nerve stimulation. ACTH, adrenocorticotropic hormone; IL-1, interleukin-1; NO, nitric oxide; RAS, renin-angiotensin system; TNF-α, tumor necrosis factor-α.

the thalamocortical circuitry, and increases serotonin and norepinephrine levels.

7. **Angina Pectoris:** The anginal pain is secondary to the mismatch between the supply and the demand, owing to the microcirculatory vasospasm of neural origin. Histological studies concluded that VNS did not improve angiogenesis. The antianginal symptoms of VNS are due to dilation of constricted micro vessels either by endothelium-dependent mechanism (NO Release) or reduction in release of norepinephrine.
8. **Peripheral vascular disease:** Various studies proved that VNS can increase walking distance in patients with peripheral arterial occlusive disease with claudication. Possible effects of VNS are mediated through endothelium-derived NO and anti-inflammatory effects by reducing IL-1, IL-6, and TNF-α.

Types of VNS Devices

VNS devices have undergone substantial modifications with time. Currently, it is available as: implantable (invasive) and transcutaneous (noninvasive) devices. Implantable VNS is approved for the treatment of DRE and depression.

Implantable VNS: Implantable VNS requires placement of stimulator electrode around cervical part of vagus nerve and an implantable pulse generator in the anterior chest wall. Along with epilepsy and depression, it has proven efficacy in cluster headache, refractory migraine, heart failure, and Alzheimer's disease. Although safe, it is associated with adverse events related to either surgical implantation or as a part of stimulation. The implantation-related adverse events include: infection (3–6%), vocal cord palsy (1%), lower facial weakness, and bradycardia. The stimulation-related adverse events include: change in voice, asystole, cough, dyspnea, headache, and pain. These are usually stimulation dependent and often subside with time, rarely necessitating explantation.

Noninvasive VNS: Stimulation of the cervical vagus nerve and its auricular branch can be achieved transcutaneously. These devices are devoid of the surgery-related complications and also are cheaper compared with the implantable device. Stimulation-related complications can be lowered by adjusting the stimulation parameters, as per the tolerability and efficacy of the patient. Minor local discomfort, mild irritation, and pain can occur with these devices.

The indications of VNS have grown from treating only DRE to various other nonneurological disorders over time. The following section will be describing the varied diseases benefitting from VNS (►**Fig. 2**).

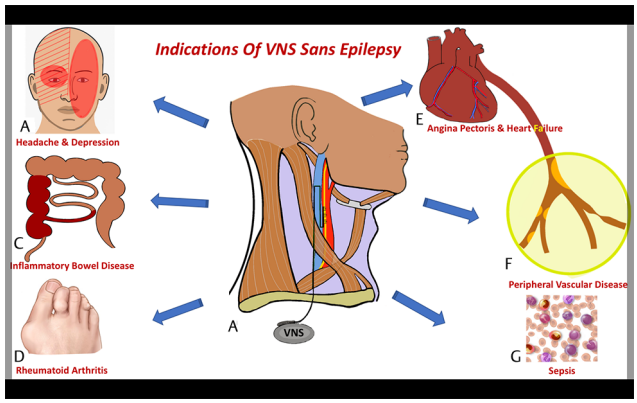

Fig. 2 Artistic representation. (**A**) Implanted vagal nerve stimulation (VNS) device with battery. (**B**) VNS is approved by the US Food and Drug Administration for depression, and for off-label use for migraine and cluster headaches, short-lasting unilateral neuralgiform headaches with conjunctival injection with tearing, and paroxysmal hemicrania continua. (**C**) Treatment of medically refractory inflammatory bowel disease (Crohn's disease). (**D**) Rheumatoid arthritis picture depicting foot deformity of Hallux valgus, hammer toe, and nodule. (**E**) Used in the treatment of both pre- (Canadian Cardiovascular Society Class II) and post-revascularization angina; effective in the treatment of New York Heart Association Class II and III heart failure (without appropriate response to medical therapy). (**F**) Fontan stage II and III peripheral vascular disease; the figure depicting atherosclerotic plaques and stenosis involving the iliac arteries. (**G**) Figure representing increased white blood cell counts; VNS restores balance between sympathetic and parasympathetic systems by reducing inflammation, especially Interleukin-6 and tumor necrosis factor-α.

Depression and Other Psychiatric Disorders

Indications

Depression is a psychiatric disorder involving the affect/mood. The FDA approved VNS for treatment-resistant depression in 2005 in patients who are > 18 years of age, with major depression or bipolar I or bipolar II, suffering a major depressive episode of at least 2-year duration, and failed at least two adequate trials of antidepressant drugs. Patients with rapid cycling depression or psychotic depression should be excluded.

Outcomes

The first pilot study comprising 30 patients showed, at the end of 10 weeks of stimulation, that VNS in combination with medical management resulted in response rate of 40% and a remission rate of 17%. The second study involving 60 patients, followed for 12 weeks, showed a response rate of 30% and remission rate (defined as 28-item Hamilton Depression Rating Scale score <10) of 15%. Patients who had never received ECT responded by a factor of four with VNS than who had received ECT (adjunctive VNS) prior to VNS implantation. None of the patients who failed more than seven antidepressant trials responded to VNS when compared with 39% response rate in other patients. In a multicenter controlled trial of VNS involving 225 patients with 1-year follow-up, it was concluded that VNS as an adjunctive measure resulted in response rates of 46% and remission rate of 29%. A recent meta-analysis of 22 studies concluded that adjunctive VNS offers improved benefit and tolerance for treatment-resistant depression over a 2-year period.

Severe obsessive compulsive disorder refractory to medical therapy is another domain were psychosurgery, especially bilateral cingulotomy and anterior capsulotomy, is highly effective. Minimally invasive procedures, like deep brain stimulation and recently robotic-guided radiofrequency ablation of bilateral cingulate gyrus, have been described

with good safety profile and efficacy. VNS has also been tried in this group of patients with significant improvement of depressive symptoms. Similar mood-elevating results have been observed in patients with Parkinson's disease and post-traumatic stress disorder at long-term follow-up.

Chronic Pain

The literature supporting the use of VNS in chronic pain is limited but growing. Trigeminal allodynia, fibromyalgia, and chronic pelvic pain are three main indications for VNS use. Oshinsky et al demonstrated the use of VNS to treat trigeminal neuralgia in a rat model. They demonstrated that increased glutamate levels in trigeminal nucleus caudalis following painful stimuli were significantly reduced with VNS. Five out of 14 patients with fibromyalgia improved significantly at 11-month follow-up. This suggests that VNS tunes down the central sensitization seen in fibromyalgia. In a small series of 15 patients with chronic pelvic pain, nVNS, called the respiratory-gated auricular vagal afferent nerve stimulation treatment, reduced evoked pain intensity and temporal summation of mechanical pain. These findings suggest that VNS has promising effect on hyperalgesia and central sensitization.

Headache Syndromes

The use of VNS in headache came from the observation that positive effect was noticed in migraine in patients with refractory epilepsy implanted with VNS. Similar effect was noticed in patients with VNS for depression. Chronic and episodic cluster headaches, migraine, short-lasting unilateral neuralgiform headaches with conjunctival injection with tearing, and paroxysmal hemicrania are various indications where VNS has been tried.

A novel, noninvasive, portable, and battery-driven device (GammaCore) was designed to stimulate the vagal nerve transcutaneously. In a study including 19 patients with cluster headache, 15 patients reported an overall improvement of 48%. The prophylactic use of nVNS resulted in significant reduction in mean duration of attack from 4.5/24 hours to 2.6/24 hours. The PREVA Study, which was a prospective randomized controlled study, compared standard of care alone versus VNS with standard of care in chronic cluster headache. The study concluded that number of cluster headaches per week was significantly reduced in nVNS patients. Further, it was also noticed that there was a significant reduction in the use of abortive medication as well as significant improvement in the quality of life. Various studies reported that nVNS resulted in ~50% reduction in pain, with 20 to 40% of pain relief observed at 2 hours following the attack.

Rheumatoid Arthritis

The first open-label study, as defined by the American College of Rheumatology/European League Against Rheumatism classification criteria, included patients with: rheumatoid arthritis of at least 6-month duration, involvement of at least four swollen joints, C-reactive protein (CRP) > 7 mg/L, active disease despite treatment with methotrexate at stable dose for 3 months, and the need for the discontinuation of biological disease modifying antirheumatic drugs (DMARDs) for any reason other than response failure.

Koopman et al, in an open-label study, analyzed the effect of VNS in two cohorts: first cohort included patients refractory to methotrexate, and second cohort consisted of patients refractory to multiple biological DMARDs. The study concluded that there was significant improvement in disease activity score based on a 28-joint count and CRP. However, on withdrawal of VNS, active disease escalated rapidly.

Sepsis and Systemic Inflammatory Response Syndrome

Huang et al showed that VNS results in restoring balance between sympathetic and parasympathetic tone and attenuating inflammatory response. Johnson et al showed that short-term stimulation of vagal nerve resulted in significant reduction in IL-6 and TNF-α. Limiting inflammation in neonates and preterm infants is very important as their immune system is immature. However, further studies are needed to establish VNS role in neonates and pediatric patients.

Traumatic Brain and Lung Injury

TBI is associated with systemic inflammation with increased chances of sepsis and multiorgan failure and the resultant poor outcomes. In an experimental study, Bansal et al showed that VNS exerted anti-inflammatory effects by reducing serum TNF-α and ghrelin levels. Regulation of inflammatory factors may have promising therapeutic role in these patients in decreasing acute lung injury and protecting gut barrier.

Heart Failure

VNS was found to be effective in patients with New York Heart Association (NYHA) Class II and III on optimal medical treatment with no change in previous 3 months with left ventricular (LV) ejection fraction < 35 to 40%, presence of sinus rhythm with heart rate of 60 to 130, and capable of performing 6-minute walk test.

In the first CardioFit multicenter study, significant improvements were seen in NYHA Class, 6-minute walk test, LV ejection fraction, and LV systolic volumes. Other ongoing trials include INNOVATE-HF (phase III), NECTAR-HF (phase II), and ANTHEM-HF (phase II). VNS use in heart failure patients may improve functional status and LV function, and reduce risk of arrythmias. However, further studies are required to confirm these results in heart failure.

Inflammatory Bowel Disease

VNS was also found to be effective in patients aged between 18 and 65 years with moderate Crohn's disease activity index of 220 to 450, diagnosed at least 3 months prior, Crohn's disease endoscopic index of severity ≥ 7, CRP > 5 mg/L, and/or fecal calprotectin (FC) > 100 µg/g.

In a 12-month pilot study conducted by Sinniger et al, the effect of VNS was studied in nine patients of Crohn's disease. After 1 year, six patients had endoscopic remission and five patients had clinical remission. CRP and FC were decreased in > 50% of patients. At 1-year follow-up, VNS

restored homeostatic parasympathetic tone and improved inflammatory state of the disease in these patients.

Consciousness

In a report involving a single subject of unresponsive wakefulness syndrome following TBI, it was demonstrated that VNS can reactivate the thalamic-cortical axis for consciousness. Another study showed improvement in coma recovery scale-revised in three out of five patients. Various other animal studies showed that VNS increases the brain-derived neurotrophic factor and thus regulates cerebral plasticity.

Angina Pectoris

In patients with coronary artery disease with Canadian Cardiovascular Society Class IV prior to surgery and patients with anginal pain following revascularization procedure, various studies reported good outcomes following VNS such as improvement in anginal symptoms in preoperative period and postoperative recovery characterized by hemodynamic stability and stable sinus rhythm.

Peripheral Arterial Disease

Patients with Fontane stage II and III can be given a trial of VNS. There is a significant increase in walking distance in 90% patients with peripheral arterial occlusive disease. Patients reported continuing improvements even after 4 weeks. Another study concluded that 60% patients had significant increase in walking distance and total SF-36 scores.

Conclusions

The therapeutic effects of VNS on DRE and treatment-resistant depression are by modulating cerebral networks and chemical homeostasis. VNS has multiple immunomodulatory effects and thus has a promising role in various autoimmune and inflammatory conditions such as: rheumatoid arthritis, inflammatory bowel disease, and chronic pain conditions. The role of VNS is currently a subject of extreme interest in heart failure, leading to multiple ongoing trials. Transcutaneous or nVNS is safe and easy-to-use device with promising results in the murine sepsis. However, further studies in future might benefit these critically ill patients, not responding to the conventional treatment.

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Conflict of Interest
None declared.

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Note: References 8-69 are available online.

