Case Report

Sign and magnitude scaling properties of heart rate fluctuations following vagus nerve stimulation in a patient with drug-resistant epilepsy

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ABSTRACT

Vagus nerve stimulation (VNS) therapy has been recently incorporated in Latin America as a treatment for drug-resistant epilepsy. In particular, it is known that linear analysis and fractal parameters of heart rate variability (HRV) are able to indirectly measure cardiac autonomic activity. This case report presents a 17-year-old female with drug-resistant epilepsy implanted with a VNS device. In order to explore cardiac autonomic changes due to VNS, linear and fractal HRV indices were calculated in the presence and absence of neurostimulation. Novel fractal scaling exponents from HRV analysis were obtained from this patient and from a healthy control subject. Our results indicate that fractal indices of HRV, such as short-term scaling parameters from magnitude and sign analyses seem to be sensitive to the presence or absence of VNS, being confirmed by linear classical methods. This study shows that VNS therapy increases the complexity of cardiac fluctuations in a patient with drug-resistant epilepsy, reflecting an augmented HRV non-linearity and a diminished anticorrelated pattern in heart rate fluctuations. A potential clinical use of these parameters includes the early identification of bradycardia, sudden un-expected death (SUDEP) risk and preoperative VNS approaches. Thus, the scaling and magnitude properties of HRV have potential importance as a non-invasive and easy method for adequate diagnostic/prognostic implications in epilepsy treatment.

1. Introduction

Vagus nerve stimulation (VNS) therapy is an alternative for patients with drug-resistant epilepsy [1]. It consists of an implantable multi-programmable device that delivers electrical signals to the vagus nerve. Particularly, studies have demonstrated that stimulation of the vagus nerve has anti-seizure effects in experimentally induced seizures [2]. Additionally, case reports suggest that VNS therapy improves the regulation of the autonomic nervous system (ANS) in severe drug-resistant epilepsy, which is conventionally measured by using linear heart rate variability (HRV) indices [3].

Novel fractal methods have been introduced to describe HRV, which present the advantage of not being affected by non-stationary effects, in comparison with typical linear HRV indices [4]. In particular, the sign and magnitude of short-term fractal scaling exponents from HRV analysis have been used to explore the role of the cholinergic anti-inflammatory pathway (CAIP) in inflammatory condition, such as endotoxemia [5] and parturition [6]. With this background, the aim of this study was to explore the linear and fractal exponents in the presence and absence of neurostimulation in a patient with drug-resistant epilepsy. We hypothesize that fractal exponents of magnitude and sign will be modified due to the onset of VNS.

2. Case report

A 17-year-old hispanic girl with drug-resistant epilepsy participated in this study. She was diagnosed with focal epilepsy at the age of five at the Central Military Hospital in Mexico City in 2004. No history of birth injury was reported. Seizures began at the age of five and were characterized by involuntary movements of face, tongue, and extremities. She started taking anti-seizure drugs (valproate), presenting limited success for the next two years. Nevertheless, seizures reoccurred on a daily basis (more than five seizures in a 24-hour period). A diagnosis of absence seizures was made at the age of ten; the absence seizures were assessed by her parents as having an infrequent recurrence of occurrence and being characterized by a duration of about 90 s. At this age, she started

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taking a new anti-seizure drug treatment that included maximum daily therapeutic doses of topiramate (400 mg), levetiracetam (3 g) and oxcarbazepine (1000 mg). At the age of 15, she started a new anti-seizure drug treatment that included lacosamide (400 mg) clobazam (20 mg) oxcarbazepine (1500 mg). However, seizures proved to be drug-resistant to all, former and new anti-seizure drugs. The child was diagnosed with drug-resistant focal epilepsy caused by a temporal lobe lesion that was supported by positron emission tomography (PET). During the pharmacological treatment her parents reported noticeable behavioral changes. She showed signs of increased fatigue, hostility, irritability and depression. In 2015 the patient was implanted with a VNS stimulator device (LivaNova, Houston, TX, USA), resulting in several positive effects such as: reduction of daily seizures by 80%, decrement doses of anti-seizure drugs and improvement of behavior and quality of life.

For comparison, a control healthy girl of a similar age, height and ethnicity was recruited. Both subjects participated under parental written consent.

3. Materials and methods

3.1. Electrocardiogram acquisition

Electrocardiogram (ECG) data was recorded with a sampling rate of 500 Hz using a BIOPAC MP150® system and an ECG100C® amplifier module (Biopac Systems Inc., Santa Barbara, CA, USA). The participant was at rest in a supine position. The VNS device was turned on and off alternately, being on for 70 s and off 3 min. The stimulation parameters of the VNS device were configured as follows: output current 1.75 mA, signal frequency 20 Hz and pulse with 250 ms. After acquisition, the variations in the instantaneous heart rate time series were calculated using the inter-beat intervals (IBI) or R-R fluctuations series. These calculations were made using Matlab® software (the MathWorks, Inc. Natick, Massachusetts, USA).

3.2. Fractal heart rate variability analysis

The scaling parameters of IBI series were evaluated by applying detrended fluctuation analysis (DFA) and the magnitude and sign analyses (MSA). The DFA provided the scaling exponent α_1 as detailed in [7]. This method has proven useful in revealing the extent of long-range correlations in time series.

The first step is the integration of the IBI series, subsequently the integrated series were divided into segments having equal number of n segments. The local trends Yn were obtained for all segments by a least-squared line fit and subtracted from $Y(k)$ to reduce the non-stationary artifacts. The average root-mean-square fluctuations, $F(n)$, were calculated:

$$F(n) = \sqrt{\frac{1}{L}\sum_{k=1}^{L}[Y(k)-Y_n(k)]^2} \qquad \text{Equation (1)}$$

The relationship between $F(n)$ and time scales n on a double-log graph were approximated by a linear model $F(n) \sim n\alpha$, provided the scaling exponent α_1 as the slope of the plot, covering the short-term range of n from 4 to 11 intervals.

Nonlinearity and time ordering were assessed by MSA [8, 9]. Original sequences were processed to obtain a series of increments by taking the differences between adjacent intervals ($RR_{i+1} - RR_i$). These series (ΔRR) were decomposed into magnitude $|\Delta RR|$ and sign series $\pm$ (ΔRR). After subtracting their respective means, magnitude and sign series were integrated and DFA was again applied as described above (Equation 1). The slope of $F(n)/n$ covering the range from 4 to 11 intervals then provided magnitude and sign scaling exponents ($\alpha_{1(MAG)}$ and $\alpha_{1(SIGN)}$, respectively).

The $\alpha_{1(SIGN)}$ exponent provides information about the temporal directionality of the original series in relation to how series increments alternate. This indicated when a positive or negative subsequent increment (decrement) was more likely to occur given a current increment (decrement). Other results suggest that interaction between the sympathetic and the parasympathetic systems is reflected by the sign of the heartbeat increments [10] (Fig. 1). On the other hand, positive correlations in magnitude series (i.e. finding $\alpha_{1(MAG)} > 0.5$) are identified as reliable markers of nonlinear properties (Table 1). Linear classic parameters of HRV such as the standard deviation of NN intervals (SDNN), the root-mean square differences of successive R-R intervals (RMSSD), the NN interval percentage increments greater than 50 ms (PNN50) and the power of LF (low frequency) and HF (high frequency) are also reported in Table 1.

4. Discussion

In this case study, the use of linear and fractal analysis of HRV was implemented to explore cardiac autonomic changes due to VNS stimulation in a patient with drug-resistant epilepsy. Fractal analysis has been applied to reveal information about the complexity of physiological signals in other clinical scenarios, which has proven to be more sensitive to characterize different autonomic conditions in comparison to linear classical HRV methods [6, 11, 12].

Here, we found that the linear parameters of HRV (SDNN, RMSSD, PNN50, LF and HF) were increased as the VNS was turned on, in conjunction with changes in the fractal (nonlinear) exponents $\alpha_{1(SIGN)}$ and $\alpha_{1(MAGN)}$ (Table 1). Furthermore, it is possible to appreciate that fractal parameters estimated in this study are sensitive to VNS stimulation (Fig. 1). Hence, our results suggest that the presence of VNS lead to cardiac fluctuations in a patient with drug-resistant epilepsy, reflecting an increment on HRV non-linearity and a diminished anticorrelated pattern in IBI's. Likewise, the cardiac autonomic regulation in presence of stimulation seems to differ less in comparison with the healthy patient, indicating a cardiac autonomic improvement in response to vagal modulation in the person with epilepsy.

Recent findings have shown that the cardiovascular system is under sympathetic influence in children with epilepsy [13]. Thus, although VNS seems to provide a substantial improvement by achieving increased parasympathetic effects in short- or long- term therapy, vagal parameters of HRV such as RMSSD, PNN50 and HF are low in comparison to healthy children [13]. Interestingly, these results are in line with our observations (VNS off vs. control, Table 1). Noteworthy studies reveal that the degree of autonomic deregulation can be also quantified with the help of nonlinear dynamics of heart rate fluctuations [14]. However, according to the literature reviewed, this is one of the first reports that focuses on the exploration of vagal stimulation effects on sign and magnitude scaling properties of HRV in a patient with drug-resistant epilepsy. In this sense, our results show that fractal characteristics of HRV can change owing to parasympathetic function evoked by VNS.

This case report is also in line with another study in which HRV increased after VNS in a 15-year-old girl with Lennox–Gastaut syndrome (LGS) [3]. The severity of the autonomic damage is much greater in LGS in comparison to our patient, thus the comparison between linear indices is not possible. Despite this, both studies report an increment of the HRV parameters associated with vagal tone after VNS. Previous relevant research has considered that seizures increase key inflammatory mediators such as necrosis factor-α (TNF-α) interleukin-6 (IL-6) and interleukin-1β (IL-1β), which in turn cause secondary damage to the brain, augmenting the likelihood of recurrent seizures [15].

The HRV analysis has received increasing attention in the epilepsy field owing to its clinically usage. As an example, the effects of HRV in epilepsy were reviewed extensively elsewhere [16], concluding that patients with epilepsy might present an increased cardiovascular risk due to autonomic imbalance. According to some authors, the HRV analysis should be implemented as a tool to assess cardiovascular risk in

a) Absence of vagal estimulation

b) Presence of vagal stimulation
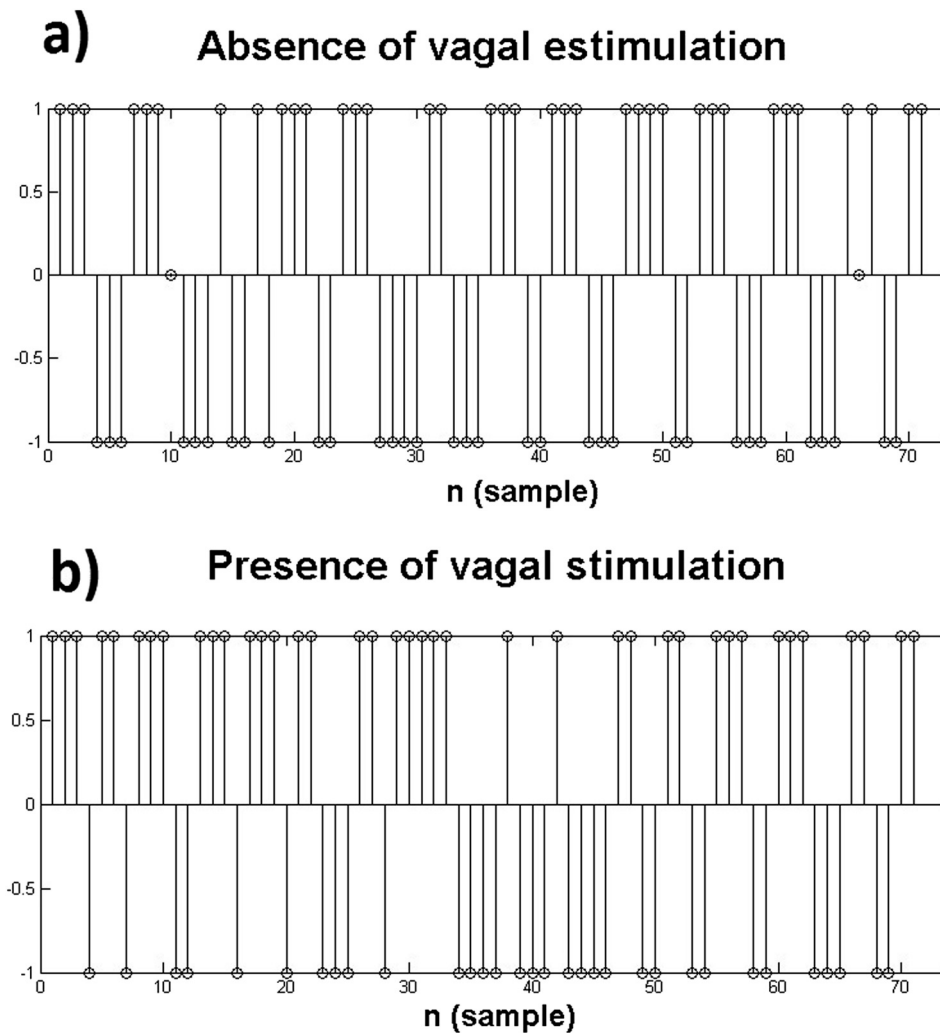
Fig. 1. Sign decomposition of inter-beat intervals (IBI) series following vagus nerve stimulation (VNS) in a patient with drug-resistant epilepsy: a) absence of VNS (the device was OFF), α_1 (SIGN) $= -0.13$ and b) presence of VNS (the device was ON), $\alpha_{1(SIGN)} = -0.07$. The sign series show more alternations without VNS, which suggest stronger anticorrelated behavior compared with the application of VNS.

epilepsy, as it is easily measured with standard electrocardiography devices and, thus, could be valuable to detect patients with increased cardiovascular risk and/or sudden unexpected death in epilepsy (SUDEP) [16]. In fact, SUDEP is the leading cause of death in persons with drug resistant epilepsy [17]. Additional studies also provide evidence that HRV is a marker of SUDEP risk. For example, it has been demonstrated that patients with drug-resistant epilepsy show increased heart rate and diminished HRV indices in comparison to healthy controls. Authors suggest that diminished HRV may constitute one of the possible

mechanisms underlying SUDEP [18]. Additionally, the RMSSD, which reflects the integrity of vagus nerve-mediated autonomic control of the heart, was highly associated with the total score on a new 7-item SUDEP risk inventory [19]. Thus, lower RMSSD values are associated with higher risk of SUDEP in epileptic patients [19].

Importantly, preliminary studies indicate that preoperative heart rhythm complexity is useful to predict the unresponsiveness to VNS treatment [20]. Furthermore, indices of linear HRV preoperatively demonstrate that responders of VNS have less impairment of parasympathetic cardiac control or vagal tone than the non-responders [20]. These results suggest that HRV parameters are clinically relevant for optimizing patient selection based on numerical measurements, which would encourage proper counseling of patients to avoid unnecessary VNS surgeries in patients expected to be non-responders [20].

A novel study indicates that patients with drug-resistant epilepsy have significantly lower linear and nonlinear HRV parameters than healthy controls [21]. This study concludes that autonomic cardiac control, especially parasympathetic cardiac control, is associated with the therapeutic effect to VNS in drug-resistant epilepsy patients [21]. In this sense, our results are also in line with these, since the linear and fractal parameters of the HRV analysis were also subtly modified in presence of VNS stimulation.

The potential clinical utility of fractal scaling exponents to explore systemic inflammatory processes involving the CAIP has been

Table 1
Linear and fractal heart rate variability indices following vagus nerve stimulation (VNS) in a patient with drug-resistant epilepsy. An additional healthy girl serving as a control (without epilepsy) was included for comparison.

	Patient (VNS off)	Patient (VNS on)	Control
Mean R-R interval (ms)	826.6	878.4	898.6
Mean Heart Rate (BPM)	73.0	68.0	67.3
SDNN (ms)	50.3	59.3	81.7
RMSSD (ms)	50.2	68.9	64.3
PNN50 (%)	37.1	59.0	44.6
Power LF (ms^2/s)	225.9	757.5	3296.2
Power HF (ms^2/s)	2038.0	2600.5	2223.2
$\alpha_{1(MAG)}$	0.03	0.34	0.36
$\alpha_{1(SIGN)}$	-0.13	-0.07	0.26

recently studied [5, 6]. Systemic inflammatory processes such as endotoxemia are characterized by a vagal withdrawal: a decrease on non-linearity and a higher anticorrelation in cardiac fluctuations [5]. For these reasons, we speculate that VNS stimulation could have potential anti-inflammatory effects that promote higher non-linearity and less anticorrelation in HRV, as indicated by $\alpha_{1(MAG)}$ and $\alpha_{1(SIGN)}$, respectively.

Finally, studies have also found that continuous stimulation can promote a tendency towards bradycardia [22] and asystoles [23], thus, a practical application of this study would be to develop a system that can monitor heart rate and fractal exponents and dynamically control the activation of VNS, automating the process of VNS switching.

5. Conclusion

Our results indicate that the activation of VNS increases the nonlinear dynamics (as indicated by higher values of $\alpha_{1(MAG)}$) and diminishes the anticorrelated behavior of heart rate fluctuations (as indicated by higher values of $\alpha_{1(SIGN)}$) in a patient with controlled drug-resistant epilepsy, suggesting a modulation of the parasympathetic system during VNS presence. We suggest that the monitoring of linear and fractal HRV properties could be implemented as a tool to assess cardiovascular risk in children with epilepsy implanted with VNS, particularly because their cardiovascular dynamics are prone to dysregulation in comparison to healthy children. A potential clinical usage of these parameters may include the detection of bradycardia, SUDEP risk and preoperative VNS approaches, however more studies are necessary to elucidate this possibility.

In general, scaling and magnitude properties of HRV analysis have a potential application offering non-invasive and fast diagnostic/prognostic information on VNS responsiveness in epilepsy treatment.

Disclosure

The authors declare no conflict of interest.

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