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Cardiovascular autonomic and hemodynamic responses to vagus nerve stimulation in drug-resistant epilepsy

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ABSTRACT

Purpose: Vagus nerve stimulation (VNS) is used as an adjunctive therapy for treating patients with drug-resistant epilepsy. The impact of VNS on cardiovascular autonomic function remains to be fully understood. We determined changes in cardiovascular sympathetic and parasympathetic, and hemodynamic function in association with VNS in patients with drug-resistant focal epilepsy.
Method: Longitudinal (n = 15) evaluation of beat-to-beat blood pressure (BP) and heart rate variability (HRV), baroreflex sensibility, and hemodynamic function performed before VNS implantation, 6-months after implantation, and a mean of 12-months after implantation; and cross-sectional study (n = 14) of BP and HR variability and baroreflex sensitivity during VNS on and VNS off.
Results: In the longitudinal study, no differences were observed between the baseline, the 6-month visit, and the final visit in markers of parasympathetic cardiovagal tone or baroreflex sensitivity. Systolic and diastolic BP upon 5-min of head-up tilt increased significantly after VNS implantation (Systolic BP: -16.69 ± 5.65 mmHg at baseline, 2.86 ± 16.54 mmHg at 6-month, 12.25 ± 12.95 mmHg at final visit, $p = 0.01$; diastolic BP: -14.84 ± 24.72 mmHg at baseline, 0.86 ± 16.97 mmHg at 6-month, and 17 ± 12.76 mmHg at final visit, $p = 0.001$).
Conclusion: VNS does not seem to produce alterations in parasympathetic cardiovagal tone, regardless of the laterality of the stimulus. We observed a slight increase in sympathetic cardiovascular modulations. These changes had no significant hemodynamic implications. These findings contribute to the understanding of potential mechanisms of action of VNS.

1. Introduction

In 1997, the US Food and Drug Administration (FDA) approved vagus nerve stimulation (VNS) as adjunctive therapy for reducing the frequency of seizures in patients >12 years of age with partial-onset seizures refractory to antiepileptic medications [1].

The mechanism of action of VNS remains largely unknown. The vagus nerve is comprised of ~20% efferent (conveying signals from the CNS to the organs) and ~80% afferent (conveying sensory information from the viscera to the CNS) fibers. Presumed anti-seizure mechanisms are mediated by modulation of vagal afferent pathways resulting in alterations of seizure-generating regions [2,3]. Conversely, modulations of vagal parasympathetic efferent pathways do not underlie anti-seizure effects [2].

Vagal efferent pathways innervating the heart induce inhibition of the pacemaker activity of the sinoatrial node resulting in decreased heart rate (HR), reduced atrioventricular conduction, and decreased excitability of the His-Purkinje system [4]. This fact has always raised concerns that VNS might affect the cardiac rhythm. However, the effects of VNS on cardiovascular autonomic tone of patients with refractory epilepsy remain to be fully understood.

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On the one hand, cardiac changes related to VNS in epilepsy have been reported to be rare (0.1%), and preliminary investigations on HR variability in patients with VNS revealed minor changes with no clinically relevant effects [5–7]; on the other hand, cases of VNS-induced bradyarrhythmia have been reported [8–13], and recent pilot studies showed higher vagal tone [14] and lower HR in patients with VNS [15].

In this work we tested the hypothesis that, because VNS acts on afferent ascending rather than efferent descending fibers, it exerts no significant effects on cardiovascular autonomic function. To this aim, we comprehensively studied cardiovascular autonomic reflexes and hemodynamics in a group of patients with drug-resistant epilepsy being treated with VNS, and documented changes overtime.

2. Methods

2.1. Patient selection

Consecutive patients with drug-resistant epilepsy [16] who were scheduled to undergo implantation of the VNS Therapy® System (Implantable Pulse Generator model 103, lead model 304; Cyberonics, Inc., Houston, TX, USA) at the Comprehensive Epilepsy Center at Cruces University Hospital (Bilbao, Spain) over a two-year period (2011–2013) were recruited [17].

Patients who agreed to participate in this study gave written informed consent prior to any study-specific procedures. The local Institutional Review Board approved the protocol and the study was conducted in accordance with the 2013 version of the Declaration of Helsinki.

Implantation, postoperative care, and ramp-up and maintenance stimulation protocols were standard. Clinicians following standard clinical protocols adjusted the VNS settings without knowledge of cardiovascular autonomic testing results. As part of daily clinical practice, antiepileptic drug changes were allowed during the study period. Because antiepileptic drugs (AEDs) that modify sodium currents may modify the cardiac function, the following drugs were recorded: carbamazepine, oxcarbazepine, eslicarbazepine acetate, lamotrigine and lacosamide.

2.2. Study design

This study had two parts. The first part was designed as a prospective longitudinal evaluation to assess autonomic and hemodynamic changes overtime in 15 patients with drug-resistant epilepsy undergoing VNS. Cardiovascular autonomic testing was performed on three occasions: 15–30 days before VNS implantation, 6-months after VNS implantation, and at the time when high stimulation parameters were achieved (in all cases 10–15 months from initial evaluation).

The second part of this study was a cross-sectional assessment of 14 patients with drug-resistant epilepsy under active treatment with VNS in whom autonomic and hemodynamic testing was performed. Eight of these patients had been under VNS therapy for at least 2 years, and hence the device was operating at therapeutic parameters. We performed cardiovascular autonomic testing while the VNS was *on* (30 s) and, subsequently while the VNS was *off*, (5-min) the same day.

2.3. Cardiovascular autonomic testing

All individuals underwent a complete battery of autonomic and hemodynamic tests. Autonomic testing was carried out in the afternoon, and patients were instructed to avoid, in the previous 24 h, the intake of any medications, food or beverages that could potentially affect cardiovascular function. Exclusion criteria were a diagnosis of hypertension, diabetes mellitus, or cardiac or renal dysfunction.

Testing was performed in a quiet environment with continuous non-invasive ECG tracing, beat-to-beat continuous blood pressure (BP, obtained with finger plethysmography), and impedance cardiography for all tests (Task Force® Monitor, CNSystems Medizintechnik AG, Austria).

Patients rested in a supine position for 10 min prior to testing. The 10-min ECG segment was used to calculate HR variability (HRV), which was analyzed in the frequency domain using the fast Fourier spectral transform. Accordingly, the beat stream of the R-to-R interval series was transformed to compute high-frequency (HF) power within the frequency band 0.150–0.400 Hz, and the low-frequency (LF) power within the frequency band 0.040–0.150 Hz, reported in milliseconds squared. The LF/HF ratio was calculated as LF frequency divided by HF frequency and is unitless. HF HRV is an indicator of parasympathetic cardiovagal tone, whereas LF HRV and LF/HF ratio are indicators of autonomic tone and balance [18]. Similarly, the LF power of the diastolic BP variability (BPV) was also calculated. LF BPV oscillations are considered as a marker of sympathetic vasomotor activity.

The HR response to paced breathing (6 cycles per minute), described as the average difference in maximum and minimum HR and the expiratory to inspiratory (E:I) ratio was evaluated and considered a measure of parasympathetic cardiovagal tone. A Valsalva maneuver was elicited by expiring against a 40-mmHg pressure for 15 s. The Valsalva ratio (a measure of parasympathetic cardiovagal function) was recorded.

Only during the first part of the study, BP and HR were also measured noninvasively at 1-min intervals with an automated cuff sphygmomanometer over the brachial artery during a 60° head-up tilt for 5 min.

HRV and BPV were also assessed during isometric muscle contraction (using a handgrip dynamometer).

Baroreflex sensitivity (BRS) is a marker of the sensitivity of the autonomic reflexes to react upon BP changes by altering the length of the RR-interval. In normal conditions, if BP increases, the RR-interval is delayed (i.e., HR decreases). Conversely, if BP drops, the RR-interval shortens (i.e., HR increases). We determined the spontaneous baroreflex sensitivity (BRS) by means of the so called 'sequence method' [19]. According to this method, RR interval and beat-to-beat SBP data are scanned and sequences of three or more beats in which the BP and RR interval concomitantly increase (or decrease) higher than a threshold value are identified (for BP, the threshold is 1 mmHg per heart beat and for RR interval 4 ms per heart beat). The BRS is defined as the slope of the regression line between the data points in these sequences. At baseline, intermediate visit, and the final visit these values are calculated at rest after 10 min of registration. In the cross-sectional study (VNS ON and OFF) the duration of the registration periods is only 30 s. For this reason we repeated several times, until a reliable number of ramps was obtained which would allow the calculation of BRS.

2.4. Hemodynamic testing

In addition, in the second part of the study, we used impedance cardiography to study specific hemodynamic parameters [20]: stroke index (SI) defined as the volume of blood the left ventricle ejects in one beat, divided by the body surface area, measured in milliliters per square meter (ml/m^2); cardiac index (CI) defined as the cardiac output divided by the body surface area, measured in liters per minute per square meter ($L/min/m^2$); left ventricular stroke work index (LVWI), a measure of left ventricular contractility, measured in $mmHg\,l/(min\,m^2)$; and acceleration index (ACI), defined as the maximum rate of change of blood velocity related to