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Chronic vagus nerve stimulation reverses heart rhythm complexity in patients with drug-resistant epilepsy: An assessment with multiscale entropy analysis

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ABSTRACT

Objective: Vagus nerve stimulation (VNS) is an adjunctive treatment in drug-resistant epilepsy. The alterations in heart rate dynamics through VNS are not well understood. This study aimed to determine changes in heart rhythm complexity in association with VNS and to relate the findings to the outcome of VNS treatment in patients with drug-resistant epilepsy.
Methods: We prospectively analyzed 32 patients with drug-resistant epilepsy, who underwent VNS implantation, and 32 age- and sex-matched healthy control subjects. The interictal heartbeat intervals were analyzed using the heart rhythm complexity with multiscale entropy (MSE) and traditional heart rate variability (HRV) analyses based on ambulatory 24-hour electrocardiograms (ECGs).
Results: Patients had significantly decreased complexity indices (Slope 5, Area 1–5, Area 6–15, Area 6–20) on MSE analysis and decreased HRV measurements (standard deviation of the heartbeat interval (SDNN), square root of the mean of sum of squares of the differences between adjacent RR intervals (RMSSD), pNN50, very low frequency (VLF), low frequency (LF), high frequency (HF), total power (TP)) in time and frequency domain analyses. After one year of VNS treatment in patients with drug-resistant epilepsy, there was a trend in an elevated MSE profile with significant higher values between the scales 1 and 9. Vagus nerve stimulation induces a more significant increase of MSE in VNS responders than those in the nonresponders. The conventional HRV measurements did not change.
Conclusion: Our results suggest that heart rhythm complexity is impaired in patients with drug-resistant epilepsy, and this is at least partially reversed by VNS treatment. Furthermore, VNS-induced effects on heart rate complexity may be associated with the therapeutic response to VNS in patients with drug-resistant epilepsy.

1. Introduction

Epilepsy, characterized by recurrent and unprovoked seizures [1,2], affects around 65 million people worldwide. Vagus nerve stimulation (VNS) is an alternative therapeutic option for patients with drug-resistant epilepsy who are not suitable for conventional craniotomy surgery or who have experienced failed cranial surgery [3]. Around 115,000 VNS systems for over 80,000 patients in more than 70 countries worldwide have been implanted and utilized for the nonpharmacologic management of medically refractory seizures since the beginning of 2015 [4].

Despite the growing application of VNS, the exact mechanisms of VNS remains poorly understood [5,6]. Studies have shown that the vagus nerve consists of 80% afferent fibers projecting from the viscera to the nucleus tractus solitarius. Approximately 20% of vague nerve efferent fibers, which originate from the paraganglionic neurons in the dorsal motor nucleus, provide parasympathetic innervation primarily to the lungs, heart, and gastrointestinal tract [7]. Although there is a close interaction between VNS and the structures controlling cardiac functions, the effects of chronic VNS on cardiac autonomic regulation

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and heart rate dynamics in patients with drug-resistant epilepsy have not been widely studied.

Heart rate variability (HRV) analyses are a noninvasive, simple, and effective method to predict potential risks of many cardiovascular diseases and neurological disorders [8]. Traditional linear analyses of HRV are widely used to assess the cardiac autonomic regulation even though the regulation of the autonomic nervous system on cardiac activity is considered to be a nonlinear physiological activity [9,10]. Therefore, efficient methods for characterizing the complex nonlinear dynamics of the heart remain to be established. Since HRV is an emergent property of interdependent regulatory systems that operate on different time scales to adapt to ever-changing environmental and psychological challenges, nonlinear approaches are considered to be effective in heart rate complexity analysis [10–12]. Though extensively used for the analysis of physiological time series, classical entropy-based complexity measures quantify only the regularity of time series on a single scale without straight-forward correspondence between regularity and complexity [10,11]. In addition, diseased systems which actually present random heart rate dynamics may lead to obtaining paradoxically higher complexity through conventional single scale entropy methods. Recently, multiscale entropy (MSE) analysis has been introduced to measure the complexity of physiological data sets over different temporal scales, offering more differentiated and exact insights into the control mechanisms underlying nonlinear dynamics [10,11]. At present, MSE has been extensively used to analyze several biological signals for diagnostics, classification, risk stratification, and prognosis of diseases such as stroke, heart failure, primary aldosteronism, Alzheimer's disease, autism spectrum disorder, and Parkinson disease [13–18]. Furthermore, several studies have applied MSE to electroencephalography (EEG) in patients with epilepsy to investigate the dynamical changes of EEG complexity [19–21].

However, MSE analysis of heart rate dynamics and its possible effects of VNS in patients with drug-resistant epilepsy have not yet been studied. The present study was designed to determine changes in heart rhythm complexity in association with chronic VNS and to relate the findings to the outcome of VNS treatment in patients with drug-resistant epilepsy.

2. Methods

2.1. Participants

The patients underwent VNS surgery at the Beijing Tian Tan Hospital, Capital Medical University between August 13, 2014 and December 31, 2014 and received a one-year follow-up evaluation. All patients underwent complete presurgical evaluations including long-term (interictal and ictal) video-EEG, 24-hour electrocardiogram (ECG) recordings, magnetic resonance imaging (MRI) or positron emission tomography (PET), and comprehensive clinical as well as neuropsychological assessments as part of their diagnoses to ascertain that their drug-resistant epilepsy was not suitable for traditional epileptic craniotomy surgery.

The inclusion criteria were (1) 5–60 years old, (2) having tried at least two appropriate antiepileptic drug (AED) tested to tolerance or to blood levels at the upper end of the target range of which at least 2 had been tolerated at the normal dose, (3) at least 1 seizure per month, (4) in good health except for the epilepsy, and (5) with a minimum mental state examination (MMSE) score ≥ 18 (no severe cognitive impairment). The exclusion criteria were (1) the MRI or PET results indicating that the epilepsy was caused by intracranial space-occupying lesions; (2) tumors, cardiopulmonary anomalies, progressive neurological diseases, asthma, mental disease, or any other known disease that may have affected the autonomic nervous system (ANS) function; (3) alcohol addiction, smoking, and sleep-related breathing disorders; and (4) a history of medication that may have impacted the autonomic function.

Eventually, 32 patients were included in the study. A total of 32 age- and sex-matched healthy control subjects were recruited into this study based on their medical history and physical examination results. Participants with a history of any known disease, sleep disorders, and/or medication that affected the ANS were excluded from the study to avoid the potential influence on the HRV. The observed variables included their demographic data, seizure type, epilepsy duration, etiology, age at VNS surgery, seizure frequency, number of AED used, total dose of AED per day, presurgical MRI or PET findings, ictal scalp video-EEG characteristic, and preoperative ECG recordings. Three months prior to the VNS surgery and during the one-year follow-up period after the VNS treatment, the number and doses of the AED regimens were kept unchanged, and the patients or their family members were asked to keep seizure diaries to determine the baseline and one-year follow-up seizure frequency. This study was approved by the Institutional Review Committee of Beijing Tian Tan Hospital Capital Medical University, and all subjects, or parents/guardians of the subjects, gave informed consent in written form, which will be included for the collection of their information and usage for research. The methods in the study were carried out in accordance with the approved guidelines.

2.2. Vagus nerve stimulation

The VNS system (PINS Inc., Beijing, China) was implanted to stimulate the left vagus nerve of the patients with drug-resistant epilepsy. The details of the surgical procedure have been described elsewhere [4]. The VNS generator was turned on about 2 weeks after implantation with initial settings at a current amplitude of 0.2 mA, frequency of 30 Hz, pulse width of 500 μs, signal on time of 30 s, and signal off time of 5 min. Adjustments were made at intervals of about 2 weeks until the stimulation reached 1.0 mA. This was followed by 1-month intervals for the first 4 months and then preceded by 4-month intervals. At each follow-up visit, the output current was progressively increased by 0.2–0.3 mA until (1) the seizures were reduced by more than 50%, (2) the patient no longer tolerated the treatment, or (3) the current reached a maximum of 3.5 mA.

The severity of epilepsy including the seizure type, seizure duration, seizure frequency, and side effects of the VNS treatment were evaluated at the 4-months, 8-months, and one-year postimplantation during clinical visits. The assessed seizure reduction during the follow-up period was used to determine the response to VNS therapy. The mean seizure frequency per month was calculated, and the responders were defined as those having at least 50% reduction in seizures.

2.3. Ambulatory ECG recording and preprocessing

All patients underwent 24-hour ambulatory ECG recording within three months before VNS implantation and one year after VNS treatment (the VNS is off to overcome the nonstationarity of sinus rhythm during intermittent VNS). Healthy control subjects also underwent 24-hour ambulatory ECG recording at the time of enrollment. A 12-lead ambulatory ECG monitoring system (MIC-12H-3S, JincoMed, Beijing) with a digital sampling rate of 500 samples/s per channel was used to record consecutive 24-hour ECG in all subjects. The conventional ambulatory ECG configurations of leads V5, which provided a stable and reliable signal, was selected as the principal analysis lead. Participants underwent 24-hour ECG monitoring in free-moving conditions and were asked to keep activity diaries to document time, duration, and type of each daily physical activity and possible seizures during the recording period. All 24-hour Holter recordings were performed automatically by a PC-based acquisition system (SkyHolter, JincoMed, Beijing). The annotated files were then carefully inspected and corrected by technicians for extracting the RR intervals from leads II and V5. The ectopic beats were interpolated by its adjacent RR intervals for adjustment and correction. At least 50% of each 24-hour ECG recording had to be suitable for traditional HRV analysis for a record to be