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Effects of vagus nerve stimulation on heart rate variability in children with epilepsy

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ABSTRACT

Purpose: The aim of this study was to evaluate the effects of vagus nerve stimulation (VNS) on heart rate variability (HRV) in children with epilepsy.
Methods: The subgroups of HRV, namely time domain (Standard deviation of NN interval (SDNN), SDNN index, Standard deviation of the averages of NN intervals (SDANN), Root mean square of successive differences (RMMSD), Adjacent NN intervals differing by more than 50 ms in the entire recording divided by the total number of all NN intervals (PNN50), triangular index) and frequency domain (Low-frequency (LF), High-frequency (HF), LF/HF), were investigated in 20 pediatric patients before and after 6 and 12 months of VNS treatment during day and night by comparing their data with those of 20 control subjects. In addition, subgroups of age, epilepsy duration and localization, and antiepileptic drugs (AEDs) were also evaluated if they had further effects on basal HRV levels.
Results: Increased heart rates (HRs); decreased SDNN, SDANN, RMMSD, and PNN50; and increased LF/HF ratios were identified before VNS therapy ($p < 0.05$). Even though remarkable improvement was seen after 6 months of VNS treatment ($p < 0.05$), no further changes were observed in 12-month compared with 6-month levels ($p > 0.05$) in all parameters, still even significantly lower than those of controls ($p < 0.05$). Longer duration of epilepsy and localization of epileptic focus, such as in the temporal lobe, were also found to further contribute to diminished basal HRV levels ($p < 0.05$).
Conclusion: The cardiovascular system is under deep sympathetic influence in children with epilepsy. Although VNS seems to provide a substantial improvement by achieving increased parasympathetic effects in short-term therapy, the levels were still lower than those of healthy children after either short- or long-term therapy. Therefore, impaired cardiovascular autonomic regulation may be associated with the epileptic process itself as well as with the contribution of some additional factors. Overall, different aspects such as age, epilepsy duration, epileptic focus, seizure frequency, and AEDs should also be considered for their further possible effects on HRV during VNS therapy.

1. Introduction

Vagus nerve stimulation (VNS) is one of the effective therapies for patients with epilepsy who are not candidates for resective surgery or had unsatisfactory seizure control after surgery [1–5]. While it is assumed that VNS is a safe and tolerable method, the mechanism is not completely understood [3,6–11]. The afferent and efferent currents are supposed to be responsible for short- and long-term effects [3,8,12]. While afferent stimulation is thought to cause increased parasympathetic outflow through the solitary tract, recent data have shown that efferent fibers can also lead to increased release of serotonin and epinephrine as long-term effects of VNS [3,8,12,13].

The relationship between VNS and cardiac rhythms, which is termed "heart rate variability (HRV)," is uncertain, with some questions being raised as to whether VNS exerts either protective or negative effects on heart compliance ability under different conditions [4,5,7,9,10,12, 14–19]. Furthermore, a dysfunction of the autonomic nervous system (ANS) is a well-known situation in patients with refractory epilepsy as a consequence of abnormal neuronal activity at the central control of

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cardiac functions [4,5]. Therefore, the interaction between ANS, HRV, and VNS is complex and unclear [14–19].

There are limited and controversial studies about VNS on HRV in children with epilepsy [5,12,14–16]. Many of these studies include mixed age groups comprising adults and children, with no detailed examinations such as circadian rhythms of sympathetic and parasympathetic parameters [4,10,14,17,18]. Some of these studies showed that VNS had no effects on HRV, while others found some improvement in or conversely diminished HRV levels, which may lead to significant complications such as sudden unexpected death in epilepsy (SUDEP) [4,5,7,9,10,12,14–19]. Therefore, the clinical relevance and importance of changes in HRV parameters are debatable and need to be cautiously and closely followed up for immediate interventions during VNS therapy [4,5,7,9,10,12,14–19].

Some contributory factors to HRV changes, such as epilepsy duration, seizure frequency, antiepileptic drugs (AEDs), and localization of epileptic focus, may have independent effects on heart compliance during VNS therapy [6,7,19–27]. Even though there are some unique investigations about these presumable factors [6,7,19–27], none of them discussed whether some additional effects occurred in addition to the VNS effects at the same time.

The purpose of this study was to investigate the effects of VNS and the possible contributory factors on cardiac autonomic control by assessing interictal HRV in children with refractory epilepsy before (basal) and after 6- and 12-month VNS treatment.

2. Materials and methods

2.1. Patients and demographics

Twenty patients (9 girls, 11 boys) with intractable epilepsy aged between 4 and 17 years (mean age: 11.7 ± 4.2 years) were evaluated retrospectively in terms of interictal HRV with 24-h electrocardiogram (ECG) recordings before and after 6 and 12 months of VNS treatment at the Epilepsy Center of the Department of Pediatric Neurology and Medicine and at the Ankara Children's Hematology Oncology Training and Research Hospital, Department of Pediatric Cardiology, between 2012 and 2014. Inclusion criteria were (1) presence of intractable epilepsy with at least two AEDs during the last 2 years; (2) the localization of the epileptogenic zone on the basis of long-term video electroencephalogram (EEG) monitoring and inappropriate MRI findings for resective surgery, such as close proximity to the eloquent cortex; or (3) the patient having already undergone surgery but experienced unsatisfactory results in terms of seizure control. Demographics, medical records, neuroimaging, and detailed cardiac examination (ECG, echocardiogram (ECHO), 24-h rhythm Holter monitoring) were obtained from the chart reviews. Epilepsy duration, seizure location and frequency, AEDs, and response to treatment were categorized and compared with HRV basal levels (Table 1).

Because there are no well-established levels of HRV for children, 20 healthy children with the same age (range: 5–18 and mean age 11.7 ± 4 years) and gender (9 girls, 11 boys) who were admitted with complaints of murmur, chest pain, or palpitation and had ECG, ECHO, and 24-h rhythm Holter findings within normal limits were used to compare with the levels of the patients.

2.2. VNS procedure

After implantation of a vagus nerve stimulator (model 103 neurocybernetic prosthesis; Cyberonics, Pulse Generator, Houston, TX, USA), the stimulation was started with the following parameters: 0.25 mA, 30-Hz frequency, 500-ms pulse width, 30-s on time, and 5-min off time. Although each patient was unique, the output current was increased by 0.25 mA every 2 weeks, with a total of 6 visits; this is consistent with the usual procedure. Subsequently, the stimulation was modified depending on the response of each patient and the applied duty cycle. The main changes were applied on "on time" and "off time," which means decreased minutes and shortened duration. The desired levels were usually obtained within 4 to 5 months of treatment. The detailed settings of VNS are presented as 6- and 12-month mean levels in Table 1.

Table 1
Demographics, etiology, risk factors, seizure, and epilepsy classification.

Variables	n: 20
Age (year)—vagus nerve stimulator implantation	11.7 (±4.2)
Epilepsy duration before VNS (year)	8 (±4.3)
The number of AEDs	3.2 (2–5)
Combination of CBZ	6 (30%)
Seizure frequency	
Daily	16 (80%)
Persistent	4 (20%)
Risk factors for epilepsy	
Hypoxia–hypoglycemia–jaundice	7 (35%)
Trauma	4 (20%)
Family history	2 (10%)
Unknown	7 (35%)
Comorbidity	
Mental-motor retardation	9 (45%)
Motor deficit	2 (10%)
Etiology	
Encephalomalacia (n: 7)–atrophy (n: 4)	7 (55%)
FCD—developmental tumors	4 (20%)
Unknown	5 (25%)
Seizure classification	
Generalized seizures	17 (85%)
GTC	8 (40%)
Atypical absence	4 (20%)
Myoclonic	2 (10%)
Atonic	2 (10%)
Tonic	1 (5%)
Focal seizures	11 (55%)
Dyscognitive seizures	6 (30%)
Motor seizures	5 (25%)
Epileptic spasms	5 (25%)
EEG findings	
Temporal lobe involvement	6 (30%)
Multilobar–hemispheric–generalized	10 (50%)
Response to VNS (50% reduction in seizure frequency)	
6th month of the therapy	14 (70%)
12th month of the therapy	18 (90%)

VNS: vagus nerve stimulation, AEDs: antiepileptic drugs, CBZ: carbamazepine, FCD: focal cortical dysplasia, GTC: generalized tonic–clonic seizures.

2.3. HRV assessment

Analysis of HRV was performed through CardioScan 11.0 (DM Software Inc., Stateline, NV, USA) software with 24-h rhythm Holter parameters by dividing it into two different time periods, daytime (between 7:00 and 23:00) and nighttime (between 23:00 and 7:00), for both patients (before and after 6 months (short term) and 12 months (long term)) and control subjects (at admission). The processed signal was derived from surface electrodes on the chest. The Ventricular depolarization prior to contraction of the ventricles (QRS) complexes were automatically identified and labeled by the software and reviewed manually to limit any potential artifacts. The interictal period, with the exclusion of the ictal, preictal, and postictal 1-h period, was used to assess time- and frequency-domain parameters [28,29].

2.3.1. Time-domain parameters (representing the changes of beat-to-beat intervals: (NN or RR intervals))

The mean, minimum, and maximum *heart rates* (HRs) and *pulse intervals* were calculated using the differences between the maximum and minimum HRs.

Standard deviation of all NN intervals (*SDNN*), Standard deviation of the averages of NN intervals in all 5-min segments of the entire