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REVIEW

Cardiovascular autonomic effects of vagus nerve stimulation

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Abstract The vagus nerve is responsible for the parasympathetic innervation of the major thoracic and abdominal organs. It also carries sensory afferent fibres from these viscera and reaches different brain structures. These connections have proven useful in the treatment of different diseases. Afferent stimulation of the left vagus nerve is used to treat epilepsy and major depression, and stimulation of the right vagus nerve is being tried for the treatment of heart failure. The device used for the therapy delivers intermittent stimuli. It is indicated worldwide for the treatment of drug-resistant epilepsy in patients who are not appropriate candidates for respective surgery. It has also received approval for the treatment of major depression, obesity and episodic cluster headache by the Food and Drug Administration. Randomised controlled trials and prospective studies have confirmed the efficacy and safety of this therapy in epilepsy. Nevertheless, sporadic cases of ventricular asystole have been reported. To evaluate the effect of vagus nerve stimulation therapy on the autonomic nervous system, different studies that assess heart function and blood pressure changes have been conducted, although the methods employed were not homogeneous. These studies have found subtle or no significant changes in heart rate variability and blood pressure in epileptic patients. Moreover, this therapy may reduce the risk of one of the most lethal conditions in epilepsy—sudden unexpected death.

Keywords Vagus nerve stimulation · Heart failure · Epilepsy · Autonomic system

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Anatomy of the vagus nerve

The vagus nerve, historically cited as the pneumogastric nerve, is the tenth cranial nerve (CN X) and provides parasympathetic innervation to the heart, lungs and digestive tract. It is the longest nerve of the autonomic nervous system in the human body and runs throughout the neck, thorax and abdomen. The vagus nerve also has sensory, motor and sympathetic function via the peripheral chemoreceptors.

The vagus nerve originates in the medulla and leaves the skull through the jugular foramen. Then it passes inside the carotid sheath throughout the neck between the internal carotid artery and the internal jugular vein and gives off branches to different viscera. All the major thoracic and abdominal organs are innervated by the vagus [1].

The vagus nerve carries mostly afferent but also efferent fibres. The afferent fibres (sensory), which constitute approximately 80% [2], originate in several organs such as the lungs, the heart, the gastrointestinal tract, the aorta and a small area in the concha of the ear, and they project bilaterally to the caudal portion of the medial nucleus of the solitary tract. This nucleus sends fibres to the parabrachial nucleus, the pons, and the respiratory and cardiovascular centres located on the ventral surface of the medulla [3]. Other nuclei in the brainstem, the locus coeruleus and the raphe nuclei, also receive projections. Other connections reach different brain centres, such as the hypothalamus, the amygdala and the thalamus, and thus reach the cortex. At the

cervical level, the afferent component of the vagus nerve is a composite of myelinated A and B fibres and unmyelinated C fibres. The afferent C fibres are the most numerous, accounting for 65–80% of the fibres in the cervical vagal trunk [4, 5]. The efferent fibres provide parasympathetic innervation to the lungs, heart and gastrointestinal tract, and motor innervation to the striated muscles of the larynx and the pharynx. Their cell bodies are located in the nucleus ambiguus and the dorsal motor nucleus, respectively. There is an asymmetrical innervation to the heart, as the left vagus nerve innervates the atrioventricular node and the right vagus nerve the sinoatrial node. When the right vagus nerve was stimulated in dogs, bradycardia was induced in a greater degree [6]. However, in animal models, when hyperstimulated the left vagal branch predisposes the heart to conduction block at the atrioventricular node.

Vagus nerve stimulation therapy

Stimulation of cranial and peripheral nerves has been investigated for the treatment of different diseases, such as chronic pain. Currently, left cervical vagus nerve stimulation (VNS) is an approved therapy for refractory epilepsy worldwide. This therapy also received approval from the Food and Drug Administration (FDA) for treatment-resistant depression. Recently, the FDA also granted approval to an abdominal VNS device for patients with obesity and to transcutaneous stimulation of the right vagus nerve at the neck for episodic cluster headache. Right cervical VNS has been effective in treating heart failure in preclinical studies and a phase II clinical trial. Small open-label studies and case series reports have described the use of VNS for rapid cycling bipolar disorder, treatment-resistant anxiety disorders, Alzheimer's disease and chronic migraine, although none of these uses has been given worldwide approval.

VNS in epilepsy

The vagus nerve stimulator is a device that was approved by the European Medicines Agency (EMA) in 1994 and the FDA in 1997 for the treatment of intractable partial epilepsy in adults and children over 12 years of age [7].

The prevalence of epilepsy is estimated in about 0.5–1% of the population. In addition to the impairment of the quality of life due to the seizures, one of the main problems is sudden unexpected death in epilepsy (SUDEP) [8]. The major risk factor for SUDEP is the occurrence of generalised tonic–clonic seizures (GTCS) [8]. More than 30% of epileptic patients will not achieve seizure freedom after two (or more) tolerated, appropriately chosen and appropriately used antiepileptic drug (AED) regimens; they are considered as suffering from drug-resistant epilepsy (DRE) [9]. VNS is indicated for those patients with DRE not amenable to epilepsy surgery or when surgery has failed. The most widely used neurostimulation therapy is VNS therapy. The possible therapeutic effect of VNS had been studied for more than a hundred years [10].

The VNS device (Cyberonics, Inc., Houston, TX, USA) consists of a pulse generator implanted in the chest and a helical electrode around the cervical portion of the left vagus nerve. This side is chosen to reduce the risk of bradycardia, by avoiding parasympathetic stimulation of the atrial node. The surgical procedure requires dissection of the carotid sheath in the neck and exposure of the vagus nerve [11], where the electrode is placed (Fig. 1). The pulse generator delivers periodic electric impulses to the vagus nerve that generate action potentials by cathodic induction while simultaneously applying asymmetric anodal blocks, activating more afferent than efferent nerve fibres [12]. These pulses propagate through various pathways into the brain in order to reduce seizures (Fig. 2). The electric stimuli may vary in intensity, frequency and duty cycle, i.e. the ratio between stimulation time ("on" period) and inactivation time ("off" period), and they are programmed using a wand connected to a handheld computer system [13]. The usual parameters are shown in Table 1 [13–15]. An extra stimulus may be delivered to prevent a seizure if a handheld magnet is placed over the generator. The latest advancement in VNS therapy, AspireSR®, also monitors for heart rate increases that may be associated with seizures. When a certain change in heart rate occurs, a burst of stimulation is delivered automatically [16]. In exceptional cases, patients who are not suitable for left-sided VNS (L-VNS) may benefit from right-sided VNS (R-VNS) [17, 18]. In a case series, albeit small, patients with right VNS therapy did not suffer from asystole or bradycardia, and the efficacy was quite similar to left-sided stimulation.

Recently, a less invasive VNS therapy has been developed—the transcutaneous VNS (t-VNS). This device

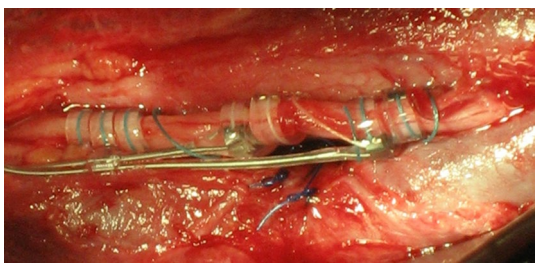

Fig. 1 Lead placement in the cervical vagus nerve during surgery. In the left, the anchor tether is in the most distal part of the lead. The positive anode is in the middle, from where the stimuli spread to the negative anode (right), and in the cranial direction to the brain. (Courtesy of Dr Galbarriatu, Neurosurgery Department, Cruces University Hospital)

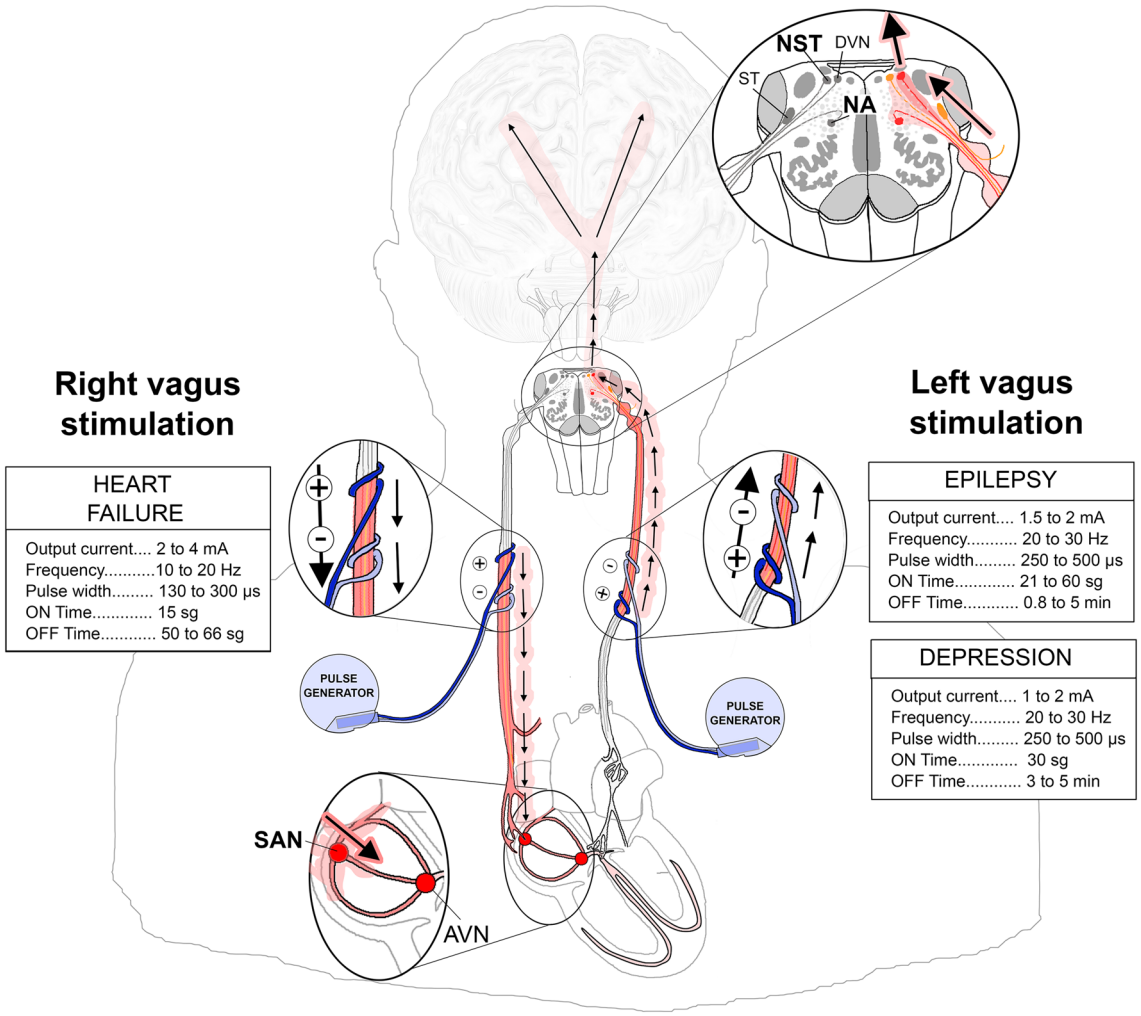

Fig. 2 Schematic view of the mechanism of action of VNS for epilepsy, depression and heart failure. AVN atrioventricular node, DVN dorsal vagus nucleus, NA nucleus ambiguus, NS nucleus solitarius, NST nucleus of the solitary tract, SAN sinoatrial node, ST solitary tract. (Courtesy of Dr Gabilondo, Biocruces Research Institute, Barakado)

Table 1 Parameters of stimulation for VNS therapy in epilepsy and depression

	Initial parameters	Efficacy parameters
Output current (mA)	0.25	1.5–2
Frequency (Hz)	20–30	20–30
Pulse width (µs)	250–500	250–500
On time (s)	30	21–60
Off time (min)	5	0.8–5

(NEMOS®, Cerbomed, Erlangen Germany) stimulates the auricular branch of the vagus nerve with a bipolar electrode attached to the left ear conch [19]. The auricular branch of the vagus nerve supplies sensory innervation to the skin of the ear canal, tragus and auricle. Although pilot studies showed a responder rate up to 50% [20], a randomised, double-blind controlled trial to assess efficacy and safety found a responder rate of about 25–27% [21]. Adverse events were usually mild to moderate, such as headache, ear pain or application site erythema.

Little is understood about exactly how vagal nerve stimulation modulates mood and seizure [22]. The antiepileptic effect seems to be mediated through myelinated fibres, as destruction of C fibres in rats did not reduce the efficacy of the VNS [23]. Proposed mechanisms include alteration of norepinephrine release by projections of the solitary tract to the locus coeruleus, elevated levels of inhibitory GABA related to vagal stimulation and inhibition of aberrant cortical activity by the reticular activating system [24]. Related to these mechanisms, cerebrospinal fluid studies in humans have also shown changes in neurotransmitters and amino acids. An increase in GABA and serotonin metabolite concentrations has been found [25]. Many findings suggest that

the VNS desynchronises the electroencephalogram (EEG), reducing the hypersynchronous cortical state which characterises the seizures [26]. Reduction in interictal epileptiform activity has also been reported. Cerebral blood flow studies have found increased activation in bilateral thalami. The thalamocortical system participates intimately in the generation of generalised seizures and is involved in the synchronisation, propagation and secondary generalisation of focal seizures as well. The action of VNS may involve enhancement of the antiseizure activity of the thalamocortical neurons.

The efficacy of VNS in the treatment of drug-resistant epilepsy has been established in pivotal trials [27, 28], long-term studies [29, 30] and daily clinical practice [31–33]. As VNS is a palliative surgical procedure, a new scale [34] considers a favourable outcome to be if seizure frequency is reduced by half or more. According to different series, the mean seizure reduction ranges from 24.5% to 58%, and the responder rate ranges from 23.4% to 63.8% (Table 2) [35–38], including in some studies of children under 12 years of age. Sustained efficacy in seizure control has also been demonstrated [39, 40]. Some small series and case reports have also shown efficacy in controlling status epilepticus [41–43]. Moreover, the results of a large long-term study suggest that patients with DRE treated with VNS have a reduced risk of SUDEP [44].

Regarding safety, adverse events may be due to the surgical procedure or to the normal functioning of the VNS. The main perioperative complications are infections, vocal cord palsy and infections [29, 30, 34]. Bradycardia and asystole have been reported during lead tests performed during implantation of the device [45, 46]. A plausible mechanism may be vagal nerve traction or injury. Other potential mechanisms are stimulation of cervical cardiac branches of the vagus nerve either by collateral current spread or directly by inadvertent placement of the electrodes on one of these branches; improper plugging of the electrodes into the pulse generator, resulting in erratic varying intensity of stimulation; or reverse polarity.

Out of the immediate postoperative period, the adverse effects are usually related to the stimuli, such as coughing, throat pain and hoarseness, and shortness of breath [30, 33, 34]. Nevertheless, central nervous system adverse effects usually associated with AEDs, such as dizziness, cognitive impairment or behaviour impairment, have not been described. Isolated cases of late-onset bradycardia and asystole have been reported, but no clear explanation can be found [47–51].

VNS in depression

Anecdotal clinical observations of mood improvement in epilepsy patients, even in the absence of better control of seizures after VNS implantation, led to a pilot prospective study of the effects of VNS on mood in epilepsy patients, treated either with the VNS device or AEDs [52, 53]. The mechanism of action in depression has not been fully determined either. An enhancement of some neurotransmitters, such as the serotonergic and dopaminergic system, were seen after chronic stimulation with VNS. Another hypothesis is that VNS promotes neuroplasticity in the hippocampus. A recent study demonstrated that the locus coeruleus plays a key role in the antidepressant effect, through noradrenergic enhancement [54]. An acute, randomised, controlled, masked trial which compared active VNS with sham treatment did not find definitive evidence of the efficacy of VNS in the treatment of depression [55]. Previously, an open study including 30 patients indicated VNS efficacy in patients with treatment-resistant major depressive disorder [56]. It was approved by the FDA for the treatment of severe, recurrent unipolar and bipolar depression in July 2005, but has not yet been approved by the EMA.

Table 2 Outcomes in different series of VNS therapy

Series	Design	Patients	Age	≥ 50% seizure reduction	Seizure free
The Vagus Nerve Stimulation Study Group [27]	Randomised controlled trial	114	Children/adults	31%	NA
Handforth et al. [28]	Randomised controlled trial	198	Children/adults	23.4%	NA
DeGiorgio et al. [30]	Prospective	195	Children/adults	35%	NA
Helmers et al. [35]	Retrospective	125	Children	51%	0%
Vonck et al. [36]	Prospective	118	Children/adults	51%	NA
De Herdt et al. [31]	Retrospective	138	Children/adults	59%	9%
Elliott et al. [32, 39]	Retrospective	436	Children/adults	63.8%	7.5%
Ryvlin et al. [38]	Open prospective randomised	48	Adults	32%	NA
Galbarriatu et al. [33]	Retrospective	59	Children/adults	34.8%	0%
Fernandez et al. [37]	Retrospective	17	Children < 3 years old	33% improved	0%

NA not assessed

VNS in obesity

In 2015 the FDA approved the use of intermittent intra-abdominal vagal blockade as a less invasive alternative to standard bariatric surgery for patients suffering from moderate to severe obesity. The device (Maestro Rechargeable System®) consists of two leads placed around the anterior and posterior vagal trunks near the gastroesophageal junction using laparoscopic surgery and a pulse generator placed subcutaneously on the thoracic wall. It delivers intermittent charges with an amplitude ranging between 6 and 8 mA for at least 12 h per day. The ReCharge trial included 239 patients with a body mass index (BMI) of 35 or greater and compared 162 patients with active blockade versus a control group of 77 patients with a sham device [57]. The study found that after 12 months, the active group lost 8.5% more of its excess weight than the control group. Although it did not achieve the desired endpoint of 10% of excess weight loss, a low rate of serious adverse events was found. A previous trial (EMPOWER) had not found significant differences regarding weight loss but demonstrated the safety of the device. An extension open label study was performed [58] and found sustained weight loss.

VNS in cluster headache

Different devices that stimulate cranial nerves have been developed with the aim of treating a variety of primary headaches. Concerning the vagus nerve, as migraine improvement in patients receiving VNS therapy for epilepsy was suggested, this nerve became a target for headache treatment. The cluster headache (CH) is the most prevalent trigeminal autonomic cephalalgia, with strong parasympathetic activation during attacks. The inhibition of pain by VNS is presumably mediated by inhibition of vagal afferents to the nucleus caudalis of the spinal trigeminal nucleus and by modulation of inhibitory neurotransmitter release. In 2012, a prospective, multicentre, open-label, randomised, controlled, parallel-group study (PREVA study) [59] evaluated the efficacy of a non-invasive VNS therapy (gammaCore®) as adjunctive prophylactic therapy for CH attacks in patients with chronic CH. The device was applied over the right side the neck twice daily, in a series of three consecutive 2-min stimulations. It showed a mean reduction of 3.9 attacks per week, with statistical significance. A year later, a randomised, double-blind, sham-controlled prospective study (ACT1) was performed [60]. Patients with chronic and episodic CH were included. Subjects administered the three consecutive stimulations at the onset of premonitory symptoms or pain. Response was defined as pain relief 15 min after treatment initiation for the first CH attack without rescue medication use through 60 min. The response rate was significantly higher in patients with episodic CH with active VNS than in patients with a sham device, but the same response was not achieved for those with chronic CH. This response in episodic CH was confirmed in another prospective randomised study (ACT2). Thus, the FDA released the use of gammaCore® for the acute treatment of pain associated with episodic CH in adult patients.

VNS in heart failure

Another pathological condition in which VNS therapy is being studied is heart failure. However, no official approval has been granted yet. The rationale for this is the imbalance in the autonomic function, with an increase in sympathetic activity and a reduction in parasympathetic when heart failure occurs [61]. The reduction of parasympathetic tone increases the risk of life-threatening arrhythmias and contributes to ventricular remodelling. Thus, VNS tries to equilibrate this imbalance. Three different devices have been developed: (1) Precision, Boston Scientific Corporation©, St. Paul, MN, USA; (2) CardioFit, BioControl Medical Ltd©, Yehud, Israel; (3) Cyberonics IPG: Model 103 Cyberonics©, Houston, TX, USA. The functioning and placement are rather different from those applied in epilepsy. First, the pulse helical electrode is placed in the right vagus nerve. The generator delivers the electrical pulses, with a preset delay from the R wave. Another difference is that the pulses head in an afferent way to the heart, instead of to the brain. The parameters also vary from those used for epilepsy. When the heart rate drops below a programmed threshold, stimulation is interrupted. To assess efficacy and safety in patients with heart failure, an open label study in a small series of 32 patients with heart failure was performed [62]. As it suggested favourable outcomes, a randomised trial, the NECTAR-HF (NEuralCardiac TherApy foR Heart Failure), started in 2011 [63]. The recommended stimulation parameters were a frequency of 20 Hz and a pulse width of 300 µs with an activity period of 10 s and an inactivity period of 50 s. The output current was the maximum tolerated or the maximum allowed (4 mA). The primary end point was the change in left ventricular end-systolic diameter (LVESD) at 6 months and secondary endpoints were other echocardiography measurements, quality-of-life assessments and other biomarkers. Ninety-six patients were randomised, in a 2:1 ratio for the VNS therapy versus patients with VNS implanted but inactivated. It failed to demonstrate a significant effect on primary and secondary endpoint measures of cardiac remodelling and functional capacity in symptomatic heart failure patients, but quality-of-life measures showed significant improvement. Another open-label multicentre study, Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF), was carried out between 2012 and 2013 to assess safety, tolerability, and efficacy [64]. This study compared VNS therapy

for heart failure stimulating either the left vagus or right vagus nerve in a 1:1 ratio. Sixty patients were randomised, 30 for each arm. In the overall combined cohort, there was significant improvement in Left Ventricular Ejection Fraction; but LVESD did not achieve statistically significant improvement. All subjective efficacy measures showed statistical improvement. Right-sided VNS obtained better results, but the differences were not statistically significant. After 12 months the improvement was maintained [65]. They also found that a subtle, beat-to-beat fluctuation in the morphology and amplitude of the ST segment or T wave in the electrocardiogram (ECG), which has been considered a biomarker of life-threatening arrhythmias named T wave alternans, was reduced in patients treated with VNS [66]. However, the INNOVATE-HF trial (Increase of Vagal Tone in Heart Failure), which included 707 patients, did not show such efficacy [67]. In this trial, 436 patients and 271 controls were compared. The estimated annual mortality rates were 9.3% in the active therapy group and 7.1% in the controls. However, quality of life, New York Heart Association functional class and 6-min walking distance improved, but the LVESD index did not. One recent study performed on guinea pigs showed that chronic VNS may preserve ventricular function after myocardial infarction by mitigating the remodelling of the intrinsic nervous system and the tissue innervated by it [68].

The adverse events reported in the series are mostly the same as those described during epilepsy treatment [63, 65, 67]. Severe device-induced bradycardia is very rare, owing to the stimulation interruption when the heart rate drops.

VNS effect on the autonomic nervous system in epileptic patients

The main indication for VNS therapy is refractory epilepsy. Epileptic seizures, especially GTCS, or the AEDs may affect the autonomic nervous function [69]. One study found differences in heart repolarisation between complex partial seizures (CPS) and secondarily GTCS [70]. For instance, sympathetic tone tends to be increased, whereas parasympathetic tone appears to be decreased in chronic epilepsy, ultimately leading to depressed heart rate variability (HRV). GTCS can also severely impair ventricular contractility in the absence of coronary pathology. This stress-induced cardiomyopathy (which is also known as Takotsubo cardiomyopathy) can dramatically decrease cardiac output, thereby leading to a cardiogenic shock. T wave alternans, which has been considered a biomarker of risk for suffering from sudden death in patients with heart disease, has also been shown to be more frequent after secondary GTCS.

More than 80,000 people have received VNS worldwide. The intimate relationship between VNS and the autonomic system may theoretically cause a disturbance in the heart function or the control of blood pressure (BP). Some series report diverse changes in heart function and BP control, but the methodology in each study is different (Table 3).

Prior to VNS approval for epilepsy, Kamath et al. studied the effect of vagal electrostimulation in HRV in eight patients [71]. They compared four patients with a high stimulation schedule (30 Hz frequency and 500 μs pulse) with four more subjects with low stimulation (2 Hz and 130 μs). Continuous ECG was assessed before and 15 days after surgical implantation. They found no presurgical differences between the groups in HRV variables. In the low stimulation group, no significant change was found in cardiac parameters, namely heart rate, high frequency peak power (HF)

Table 3 Studies assessing effects of VNS therapy in the autonomic system

Series	Design	Patients	Controls	Cardiac function assessment	Blood pressure assessment
Setty et al. [72]	Cross-sectional	10	No	Yes	No
Frei and Osorio [73]	Cross-sectional	5	No	Yes	No
Galli et al. [74]	Prospective	7	Patients before implantation	Yes	No
Ronkainen et al. [75]	Prospective	14	Patients before implantation Healthy controls	Yes	No
Stemper et al. [76]	Cross-sectional	21	No On/off periods	Yes	Yes
Zaaimi et al. [77, 78]	Cross-sectional	10	No On/off periods	Yes	No
Cadeddu et al. [79]	Prospective	10	Patients before implantation	Yes	Yes
Garamendi et al. [82]	Prospective	15	Patients before implantation	Yes	Yes
	Cross-sectional	14	On/off periods		

or low frequency/high frequency (LF/HF) ratios. On the contrary, when a high stimulation schedule was used, the LF/HF peak power ratio decreased, and patients showed a significantly higher HF compared to those with low stimulation. Thus, an increased parasympathetic cardiac tone was suggested.

In 1998, Setty et al. performed a study centred on the effect of VNS on cardiac function in humans [72]. They selected ten patients who were participating in the open-label continuation study (Cyberonics XE5 protocol). Some VNS parameters were fixed: frequency of 30 Hz, pulse width of 750 μs, on-time of 30 s and off-time of 5 min. The output current was set at the maximum tolerable level for a minimum of 1 month prior to the study. Heart rate changes were studied using prolonged ECG. A 7-min baseline segment was obtained with the pulse generator inactivated. Then the stimulator was activated for five 30-s stimulation periods for a total continuous stimulation period of 2.5 min. It is followed by a vagal nerve post-stimulation period in which the stimulator was again inactivated for 7 min. They found no significant changes in RR intervals (RRI), the total power or the low frequency (LF) and high frequency (HF) bands with stimulation of the left vagus nerve. So, they concluded that left vagal nerve stimulation has little acute effect on cardiac rhythm or heart period variability.

Frei and Osorio [73] studied five patients who had VNS implanted and had not obtained benefit from this therapy. They performed prolonged ECG (mean 45.6 h per subject) in order to study changes in the heart rate and its variability. They found that VNS had a complex chronotropic effect with appreciable interindividual variability. In some patients they found bradycardia and in others tachycardia followed by bradycardia. HRV was either increased or decreased depending on the subject and on the stimulation parameters.

Galli et al. evaluated the cardiac vagal tone in patients chronically treated with VNS by carrying out 24-h electrocardiography monitoring before the device implantation, 1 month and 36 months after VNS therapy onset [74]. Analysis of RRI variability was performed. They did not observe significant changes in the mean values of the following spectral parameters: total power, very low frequency (VLF), LF, HF and LF/HF ratio. However, they found a reduction of the HF component of the spectrum during the night and a flattening of sympathovagal circadian changes, not inducing, however, clinically relevant cardiac side effects after long-term VNS. The responder rate was 57.1% (4 out of 7), and one of them was seizure free.

The study reported by Ronkainen et al. included 14 patients with refractory epilepsy who underwent VNS implantation, and 28 healthy sex- and age-matched controls, in which a 24-h ECG was performed [75]. Patients who underwent VNS therapy were evaluated before and 1 year after implantation. No significant changes in HRV were found between the basal and the 1-year evaluations. However, in patients with refractory epilepsy, even before the VNS implantation, the mean value of the RRI, standard deviation of NN intervals (SDNN), VLF, LF and HF spectral components of HRV, and the Poincaré components SD(1) and SD(2) were significantly lower than those of the control subjects before VNS implantation. In the same way, patients with refractory epilepsy did not show the circadian HR fluctuation seen in healthy control subjects, and VNS therapy did not seem to affect the circadian HRV. In this series, a seizure response was achieved in nine patients (64.3%), which is higher than previous series.

Stemper et al. studied 21 patients with active VNS therapy, but analysing the on and off phases for each patient [76]. It comprised an assessment of the heart and BP control, using an ECG, and a non-invasive arterial tonometry. The VNS generator was programmed at fixed parameters of frequency and pulse width, and to stimulate for 60 s ("on") and then pause for 5 min ("off"), and the measures were assessed for each period. RRI, systolic and diastolic BP did not show significant changes during the on and off phases. They also found that the baroreflex sensitivity (BRS) increased slightly during stimulation. The LF power of BP and the LF and HF power of RRI increased significantly. They concluded that VNS influences both sympathetic and parasympathetic cardiovascular modulation. Nevertheless, they stated that VNS does not negatively influence autonomic cardiovascular regulation.

Ten children (between 7 and 18 years old) with active VNS treatment were studied by Zaaimi et al., who performed polysomnography recordings to detect changes during sleep [77], comparing the on and off phases. While the VNS generator was stimulating, the heart rates of four children increased significantly, decreased for one child and increased at the end of the stimulation for one child. Changes in heart rate varied during VNS, within stimulation cycles for individual children and from one child to another. They also found that in six of the ten children the respiratory sinus arrhythmia (RSA) magnitude decreased significantly [78]. These changes in RSA magnitude varied from one child to another.

Cadeddu et al. performed a prospective study to evaluate both heart function and BP changes in ten patients, prior to and during active VNS treatment [79]. They performed an ECG, echocardiography examination and 24-h BP monitoring. They found that while the echocardiography assessment did not vary from baseline to active VNS therapy, a significant increase in the high frequency components and a significant reduction in the LF/HF ratio was observed. Blood pressure showed a significant increase in both systolic and diastolic values. Thus, they concluded that VNS therapy is safe regarding cardiac function and suggested an increase in the parasympathetic activity. Eight of the ten patients (80%)

improved their seizure frequency by 50% or more, which is much higher than reported by other series.

In 2011, 17 children with refractory epilepsy were studied before and after VNS implantation [80]. Twenty-four-hour EEG and ECG were performed, but only data from during sleep stages were analysed. To determine whether an imbalance in autonomic cardiac control due to chronic epilepsy was present, a sex- and age-matched cohort of healthy subjects was also evaluated. Children with drug-resistant epilepsy, before VNS implantation, showed a lower parasympathetic activity in stage 2 sleep compared with subjects without epilepsy. Conversely, during slow-wave sleep, patients with refractory epilepsy exhibited sympathetic dominance. VNS treatment seemed to increase sympathetic activity in every sleep stage.

To evaluate the effect of the stimulation therapy in exercise and rest, Mulders et al. studied ten patients with VNS therapy, five who had reported side effects (shortness of breath) and five who had not. Five healthy subjects were also recruited. ECG, oxygen and respiratory monitoring were performed during a 20-min rest period and 20 min of exercise. For each patient, data from "on" and "off" periods were obtained [81]. During active stimulation, patients showed a decrease in HR, compared with the "off" periods, both in rest and exercise. Regarding respiratory parameters, a small decrease in tidal volume and an increase in breathing frequency were observed, but no significant changes in oxygen saturation. All patients had achieved good response to VNS therapy

In our centre we conducted a study to determine the effect of VNS therapy on patients with DRE in the autonomic nervous system [82]. This study comprised two parts. The first was a prospective longitudinal evaluation comparing the pre-implantation period and two post-implantation periods, one using intermediate parameters and later using the best stimulation setting. The second was a cross-sectional assessment comparing the on and off periods of the stimulation cycles. All the patients underwent continuous non-invasive ECG tracing, beat-to-beat continuous BP (obtained with finger plethysmography) and impedance cardiography (Task Force® Monitor, CNSystems © Medizintechnik AG, Austria). Fifteen patients were included in the first part of the study and 14 in the second. One patient was on active right-sided VNS. This patient had previously undergone implantation in the left vagus nerve but as malfunction due to nerve fibrosis occurred, it was removed and changed to the right vagus nerve. In the prospective study, no differences were observed between the baseline, the intermediate visit and the final visit for the variables related to parasympathetic cardiovagal tone, namely expiratory to inspiratory (E/I) ratio, Valsalva ratio or HRV HF. Regarding the markers of sympathetic tone, only systolic and diastolic BP upon 5 min of head-up tilt increased significantly after VNS implantation. BRS was not different between visits. Similar results were observed in the patient with right VNS. In the cross-sectional part no changes were found in the parasympathetic cardiovagal markers between on and off situations. The LF/HF ratio was higher during the on situation, showing a trend toward sympathetic tone dominance. No other markers of sympathetic tone showed significant changes. Baroreflex sensitivity and haemodynamic parameters, such as stroke index (SI), acceleration index (ACI) or left ventricular stroke work index (LVSWI), were the same during the on and off situations. This result supports the conclusion that VNS has no major autonomic cardiovascular or haemodynamic effects. The responder rate was 42.9% and 45.5% at the intermediate and final visits, respectively.

Regarding SUDEP, Schomer et al. found that, as occurred with VNS for heart failure, VNS therapy for epilepsy may also have a protective effect on the heart [83]. They performed ambulatory 24-h ECG in nine patients undergoing VNS therapy and evaluated the HRV and the T wave alternans. Six patients were also evaluated prior to VNS implantation. They found reduction in LF HRV and the LF/HF ratio pointing to a dominance of parasympathetic function. The T wave alternans was also reduced, suggesting protection against lethal arrhythmias. In the same way, Verrier et al. studied 28 patients who underwent VNS therapy with the cardiac frequency-triggered device (AspireSR Model 106 VNS Therapy®) before and after implantation [84]. They also found that T wave alternans was elevated prior to VNS surgery and decreased when the patients were undergoing active therapy. Neither heart rate reduction nor modification in HRV was observed. This study supports the protective effect of VNS.

Conclusion

The vagus nerve connects, through different afferent and efferent fibres, several areas of the brain and major organs of the thorax and abdomen, providing parasympathetic innervation to those organs and receiving sensory inputs from them. Electric stimulation of the afferent fibres of the cervical left vagus nerve has demonstrated efficacy in reducing the epileptic activity and improving mood, and the activation of the efferent fibres of the right vagus has done so in preventing lethal arrhythmias in heart failure, and also reducing the severity of episodic CH. Vagus nerve stimulation is the only neurostimulation therapy for epilepsy approved worldwide. It is indicated for drug-resistant epilepsy not amenable to the respective surgery in patients 12 years and older. The adverse events are usually stimuli-related, usually throat pain, hoarseness and cough, but sporadic cases of ventricular asystole have been reported. In order to establish the autonomic effects on the autonomic function, many studies

of cardiac function and BP control have been performed. Some of them have suggested that this therapy has a possible protective effect against SUDEP.

Why were differences found in all these studies? The first observation is that the studies were performed in different situations, namely some at rest, some for prolonged periods of time and others include night sleep. The series comprised small numbers of patients, so none were fully representative of the majority of patients on VNS therapy. For instance, the responder rate ranges from 45% to 100%. Moreover, there are no homogeneous groups regarding pharmacological treatment, so comparisons may be difficult to establish. It should be noted that some AEDs, such as sodium channel blockers, are negative chronotropic drugs. In addition, the study methodology was not the same, as some performed a spectral analysis of the heart rate, some monitored BP and others simply analysed the heart rate in the prolonged ECG. The main conclusion that can be drawn is that as long as the vagus nerve is undamaged and the stimulus is afferent to the solitary tract nucleus, there is no interference with the vagal stimulation of the heart. The few changes in the vegetative nervous system are subtle, and afferent. As in other diseases in which nerve stimulation is applied, the frequency, pulse width and amplitude of the stimulus can modify the effect on the different types of nerve fibres. Studying the different stimulation parameters on the vagus nerve in animal models can clarify these subtle differences.

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Compliance with ethical standards

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References

1. Krahl SE (2012) Vagus nerve stimulation for epilepsy: a review of the peripheral mechanisms. Surg Neurol Int 3:S47–S52. doi:10.4103/2152-7806.103015
2. Foley JO, DuBois F (1937) Quantitative studies of the vagus nerve in the cat. I. The ratio of sensory and motor fibers. J Comp Neurol 67:49–97. doi:10.1002/cne.900670104
3. Krahl SE, Clark KB (2012) Vagus nerve stimulation for epilepsy: a review of the central mechanisms. Surg Neurol Int 3:255–259. doi:10.4103/2152-7806.103015
4. Agostini E, Chinnock JE, Daly MD, Murray JG (1957) Functional and histological studies of the vagus nerve and its branches to the heart, lungs, and abdominal viscera in the cat. J Physiol 135:182–205
5. Verlinden TJM, Rijkers K (2016) Morphology of the human cervical vagus nerve: implications for vagus nerve stimulation treatment. Acta Neurol Scand 133:173–182. doi:10.1111/ane.12462
6. Randall WC, Milosavljevic M, Wurster RD, Geis GS, Ardell JL (1986) Selective vagal innervation of the heart. Ann Clin Lab Sci 1986:198–208
7. Ben-Menachem E, Revesz D, Simon BJ, Silberstein S (2015) Surgically implanted and non-invasive vagus nerve stimulation: a review of efficacy, safety and tolerability. Eur J Neurol 22:1260–1268. doi:10.1111/ene.12629
8. Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, French JA, Gil-Nagel A, Hesdorffer DC, Smithson WH, Spitz MC, Walczak TS, Sander JW, Ryvlin P (2017) Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 88:1674–1680. doi:10.1212/WNL.0000000000003685
9. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 51:1069–1077. doi:10.1111/j.1528-1167.2009.02397
10. Ben-Menachem E (2002) Vagus-nerve stimulation for the treatment of epilepsy. Lancet Neurol 1:477–478. doi:10.1016/S1474-4422(02)00220-X
11. Giordano F, Zicca A, Barba C, Guerrini R, Genitori L (2017) Vagus nerve stimulation: surgical technique of implantation and revision and related morbidity. Epilepsia 58:S85–S90. doi:10.1111/epi.13678
12. Tarver WB, George RE, Maschino SE (1992) Clinical experience with a helical bipolar stimulating lead. Pacing Clin Electrophysiol 15:1545–1556. doi:10.1111/j.1540-8159.1992.tb02933.x
13. Labiner DM, Ahern GL (2007) Vagus nerve stimulation therapy in depression and epilepsy: therapeutic parameter settings. Acta Neurol Scand 115:23–33. doi:10.1111/j.1600-0404.2006.00732.x
14. DeGiorgio C, Heck C, Bunch S, Britton J, Green P, Lancman M, Murphy J, Olejniczak P, Shih J, Arrambide S, Soss J (2005) Vagus nerve stimulation for epilepsy: randomized comparison of three stimulation paradigms. Neurology 65:317–319. doi:10.1212/01.wnl.0000168899.11598.00
15. Liporace J, Hucko D, Morrow R, Barolat G, Nei M, Schnur J, Sperling M (2001) Vagal nerve stimulation: adjustments to reduce painful side effects. Neurology 57:885–886. doi:10.1212/WNL.57.5.885
16. Boon P, Vonck K, van Rijckevorsel K, El Tahry R, Elger CE, Mullatti M, Schulze-Bonhage A, Wagner L, Diehl B, Hamer H, Reuber M, Kostov H, Legros B, Noachtar S, Weber YG, Coenen VA, Rooijakkers V, Schijns OEMG, Selway R, Van Roost D, Eggleston KS, Van Grunderbeek W, Jayewardene AK, McGuire RM (2015) A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation. Seizure 32:52–61. doi:10.1016/j.seizure.2015.08.011
17. McGregor A, Wheless J, Baumgartner J, Bettis D (2005) Right-sided vagus nerve stimulation as a treatment for refractory epilepsy in humans. Epilepsia 46:91–96. doi:10.1111/j.0013-9580.2005.16404.x
18. Navas M, García Navarrete A, Pascual JM, Carrasco R, Núñez JA, Shakur SF, Pastor J, Sola RG (2010) Treatment of refractory epilepsy in adult patients with right-sided vagus nerve stimulation. Epilepsy Res 90:1–7. doi:10.1016/j.eplepsyres.2010.04.007
19. Bauer S, Baier H, Baumgartner C, Bohlmann K, Fauser S, Graf W, Hillenbrand B, Hirsch M, Last C, Lerche H, Mayer T, Schulze-Bonhage A, Steinhoff BJ, Weber Y, Hartlep A, Rosenow F, Hamer HM (2016) Transcutaneous vagus nerve stimulation (tVNS) for treatment of drug-resistant epilepsy:

a randomized, double-blind clinical trial (cMPsE02). Brain Stimul 9:356–363. doi:10.1016/j.brs.2015.11.003
20. He W, Jing X, Wang X, Rong P, Li L, Shi H, Shang H, Wang Y, Zhang J, Zhu B (2013) Transcutaneous auricular vagus nerve stimulation as a complementary therapy for pediatric epilepsy: a pilot trial. Epilepsy Behav 28:343–346. doi:10.1016/j.yebeh.2013.02.001
21. Stefan H, Kreiselmeyer G, Kerling F, Kurzbuch K, Rauch C, Heers M, Kasper BS, Hammen T, Rzonsa M, Pauli E, Ellrich J, Graf W, Hopfengärtner R (2012) Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. Epilepsia 53:e115–e118. doi:10.1111/j.1528-1167.2012.03492.x
22. Vonck K, Van Laere K, Dedeurwaerdere S, Caemaert J, De Reuck J, Boon P (2001) The mechanism of action of vagus nerve stimulation for refractory epilepsy. J Clin Neurophysiol 18:394–401
23. Krahl SE, Senanayake SS, Handforth A (2001) Destruction of peripheral C-fibers does not alter subsequent vagus nerve stimulation-induced seizure suppression in rats. Epilepsia 42:586–589. doi:10.1046/j.1528-1157.2001.09700.x
24. Krahl SF, Clark KB, Smith DC et al (1998) Locus coeruleus lesions suppress the seizure attenuating effects of vagus nerve stimulation. Epilepsia 39:709–714. doi:10.1111/j.1528-1157.1998.tb01155.x
25. Henry TR (2002) Therapeutic mechanisms of vagus nerve stimulation. Neurology 59(Suppl 4):S3–S14. doi:10.1212/WNL.59.6_suppl_4.S3
26. Jaseja H (2010) EEG-desynchronization as the major mechanism of anti-epileptic action of vagal nerve stimulation in patients with intractable seizures: clinical neurophysiological evidence. Med Hypotheses 74:855–856. doi:10.1016/j.mehy.2009.11.031
27. The Vagus Nerve Stimulation Study Group (1995) A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology 45:224–230. doi:10.1212/WNL.45.2.224
28. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM et al (1998) Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 51:48–55. doi:10.1212/WNL.51.1.48
29. Morris GL, Mueller WM, Vagus Nerve Stimulation Study Group EO1–EO5 (1999) Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. Neurology 53:1731–1735. doi:10.1212/WNL.53.8.1731
30. DeGiorgio CM, Schachter SC, Handforth A, Salinsky M, Thompson J, Uthman YB, Reed R, Collins S, Tecoma E, Morris LG, Vaughn B, Naritoku DK, Henry T, Labar D, Gilmartin R, Labiner D, Osorio I, Ristanovic R, Jones J, Murphy J, Ney G, Wheless J, Lewis P, Hecket C (2000) Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia 41:1195–1200. doi:10.1111/j.1528-1157.2000.tb00325.x
31. De Herdt V, Boon P, Ceulemans B, Hauman H, Lagae L, Legros B, Sadzot B, Van Bogaert P, van Rijckevorsel K, Verhelst H, Vonck K (2007) Vagus nerve stimulation for refractory epilepsy: a Belgian multicenter study. Eur J Paediatr Neurol 11:261–269. doi:10.1016/j.ejpn.2007.01.008
32. Elliott RE, Morsi A, Kalhorn SP, Marcus J, Sellin J, Kang M, Silverberg A, Rivera E, Geller E, Carlson C, Devinsky O, Doyle WK (2011) Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy Behav 20:57–63. doi:10.1016/j.yebeh.2010.10.017
33. Galbarriatu L, Pomposo I, Aurrecoechea J, Marinas A, Agúndez M, Gómez JC, Acera MA, Martínez MJ, Valle E, Maestro I, Mateos B, Cabrera A, Fernández J, Iturri F, Garamendi I (2015) Vagus nerve stimulation therapy for treatment-resistant epilepsy: a 15-year experience at a single institution. Clin Neurol Neurosurg 137:89–93. doi:10.1016/j.clineuro.2015.06.023
34. McHugh JC, Singh HW, Phillips J, Murphy K, Doherty CP, Delanty N (2007) Outcome measurement after vagal nerve stimulation therapy: proposal of a new classification. Epilepsia 48:375–378. doi:10.1111/j.1528-1167.2006.00931.x
35. Helmers SL, Wheless JW, Frost M et al (2001) Vagus nerve stimulation therapy in pediatric patients with refractory epilepsy: retrospective study. J Child Neurol 16:843–848. doi:10.1177/088307380101601111101
36. Vonck K, Thadani V, Gilbert K, Dedeurwaerdere S, De Groote L, De Herdt V, Goossens L, Gossiaux F, Achten E, Thiery E, Vingerhoets G, Van Roost D, Caemaert J, De Reuck J, Roberts D, Williamson P, Boon P (2004) Vagus nerve stimulation for refractory epilepsy: a transatlantic experience. J Clin Neurophysiol 21:283–289
37. Fernandez L, Gedela S, Tamber M, Sogawa Y (2015) Vagus nerve stimulation in children less than 3 years with medically intractable epilepsy. Epilepsy Res 112:37–42. doi:10.1016/j.eplepsyres.2015.02.009
38. Ryvlin P, Gilliam G, Nguyen DK, Colicchio G, Iudice A, Tinuper P, Zamponi N, Aguglia U, Wagner L, Minotti L, Stefan H, Boon P, Sadler M, Benna P, Raman P, Perucca E (2014) The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. Epilepsia 55:893–900. doi:10.1111/epi.12611
39. Elliott RE, Morsi A, Tanweer O, Grobelny B, Geller E, Carlson C, Devinsky O, Doyle WK (2011) Efficacy of vagus nerve stimulation over time: review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS N10 years. Epilepsy Behav 20:478–483. doi:10.1016/j.yebeh.2010.12.042
40. Ardesch JJ, Buschman HP, Wagener-Schimmel LJ, van der Aa HE, Hageman G (2007) Vagus nerve stimulation for medically refractory epilepsy: a long-term follow-up study. Seizure 16:579–585. doi:10.1016/j.seizure.2007.04.005
41. Winston KR, Levisohn P, Miller BR, Freeman J (2001) Vagal nerve stimulation for status epilepticus. Pediatr Neurosurg 34:190–192. doi:10.1159/000056018
42. Patwardhan RV, Dellabadia J Jr, Rashidi M, Grier L, Nanda A (2005) Control of refractory status epilepticus precipitated by anticonvulsant withdrawal using left vagal nerve stimulation: a case report. Surg Neurol 64:170–173. doi:10.1016/j.surneu.2004.11.026
43. Sierra-Marcos A, Maestro I, Rodríguez-Osorio X, Miró J, Donaire A, Aparicio J, Rumiá J, Forcadas M, Garamendi I, Pardo J, López J, Prieto Á, Plans G, Falip M, Carreño M (2012) Successful outcome of episodes of status epilepticus after vagus nerve stimulation: a multicenter study. Eur J Neurol 19:1219–1223. doi:10.1111/j.1468-1331.2012.03707.x
44. Annegers JF, Coan SP, Hauser WA, Leestma J (2000) Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. Epilepsia 41:549–553. doi:10.1111/j.1528-1157.2000.tb00208.x
45. Tatum WO IV, Moore DB, Stecker MM, Baltuch GH, French JA, Ferreira JA, Carney PM, Labar DR, Vale FL (1999) Ventricular asystole during vagus nerve stimulation for epilepsy in humans. Neurology 52:1267–1269. doi:10.1212/WNL.52.6.1271
46. Ardesch JJ, Buschman HP, van der Burgh PH, Wagener-Schimmel LJ, van der Aa HE, Hageman G (2007) Cardiac responses of vagus nerve stimulation: intraoperative bradycardia and subsequent chronic stimulation. Clin Neurol Neurosurg 109:849–852. doi:10.1016/j.clineuro.2007.07.024
47. Schuurman PR, Beukers RJ (2009) Ventricular asystole during vagal nerve stimulation. Epilepsia 50:967–968. doi:10.1111/j.1528-1167.2008.01907.x

48. Amark P, Stodberg T, Wallstedt L (2007) Late onset bradyarrhythmia during vagus nerve stimulation. Epilepsia 48:1023–1024. doi:10.1111/j.1528-1167.2007.01023.x
49. Borusiak P, Zilbauer M, Cagnoli S, Heldmann M, Jenke A (2009) Late-onset cardiac arrhythmia associated with vagus nerve stimulation. J Neurol 256:1578–1580. doi:10.1007/s00415-009-5162-y
50. Iriarte J, Urrestarazu E, Alegre M et al (2009) Late-onset periodic asystolia during vagus nerve stimulation. Epilepsia 50:928–932. doi:10.1111/j.1528-1167.2008.01918.x
51. Shankar R, Olotu VO, Cole N, Sullivan H, Joryet C (2013) Case report: vagal nerve stimulation and late onset asystole. Seizure 22:312–314. doi:10.1016/j.seizure.2012.12.011
52. Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE (2000) Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res 42:203–210. doi:10.1016/S0920-1211(00)00181-9
53. Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper JP, Labar DR (2000) A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. Epilepsy Behav 1:93–99. doi:10.1006/ebeh.2000.0046
54. Grimonprez A, Raedt A, Portelli J, Dauwe I, Larsen LE, Bouckaert C, Delbeke J, Carrette E, Meurs A, De Herdt V, Boon P, Vonck K (2015) The antidepressant-like effect of vagus nerve stimulation is mediated through the locus coeruleus. J Psychiatr Res 68:1–7. doi:10.1016/j.jpsychires.2015.05.002
55. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, Kling MA, Rittberg BR, Burke WJ, Rapaport MH, Zajecka J, Nierenberg AA, Husain MM, Ginsberg D, Cooke RG (2005) Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry 58:347–354. doi:10.1016/j.biopsych.2005.05.025
56. Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM et al (2005) Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biol Psychiatry 58:355–363. doi:10.1016/j.biopsych.2005.05.024
57. Ikramuddin S, Blackstone RP, Brancatisano A, Toouli J, Shah SN, Wolfe BM, Fujioka K, Maher JW, Swain J, Que FG, Morton JM, Leslie DB, Brancatisano R, Kow L, O'Rourke RW, Deveney C, Takata M, Miller CJ, Knudson MB, Tweden KS, Shikora SA, Sarr MG, Billington CJ (2014) Effect of reversible intermittent intra-abdominal vagal nerve blockade on morbid obesity: the ReCharge randomized clinical trial. JAMA 312:915–922. doi:10.1001/jama.2014.10540
58. Apovian CM, Shah SN, Wolfe BM, Ikramuddin S, Miller CJ, Tweden KS, Billington CJ, Shikora SA (2017) Two-year outcomes of vagal nerve blocking (vBloc) for the treatment of obesity in the recharge trial. Obes Surg 27:169–176. doi:10.1007/s11695-016-2325-7
59. Gaul C, Diener HC, Silver N, Magis D, Reuter U, Andersson A, Liebler EJ, Straube A, on behalf of PREVA Study Group (2016) Non-invasive vagus nerve stimulation for PREVention and Acute treatment of chronic cluster headache (PREVA): a randomised controlled study. Cephalalgia 36:534–546. doi:10.1177/0333102415607070
60. Silberstein SD, Mechtler LL, Kudrow DB, Calhoun AH, McClure C, Saper JR, Liebler EJ, Rubenstein Engel E, Tepper SJ, on behalf of ACT1 Study Group (2016) Non-invasive vagus nerve stimulation for the acute treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. Headache 56:1317–1332. doi:10.1111/head.12896
61. Klein HU, De Ferrari GM (2010) Vagus nerve stimulation: a new approach to reduce heart failure. Cardiol J 17:638–643
62. De Ferrari GM, Crijns HJGM, Borggrefe M, Milasinovic G, Smid J, Zabel M, Gavazzi A, Sanzo A, Dennert R, Kuschyk J, Raspopovic S, Klein H, Swedberg K, Schwartz PJ, for the CardioFit Multicenter Trial Investigators (2011) Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. Eur Heart J 32:847–855. doi:10.1093/eurheartj/ehq424
63. Zannad F, De Ferrari GM, Tuinenburg AE, Wright D, Brugada J, Butter C, Klein H, Stolen C, Meyer S, Stein KM, Ramuzat A, Schubert B, Daum D, Neuzil P, Botman C, Castel MA, D'Onofrio A, Solomon SD, Wold N, Ruble SB (2015) Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. Eur Heart J 36:425–433. doi:10.1093/eurheartj/ehu345
64. Premchand RK, Sharma K, Mittal S, Monteiro R, Dixit S, Libbus I, DiCarlo LA, Ardell JL, Rector TS, Amurthur B, KenKnight BH, Anand IS (2014) Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. J Cardiac Fail 20:808–816. doi:10.1016/j.cardfail.2014.08.009
65. Premchand RK, Sharma K, Mittal S, Monteiro R, Dixit S, Libbus I, DiCarlo LA, Ardell JL, Rector TS, Amurthur B, KenKnight BH, Anand IS (2016) Extended follow-up of patients with heart failure receiving autonomic regulation therapy in the ANTHEM-HF study. J Cardiac Fail 22:639–642. doi:10.1016/j.cardfail.2015.11.002
66. Libbus I, Nearing BD, Amurthur B, KenKnight BH, Verrier RL (2016) Autonomic regulation therapy suppresses quantitative T-wave alternans and improves baroreflex sensitivity in patients with heart failure enrolled in the ANTHEM-HF study. Heart Rhythm 13:721–728. doi:10.1016/j.hrthm.2015.11.030
67. Gold MR, Van Veldhuisen DJ, Hauptman PJ, Borggrefe M, Kubo SH, Lieberman RA, Milasinovic G, Berman BJ, Djordjevic S, Neelagaru S, Schwartz PJ, Starling RC, Mann DL (2016) Vagus nerve stimulation for the treatment of heart failure: the INOVATE-HF trial. J Am Coll Cardiol 68:149–158. doi:10.1016/j.jacc.2016.03.525
68. Beaumont E, Southerland EM, Hardwick JC, Wright GL, Ryan S, Li Y, KenKnight BH, Armour JA, Ardell JL (2015) Vagus nerve stimulation mitigates intrinsic cardiac neuronal and adverse myocyte remodeling postmyocardial infarction. Am J Physiol Heart Circ Physiol 309:H1198–H1206. doi:10.1152/ajpheart.00393.2015
69. Tomson T, Ericson M, Ihrman C, Lindblad LE (1998) Heart rate variability in patients with epilepsy. Epilepsy Res 30:77–83. doi:10.1016/S0920-1211(97)00094-6
70. Strzelczyk A, Adjei P, Scott CA, Bauer S, Rosenow F, Walker MC, Surges R (2012) Postictal increase in T-wave alternans after generalized tonic–clonic seizures. Epilepsia 52:2112–2117. doi:10.1111/j.1528-1167.2011.03266.x
71. Kamath MV, Upton ARM, Talalla A, Fallen EL (1992) Neurocardiac responses to vagoafferent electrostimulation in humans. Pacing Clin Electrophysiol 15:1581–1587. doi:10.1111/j.1540-8159.1992.tb02937.x
72. Setty AB, Vaughn BV, Quint SR, Robertson KR, Messenheimer JA (1998) Heart period variability during vagal nerve stimulation. Seizure 7:213–217. doi:10.1016/S1059-1311(98)80038-1
73. Frei MG, Osorio I (2001) Left vagus nerve stimulation with the neurocybernetic prosthesis has complex effects on heart rate and on its variability in humans. Epilepsia 42:1007–1016. doi:10.1046/j.1528-1157.2001.0420081007.x
74. Galli R, Limbruno U, Pizzanelli C, Giorgi FS, Lutzemberger L, Strata G, Pataleo L, Mariani M, Iudice A, Murri L (2003) Analysis of RR variability in drug-resistant epilepsy patients chronically treated with vagus nerve stimulation. Auton Neurosci 107:52–59. doi:10.1016/S1566-0702(03)00081-X
75. Ronkainen E, Korpelainen JT, Heikkinen E, Myllylä VV, Huikuri HV, Isojärvi JIT (2006) Cardiac autonomic control in patients with refractory epilepsy before and during vagus nerve stimulation

treatment: a one-year follow-up study. Epilepsia 47:556–562. doi:10.1111/j.1528-1167.2006.00467.x
76. Stemper B, Devinsky O, Haendl T, Welsch G, Hilz MJ (2008) Effects of vagus nerve stimulation on cardiovascular regulation in patients with epilepsy. Acta Neurol Scand 117:231–236. doi:10.1111/j.1600-0404.2007.00944.x
77. Zaaimi B, Grebe R, Berquin P, Wallois F (2007) Vagus nerve stimulation therapy induces changes in heart rate of children during sleep. Epilepsia 48:923–930. doi:10.1111/j.1528-1167.2006.01019.x
78. Zaaimi B, Grebe R, Berquin P, Wallois F (2009) Vagus nerve stimulation induces changes in respiratory sinus arrhythmia of epileptic children during sleep. Epilepsia 50(11):2473–2480. doi:10.1111/j.1528-1167.2009.02190.x
79. Cadeddu C, Deidda M, Mercuro G, Tuveri A, Muroni A, Nocco S, Puligheddu M, Maleci A, Marrosu F (2010) Cardiovascular modulation during vagus nerve stimulation therapy in patients with refractory epilepsy. Epilepsy Res 92:145–152. doi:10.1016/j.eplepsyres.2010.08.012
80. Jansen K, Vandeput S, Milosevic M, Ceulemans B, Van Huffel S, Brown L, Penders J, Lagae L (2011) Autonomic effects of refractory epilepsy on heart rate variability in children: influence of intermittent vagus nerve stimulation. Dev Med Child Neurol 53:1143–1149. doi:10.1111/j.1469-8749.2011.04103.x
81. Mulders DM, de Vos CC, Vosman I, van Putten MJ (2015) The effect of vagus nerve stimulation on cardiorespiratory parameters during rest and exercise. Seizure 33:24–28. doi:10.1016/j.seizure.2015.10.004
82. Garamendi I, Acera M, Agundez M, Galbarriatu L, Marinas A, Pomposo I, Valle E, Palma JA, Gomez-Esteban JC (2017) Cardiovascular autonomic and hemodynamic responses to vagus nerve stimulation in drug-resistant epilepsy. Seizure 45:56–60. doi:10.1016/j.seizure.2016.11.018
83. Schomer AC, Nearing BD, Schachter SC, Verrier RL (2014) Vagus nerve stimulation reduces cardiac electrical instability assessed by quantitative T-wave alternans analysis in patients with drug-resistant focal epilepsy. Epilepsia 55:1996–2002. doi:10.1111/epi.12855
84. Verrier RL, Nearing BD, Olin B, Boon P (2016) Baseline elevation and reduction in cardiac electrical instability assessed by quantitative T-wave alternans in patients with drug-resistant epilepsy treated with vagus nerve stimulation in the AspireSR E-36 trial. Epilepsy Behav 62:85–89. doi:10.1016/j.yebeh.2016.06.016