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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.

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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

recording (*SDANN*), and Standard deviations of all NN intervals for all 5-min segments of the entire recording (*SDNN index*) represent sympathetic activity and reflect diurnal and daytime effects. *SDNN* is a standard deviation of all NN intervals; *SDANN* is a standard deviation of the averages of NN intervals in all 5-min segments of the entire recording; *SDNN index* is standard deviations of all NN intervals for all 5-min segments of the entire recording.

RMMSD and *PNN50* represent direct parasympathetic activity and reflect nighttime effects independently from diurnal effects. *RMSSD* shows the square root of the mean of the sum of the squares of differences between adjacent NN intervals; *PNN50* shows adjacent NN intervals differing by more than 50 ms in the entire recording divided by the total number of all NN intervals.

Triangular index is a basic parameter for overall HRV; it is also known as the "heart rate variability index" and is suppressed by sympathetic effects. The triangular index is calculated by measuring the integral of the density distribution (the number of all NN intervals divided by the maximum of the density distribution).

2.3.2. Frequency-domain parameters (representing the occurrence of oscillations in the cardiac rhythm in certain frequencies)

Low-frequency band (LF: 0.04–0.15 Hz) shows sympathetic activity especially during daytime with some intermixed parasympathetic activity.

High-frequency band (HF: 0.15–0.4 Hz) represents parasympathetic activity during nighttime.

LF/HF ratio is calculated to exclude parasympathetic components in the LF. While high LF/HF ratios reflect an increase in sympathetic activity, low ratios show an increase in parasympathetic activity.

Total power reflects oscillations of the HR and represents the frequency of HR oscillations during the day.

2.4. Assessment of contributory factors

As the last step, we compared all the results of HRV before and after 6 and 12 months of treatment by dividing the participants into specific age groups: younger than 6 years (n: 3, 15%), school-aged (6–12 years, n: 8, 40%), and adolescent (older than 12 years, n: 9, 45%).

Effects of epilepsy duration, localization of the epileptogenic zone confining temporal lobe involvement, use or no use of AEDs such as carbamazepine (CBZ), and 50% decrease in seizure frequency after treatment were also comprehensively analyzed to assess whether they contribute to HRV levels as mentioned in the statistical analysis.

2.5. Statistical analysis

Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0 for Windows was used for analysis and comparison of the data. Descriptive data were expressed as mean values ± standard deviations. Distribution of variables was analyzed through Levene's test; afterwards, analysis of variance (ANOVA) was used to compare the value of HRV for the basal period and 6 and 12 months after VNS treatment, and control groups. The same tests were also applied to calculate if there were any differences between VNS settings when comparing 6- and 12-month values.

The Kruskal–Wallis test was performed to determine whether any differences existed between the HRV levels in the three age subgroups before and after VNS treatment. The Mann–Whitney U test was used to evaluate whether differences existed between HRV and seizure frequency, CBZ usage, and localization of the epileptogenic zone. The relationship between epilepsy duration and HRV measurements was assessed through Spearman's correlation before VNS. A p-value of <0.05 was considered statistically significant.

Approval for this study was granted by the Gazi University School of Medicine Ethical Committee (number: 83824). Informed consent was also obtained from the parents before the procedures.

3. Results

3.1. Patients and demographics

Twenty patients had long-lasting epilepsy (2–15 years) with daily frequency (80%) and multiple seizure types (30%). All children received polytherapy (n: 2–5), 6 (30%) of whom were using combination of CBZ and another drug/other drugs. Almost half of the patients had a widely distributed and multilobar epileptogenic zone which was in close association with the eloquent cortex. Temporal lobe involvement was noted (n: 6, 30%) as a part of either anterior or posterior cortex epilepsy or given an independent focus depending on EEG findings (Table 1). Six-month treatment results were named "short- or early-term" outcome, while 12-month treatment results were called "long-term" outcome. The terms "markedly" or "remarkable" represent a statistically significant value of $p < 0.05$. Control groups refer to "healthy children."

3.2. HRs and pulse intervals

Patients had increased mean HRs (95 ± 12 beats/min) with narrowed pulse intervals (94 ± 23) compared with controls before VNS treatment ($p < 0.05$). Interestingly, despite a decrease in mean HR (90 ± 9) at 6 months ($p < 0.05$), this improvement tended to disappear at 12 months (92 ± 8 min/s) and reached closer to the basal levels. Overall, even if some improvement was observed in the early periods of treatment, there were still remarkable differences in HR and pulse intervals between the group with epilepsy and healthy children before and after VNS treatment ($p < 0.05$) (Table 2, Fig. 1).

3.3. Time-domain parameters

The sympathetic system had dominant effects during daytime, whereas the parasympathetic system was deeply suppressed before the treatment. Therefore, the SDNN, SDNN index, and SDANN of the patients were significantly lower than those of the control group not only during the day but also at night before the treatment ($p < 0.001$). Despite a remarkable improvement at 6 and 12 months of treatment ($p < 0.05$), these parameters were still significantly lower than those of the healthy children ($p < 0.001$). These levels became stable, and the differences were decreased at 12 months compared with those at 6 months. Furthermore, the significance achieved for the SDNN index at 6 months disappeared at 12 months of treatment ($p = 0.2$). On the other hand, SDNN before treatment was remarkably improved at both 6 and 12 months during daytime ($p < 0.01$) (Table 2, Fig. 1).

RMMSD and PNN50 values were approximately twice lower than those before treatment ($p < 0.001$). Even if there were significantly increased parasympathetic effects, those are still under remarkable sympathetic currents after 6 months of treatment compared with those of controls ($p < 0.05$). However, RMSSD and PNN50 deteriorated during the last 6 months and reached closer to pretreatments levels at 12 months of treatment ($p > 0.05$) (Table 2, Fig. 1).

The HRV index (triangular index) of the patients was decreased almost twice compared with that of controls because of suppressed parasympathetic effects ($p < 0.001$). This suppression remained for the patient group at both 6 and 12 months compared with that of controls ($p < 0.001$), even though there was a significant increase at 6 ($p < 0.01$) and 12 months ($p < 0.05$) of treatment, with no further improvement as compared with that measured at 6 months (Table 2, Fig. 1).

3.4. Frequency-domain parameters

Patients' total, daytime, and nighttime levels for both LF and HF were significantly lower than those of the control group before and after 6 and 12 months of treatment ($p < 0.001$). Although some significant

Table 2
HRV parameters and VNS settings.

Parameters	Before VNS	6th month	12th month	Control	P1 B-C	P2 6-C	P3 12-C	P4 B-6	P5 B-12	P6 6–12
Time-domain parameters										
Minimum HR	58 ± 10	54 ± 9	55 ± 7	48 ± 4	<**0.001**	<**0.01**	<**0.001**	0.2	0.2	0.7
Maximum HR	152 ± 23	155 ± 17	155 ± 20	168 ± 16	<**0.05**	<**0.05**	<**0.05**	0.9	0.5	0.9
Mean HR	95 ± 12	90 ± 9	92 ± 8	83 ± 7	<**0.001**	<**0.05**	<**0.001**	<**0.05**	0.1	0.3
Pulse interval	94 ± 23	100 ± 15	100 ± 20	120 ± 17	<**0.001**	<**0.01**	<**0.001**	0.4	0.3	0.8
SDNN	93 ± 30	111 ± 24	111 ± 29	151 ± 36	<**0.001**	<**0.001**	<**0.001**	<**0.01**	<**0.05**	0.6
SDNN index	41 ± 15	49 ± 13	46 ± 10	73 ± 15	<**0.001**	<**0.001**	<**0.001**	<**0.05**	0.2	0.1
SDANN	83 ± 31	100 ± 24	100 ± 29	131 ± 36	<**0.001**	<**0.01**	<**0.01**	<**0.01**	<**0.05**	0.6
RMMSD	29 ± 15	38 ± 18	33 ± 11	49 ± 15	<**0.001**	<**0.05**	<**0.001**	<**0.05**	0.2	0.1
PNN50	10 ± 10	15 ± 12	11 ± 8	22 ± 9	<**0.001**	<**0.05**	<**0.001**	<**0.05**	0.4	0.1
Daytime SDNN	77 ± 25	97 ± 21	96 ± 29	127 ± 33	<**0.001**	<**0.01**	<**0.01**	<**0.01**	<**0.01**	0.8
Daytime RMMSD	25 ± 12	33 ± 14	28 ± 9	42 ± 14	<**0.001**	<**0.05**	<**0.001**	<**0.01**	0.1	0.1
Daytime PNN50	7 ± 7	11 ± 9	8 ± 6	18 ± 9	<**0.001**	<**0.05**	<**0.001**	<**0.05**	0.5	0.1
Nighttime SDNN	68 ± 28	80 ± 24	78 ± 24	115 ± 24	<**0.001**	<**0.001**	<**0.001**	0.1	0.1	0.9
Nighttime RMMSD	37 ± 21	46 ± 23	41 ± 16	64 ± 21	<**0.001**	<**0.05**	<**0.001**	<**0.05**	0.4	0.3
Nighttime PNN50	16 ± 16	22 ± 17	19 ± 13	36 ± 12	<**0.001**	<**0.01**	<**0.001**	0.1	0.4	0.3
Triangular index	24 ± 10	31 ± 9	30 ± 10	46 ± 13	<**0.001**	<**0.001**	<**0.001**	<**0.01**	<**0.05**	0.9
Frequency-domain parameters										
LF	345 ± 250	505 ± 263	421 ± 179	1030 ± 336	<**0.001**	<**0.001**	<**0.001**	<**0.01**	0.1	<**0.05**
HF	259 ± 206	388 ± 243	332 ± 187	629 ± 266	<**0.001**	<**0.01**	<**0.001**	<**0.001**	0.1	0.1
LF/HF	1.85 ± 1.26	1.58 ± 0.79	1.47 ± 0.61	1.77 ± 0.62	0.8	0.4	0.1	0.2	0.2	0.5
Total power	1637 ± 1149	2331 ± 1074	2027 ± 823	5199 ± 2124	<**0.001**	<**0.001**	<**0.001**	<**0.01**	<**0.05**	<**0.05**
Daytime LF	295 ± 211	444 ± 222	387 ± 141	890 ± 298	<**0.001**	<**0.001**	<**0.001**	<**0.01**	<**0.05**	0.2
Daytime HF	189 ± 187	287 ± 179	232 ± 136	470 ± 242	<**0.001**	<**0.05**	<**0.001**	<**0.01**	0.3	0.2
Daytime LF/HF	2.36 ± 1.55	1.8 ± 0.76	1.88 ± 0.62	2.16 ± 0.84	0.8	<**0.05**	0.2	0.1	0.2	0.6
Daytime total power	1428 ± 986	2103 ± 1048	1798 ± 786	4715 ± 2092	<**0.001**	<**0.001**	<**0.001**	<**0.01**	<**0.01**	0.1
Nighttime LF	428 ± 372	579 ± 335	477 ± 276	1311 ± 602	<**0.001**	<**0.001**	<**0.001**	<**0.05**	0.6	0.1
Nighttime HF	387 ± 306	544 ± 385	505 ± 320	918 ± 387	<**0.001**	<**0.01**	<**0.001**	<**0.05**	0.1	0.5
Nighttime LF/HF	1.55 ± 1.21	1.46 ± 0.99	1.22 ± 0.74	1.56 ± 0.71	0.9	0.7	0.2	0.6	0.3	0.2
Nighttime total power	1975 ± 1535	2680 ± 1234	2329 ± 1090	6014 ± 2727	<**0.001**	<**0.001**	<**0.001**	<**0.05**	0.3	0.1
VNS settings										
Amplitude (mA)	–	1.36 ± 0.71	1.5 ± 0.5	–	–	–	–	–	–	>0.05
Frequency (Hz)	–	29 ± 2.05	29 ± 1.5	–	–	–	–	–	–	>0.05
Pulse width (ms)	–	28.5 ± 2.8	29.5 ± 1.5	–	–	–	–	–	–	>0.05

B: before VNS; C: control group; 6: 6th month; 12: 12th month.
P1: HRV levels before VNS—control group; P2: after 6-month treatment—control group, P3: after 12-month treatment—control group, P4: before VNS—after 6 months; P5: before VNS—after 12 months; P6: after 6 and 12 months—comparison.
Distribution of variables was analyzed through Levene's test; afterwards, comparison of the groups between each other was performed using ANOVA test.
Bold color represents statistically significant values.

improvement was observed at 6 months ($p < 0.05$), these levels gradually decreased and tended to be close to the pretreatment levels at 12 months of therapy ($p > 0.05$). The LF/HF ratios were stable, and no significant differences were observed between patients (before and 6- and 12-month treatment periods) and controls for total and nighttime levels ($p > 0.05$). On the other hand, patients' LF/HF levels were

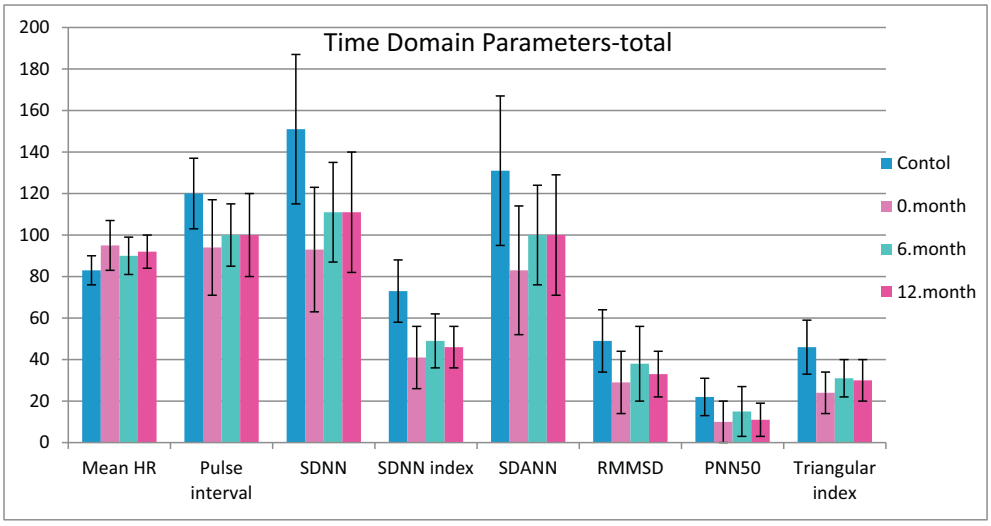


Fig. 1. Before treatment (0. month): Significant suppressed levels ($p < 0.05$). Six-month-treatment: Significant improvement ($p < 0.05$). Twelve-month-treatment: No further improvement, even getting closer to the basal rhythm. Refer to Table 2 for details of the p values.

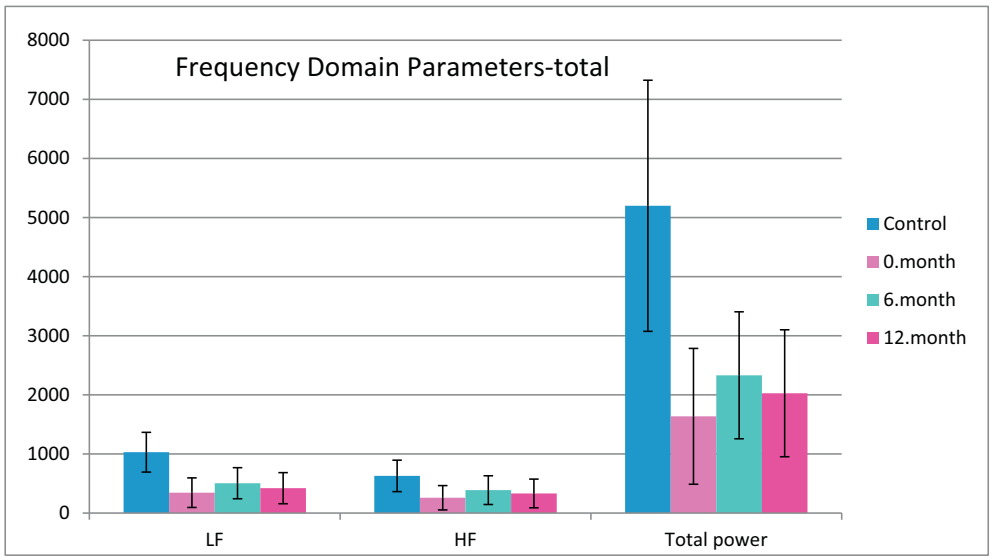


Fig. 2. Before treatment (0. month): Significant suppressed levels ($p<0.05$). Six-month-treatment: Significant improvement ($p<0.05$). Twelve-month-treatment: No further improvement, even getting closer to the basal rhythm. Refer to table 2 for details of the p values.

decreased at 6 months compared with those of controls ($p < 0.05$) during daytime; this may be an effect of VNS because of increased parasympathetic effects. However, this parasympathetic increment along with the reduced sympathetic effects was temporary, and no noteworthy changes were observed at 12 months compared with 6-month results (Table 2, Figs. 2 and 3).

Overall, when the measurements of HRV were compared between 6 and 12 months, there were differences only in total power and LF levels ($p < 0.05$). There were no differences for all the remaining parameters of HRV (both time and frequency domains) between 6 and 12 months ($p > 0.05$) (Table 2, Figs. 2 and 3).

Total power in the patient group was decreased by approximately three times before VNS treatment compared with that of the control group ($p < 0.001$). Although there was a significant improvement at 6 and 12 months of treatment, total power in patients was still lower than that of the control group ($p < 0.001$). Interestingly, this improvement was reduced at 12 months compared with the 6-month levels ($p < 0.05$). Total power was significantly increased at both 6 and 12 months during daytime, and these differences regressed to pretreatment levels at 12 months during nighttime (Table 2, Figs. 2 and 3).

3.5. Relationship between possible contributing factors and HRV

When we compared HRV by dividing the participants into specific age groups, there were no differences between the levels of HRV before and after 6 and 12 months of treatment among preschool (n: 3), school-aged (n: 8), and adolescent (n: 9) subgroups ($p > 0.05$).

Longer durations of epilepsy were related to more decreased parasympathetic effects during daytime RMSSD (r: −0.487) and HF (r: −0.452) levels at the beginning of the VNS therapy ($p < 0.05$). Involvement of the temporal lobe (6 patients, 30%) seemed to be one

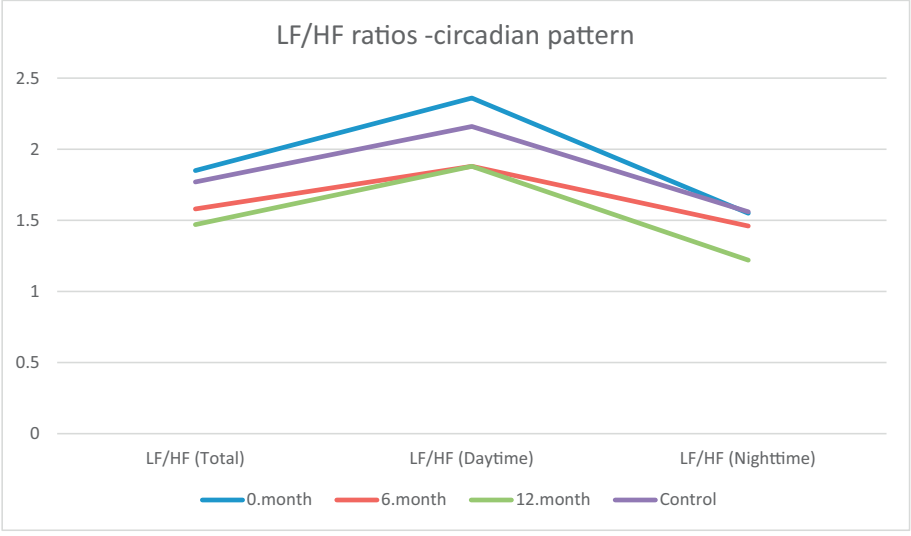


Fig. 3. LH/HF ratios pointed to deep sympathetic effects before the treatment. No significant improvement during treatment was observed, while a temporary improvement was observed after 6-month therapy with VNS.

of the reasons for increased daytime sympathetic effects with higher levels of LF ($p < 0.005$) both before and after one year of treatment.

A total of 70% (n: 14) and 90% (n: 18) of patients had at least 50% less seizures at 6 and 12 months, respectively. However, there was no correlation between these reduction rates and HRV ($p > 0.05$) levels during any time of the treatment.

As the final step, the effects of AEDs were investigated by comparing with CBZ usage as part of polytherapy (6 patients, 30%). No differences were observed in HRV between the groups regardless of whether they took CBZ combination with other drugs or not ($p > 0.05$).

4. Discussion

Heart rate variability is an important tool for the evaluation of heart compliance to different conditions and stimuli [5,10,12,14–16,30]. Our study is one of the rare and comprehensive attempts to evaluate the relationship between HRV and VNS by considering further contributing factors such as epilepsy duration, seizure frequency, and epileptic focus in children with epilepsy. We revealed some significant evidence about impaired HRV before VNS therapy and remarkable improvement after short-term therapy, while some rebound effects occurred during long-term follow-up.

Interaction between VNS and HRV is complex and cannot be clearly understood [3,6–11]. It is assumed that a wide variety of afferent and efferent signals are sent throughout the forebrain, thalamus, limbic structures, and brainstem during VNS action [4,5,9,30]. Some studies indicate that VNS may have some protective effects against myocardial infarction and ventricular arrhythmia [9], while some authors argue that VNS cannot provide significant improvement on HRV [4,10,17,30] and even an impaired HRV presented with higher HRs in adults and children [5]. In agreement with these findings, the results of our study indicate that our patients had tachycardia as a basal cardiac rhythm before VNS, and then they had larger pulse intervals after short-term follow-up with VNS, even though these effects were temporary and tended to revert to pretreatment levels in time.

SDNN and SDANN are the time-domain parameters that represent daytime sympathetic currents, while RMMSD and PNN50 increase at night because of representation of parasympathetic currents [27,28]. In some studies with adult participants, even if there was a mild improvement in SDNN and SDANN, these levels in patients were still significantly lower than those of controls [4,17]. Similarly, we found decreased levels of SDNN and SDANN with deeply suppressed night RMMSD and PNN50 levels. There was a significant improvement in all the parameters within 6 and 12 months of treatment; however, dominant sympathetic effects were still ongoing in children with epilepsy compared with healthy children and became stable in time with a tendency to revert to prior levels at the end of one year of VNS therapy. In contrast to all these abovementioned findings, Jansen et al. demonstrated increased sympathetic effects with decreased RMSSD and PNN50 levels without any improvement from the beginning to the long-term (36 months) follow-up, with a tendency of increased trends in all sleep stages [5]. Hence, almost no changes or further decrease in all frequency domains may imply that deep sympathetic impacts of epilepsy cannot completely heal because of the ongoing stimulation by the existing disease [4,5,9,10,12,14,16,17]. Consequently, epilepsy can cause sustained brain injury and vagal suppression with some irreversible functional and structural changes, such as gaining autonomy in ANS [4,5,9,15,22,23].

It has been postulated that impaired fluctuations of frequency domains (LH, HF, LF/HF) may cause poor adaptation ability to different stimuli. Either improved [10] or suppressed [4] levels of LF (sympathetic) and HF (parasympathetic) were shown during long- or short-term follow-up with VNS in some studies with adult participants [4,10]. In the present study, we demonstrated decreased sympathetic effects with remarkably increased parasympathetic currents of HF levels at 6 months of VNS treatment. Similar to time-domain parameters, this improvement was temporary and tended to return to levels closer to the previous levels of the treatment at 12 months. However, Pruvost et al. showed that VNS can improve HRV by increasing HF levels between 7 and 34 months without any evidence of rebound effects in children with epilepsy [14]. On the other hand, Ronkainen et al. showed neither worsened nor improved patterns compared with pretreatment levels [4]. The different settings of the studies in terms of comparison with controls, consideration of circadian patterns, follow-up durations, and alternate mechanisms of VNS may explain these varied results in different age groups, even among children [5,14,15]. Therefore, some authors suggest that HRV should be rearranged according to age groups because basal levels and response to various stimuli can change depending on the maturational steps of the brain and heart [5,7,14]. In this respect, as age increases, the balance between the sympathovagal tonus switches to the sympathetic side, especially during sleep [5]. Conversely, we could not confirm this assumption when HRV levels were compared by dividing the participants into preschool, school-aged, and adolescent groups; this may be a result of a limited number of patients in each group or due to contribution of other factors that can affect HRV independently.

Daytime or nighttime fluctuations should be considered when evaluating circadian patterns of HRV [4,5,12,14,16,17]. Jansen et al. showed decreased HRV with increased sympathetic activity during all sleep stages even before or after VNS therapy in children [3]. They also found less sympathetic activity (lower LF/HF) at stage 2, while sympathetic activity increased (higher LF/HF) at slow-wave sleep in the patient group compared with the controls [3]. Related to this result, our study has strengthened arguments that cardiac autonomic control was under sympathetic effects as it constituted increased LF/HF ratios during both daytime and nighttime. Parasympathetic increments along with reduced sympathetic levels were seen during the first 6 months of treatment; however, these effects were temporary as shown in our previous results. Similar to our results, those of Galli et al. have also shown decreased parasympathetic effects during sleep and significantly narrowed and blunted day-to-night change in LF/HF levels in the long-term follow-up of VNS [17]. On the other hand, during activation procedures such as supine or head-up tilted position, there were no differences in the levels of LF, HF, and LF/HF ratios in patients with epilepsy, while increased sympathetic currents and LF/HF ratios were found in healthy subjects [15]. Recently, Garamendi et al. showed that VNS had no effects on HRV during stretching and some activation procedures [30]. Thus, awareness for possible loss of variability in HRV might be important during stressful conditions in patients with epilepsy [4,5,7,12,14,16,17].

Overall, abnormal distribution of sympathetic and parasympathetic currents may lead to irregular and monotonous heart rhythms, which may appear as arrhythmia and SUDEP [3–7,10–25]. The evaluation of the oscillation capacity of HR may be a reliable approach to predict some complications and the possibility of SUDEP [4,5,9,15,22,23]. Related to this, Schomer et al. evaluated the relationship between T-wave alternans (TWA), which is a proven parameter for SUDEP in cardiovascular disease, and HRV during VNS therapy. They found that lower TWA levels was correlated with improved HRV, which was related to VNS intensity at times [19]. In light of those findings, we evaluated “total power” and “triangular index,” its supportive parameter, to identify compliance capacity of the heart and its relationship with VNS. We identified an oscillation capacity of HR in our patient group two to three times lower than in the healthy children. Even if some improvement occurs at 6 and 12 months, these levels still fail to reach the desired levels at night, and furthermore, some rebounded at the one-year treatment to presurgery levels. As recently assumed, the possible reasons for this temporary improvement may be due to the long-term effects of VNS on the locus coeruleus and dorsal motor nucleus, which presented as increased sympathetic currents like serotonin and norepinephrine, into the hippocampus and prefrontal cortex, beyond the well-known effects of VNS via nucleus tractus solitaries in

a short-term period [1,3,8–14]. Therefore, the short- and long-term influences of VNS can change depending on the duration of treatment [26]. As a consequence, a dominant effect seems to occur on the sympathetic pathway over a time period and can provide some preventive effects against SUDEP [1,3,8–14].

Decreased balance between central sympathetic and parasympathetic outflow is a well-known situation in cases of intractable epilepsy [4,5,9,14]. Epilepsy duration, seizure localization and frequency, and AEDs can affect HRV and further influence the outcome during VNS therapy [1,4–7,15,17,20–24]. Mukherjee et al. compared HRV levels between a group with well-controlled seizures and a group with refractory seizures. The group with uncontrolled seizures showed increased sympathetic tonus with reduced HRV parameters [27]. Related to this, Liu et al. showed that better improvement in HRV levels was strongly associated with better seizure control after VNS treatment. Therefore, they argued that pretreatment HRV levels may predict both improved cardiac functions as well as decreased seizure frequency after VNS therapy [18]. In concordance with these studies, we found that a longer duration of epilepsy was related to more suppressed parasympathetic outflows, which was related to decreased levels in both time and frequency domains before VNS therapy. Therefore, chronic and repetitive stimulation may lead to ischemia and fibrosis of the heart as well as unstable and decreased HRV with increasing ventricular automaticity and arrhythmias [3–7,10–25]. Sympathetic outputs of the cardiovascular system are controlled by the higher cortical areas known as the limbic system, which include the insula, orbitofrontal cortex, mesial temporal lobe structures, and cingulate gyrus [1,5–7,15]. Decreased HRV and baroreflex dysfunctions represented by lower LF were reported in TLE [3,10,20]. In support of these findings, 30% of our patients had temporal lobe involvement with increased daytime sympathetic effects and higher levels of LF before or after treatment with VNS.

There is some evidence that a better HRV can be established from the responders to VNS treatment, while some studies have shown no correlation between seizure frequency and HRV during treatment [4,15,20,21]. As a striking point of our study, even though at least 50% seizure reduction was observed in 70% of the patients at 6 months and 90% at one year of treatment, no significant changes were observed in terms of HRV. Therefore, we agree with the argument that epilepsy is a chronic condition and may cause decreased HRV independent of the seizure reduction rate [4,8,15,17,21,26]. Furthermore, in contrast to previous studies, we could not show any relationship between AED therapy with combination of CBZ and another drugs or not and HRV [22,23]. Overall, many factors beyond VNS itself seem to contribute to the fluctuation of HRV and should be considered while evaluating VNS effects on HRV [1,4–7,15,17,20–24].

As a limitation of our study, we measured HRV levels for the patient group at multiple time points (0, 6, and 12 months) compared with only one time point for the control group. Thus, there is only one dataset for the control group. Because repeated testing was performed, information on intra-individual changes can be affected because of age-related changes in HRV, which is especially pronounced at younger ages, even though our patients (4–17 years of age, mean age: 11.7 ± 4.2 years) were still in the same age groups with the controls (5–18 years of age, mean age: 11.7 ± 4 years) at the end of one year. Eventually, the effects of time- and age-related changes in HRV are still unclear when evaluating the data in the time series. More detailed studies are needed by considering this age-related point in the future.

5. Conclusion

In the present study, we showed that the deep sympathetic effect of cardiac autonomic control suppressed time- and frequency-domain parameters in both daytime and nighttime before or after VNS treatment. Although there was an improvement in parasympathetic effects in short-term therapy, these effects are transient, and some “rebound” effects were observed in the long-term follow-up. Therefore, our study has strengthened the idea that the short-term effect of VNS is from the parasympathetic pathway, and temporary, long-term antiepileptic effects are possible with the central sympathetic system. However, some contributory factors should not be ignored as independent factors for decreased HRV. The duration of follow-up and the epileptogenic zone can show further negative effects on HRV and may be important when assessing the modulation capacity of the heart during VNS treatment. Overall, some basic parameters should be developed and controlled with periodic intervals to prevent mortal complications such as SUDEP. To our knowledge, the current study is one of the only detailed efforts to investigate the effects of VNS on HRV along with further contributory factors in children with epilepsy.

Conflict of interest

None of the authors have any conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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