



Can heart rate variability in children with epilepsy be used to predict seizures?



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ABSTRACT

Purpose: The aim of this study was to examine interictal, pre-ictal and ictal autonomic system disturbance by comparing heart rate variability in children with uncontrolled epilepsy with that seen in healthy controls and children with controlled epilepsy.

Methods: Our study group included 20 children with refractory epilepsy, our control groups were composed of 20 children with well-controlled epilepsy and 20 healthy children. All subjects were evaluated by Holter ECG monitoring and 12-lead ECG to assess heart rate variability and QTc dispersion. The study group was also evaluated by Holter ECG during seizures.

Results: The study group exhibited significantly more pathological QTc dispersion than did the control groups. Heart rate variability was significantly suppressed: reduced parasympathetic activity with lower low frequency (LF) and high frequency (HF) band values were observed in the study group. Findings were similar in the well-controlled epilepsy group and the healthy group but differed from the uncontrolled epilepsy group. The examination of heart rate variability parameters during and before seizures revealed higher nLF and LF/HF ratio and lower nHF values demonstrating increased sympathetic activity.

Conclusion: We suggest that children with refractory epilepsy have abnormalities of autonomic nervous system functioning which could be linked to the increased risk of sudden unexpected death seen in the patient group. It is possible that a chronically reduced vagal tone predisposes patients to a more dramatic stress response during their seizures. It is possible that heart rate variability parameter arising prior to seizures could be used to predict future seizures.

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1. Introduction

The mortality rate of patients with epilepsy is two- to threefold higher than that of the general population.^{1,2} This increased mortality rate is caused by accidents during seizures, status epilepticus and sudden unexplained death in epilepsy (SUDEP).

SUDEP has been defined as “sudden, unexpected, witnessed or unwitnessed, nontraumatic and non-drowning death in patients with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, where postmortem examination does not reveal a toxicological or anatomical cause of death”.³ SUDEP is rare in newly diagnosed epilepsy patients but is a common cause of death that may reach rates as high as 9/1000 per year in patients with refractory epilepsy.^{4–6} Ictal bradycardia,

asystole and pulmonary congestion are suspected causes of SUDEP, but recent studies have demonstrated that disturbances of the autonomic system disturbance could be the root of all of these suspected causes of SUDEP.^{7–9}

Normal heart rate variation depends on the balance between the sympathetic and parasympathetic systems. Spectral analysis of heart rate variability (HRV) is a non-invasive method for the assessment of autonomic cardiac control.¹⁰ Highly variable heart rates are a sign of good adaptability and good autonomic control. There are only a small number of studies that have shown autonomic disturbances via HRV evaluation in children with epilepsy; whereas many studies of adult patients exist.^{11–14} Harnod et al. found lower RR and HF levels in children with refractory epilepsy that were suggestive of parasympathetic reductions.¹¹ Delogu et al. showed that HRV levels are depressed in children with Dravet syndrome.¹² Assaf et al. analysed HRV changes during epileptiform events and observed no significant differences between patient and control groups.¹³

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Haliloğlu et al. found suppressed HRV levels in children with epilepsy.¹⁴

Pathological cardiac repolarisation increases the risk of fatal ventricular tachyarrhythmia and is an established predictor of sudden cardiac death.¹⁵ Therefore, prolongation of the QT interval during seizure can be a cause of SUDEP.¹⁶ Moreover, the prolongation of QT dispersion (QTd) has been demonstrated in patients with epilepsy.^{17,18} Increases in QTd indicate disturbances in the autonomic system that favour the sympathetic system; this phenomenon can cause ventricular tachycardia and fibrillation.

The aims of this study were to compare the severity of autonomic dysfunction by measuring heart rate variability parameters in patients with refractory epilepsy and patients with well-controlled epilepsy and to examine the cardiac changes that occur before and during the patients' seizures.

2. Methods

This study included 40 consecutive children with epilepsy who were referred to our institute for evaluation and treatment between January to June 2011. Patients were divided into two groups: group 1 was composed of 20 children with refractory epilepsy who were admitted to the video EEG unit of the paediatric neurology department for the evaluation of potential surgical interventions, and group 2 was composed of 20 patients with controlled epilepsy. An additional group (group 3) of 20 healthy children were included as the control group. Study group consists of children with refractory epilepsy who are using three or more antiepileptic drugs without seizure control. Group 2 consists of children with epilepsy who are using only one antiepileptic drug and had no seizure within last 6 months. Brain MRI findings, antiepileptic drug types and number and names of antiepileptic drugs used were also evaluated.

All patients were evaluated by a paediatric cardiologist via a standard 13-derivation ECG (including V4 R derivation) and a complete blood count. Echocardiographic examination was conducted using M-mode, 2-dimensional, colour, pulse and continuous wave Doppler echocardiograms with a GE Vivid 7 (Wisconsin, USA). Two-dimensional echocardiographic pictures were recorded in standard parasternal long axis, short axis, apical 4-chamber, subcostal and suprasternal views. ECG sampling was made only for one time.

The T morphologies, PR, QRS, QT, and corrected QT intervals and QT dispersions of all participants were evaluated from the ECG records. QTc was calculated via "Bazett" ($QTc = QT/RR^{1/2}$) formula.

2.1. Heart rate variability

Twenty-four hour cardiac holter monitorization was done by "Medilog FD-2 (Oxford Instruments Medical Sytem)" digital holter device. Heart rate variability analyse was based on 24 h digitally recorded ECG signal with 100 Hz sampling rate. Holter Data acquisition and analysis were performed using the MediLog Cardiology Information System V 1.41 PC-compatible software that was developed by Oxford Instruments Medical System (USA). The processed signal was derived from surface electrodes on the chest. QRS complexes were automatically identified and labelled by the software and reviewed manually to limit any potential artefacts. The temporal parameters analysed were the mean of the RR interval (mean RR), the standard deviation of RR interval (SDNN), the standard deviation of the difference between consecutive RR intervals (SDANN), and the root mean square of difference between successive normal intervals (RMSSD). Both absolute and normalised low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.4 Hz) spectral powers were evaluated. The LF value mainly provides a measure of sympathetic activity but

is somewhat influenced by the parasympathetic nervous system. The HF value solely reflects parasympathetic activity. To remove the influence of parasympathetic activity in the LF spectral power, the LF/HF ratio was calculated, and high LF/HF ratios reflects the predominance of sympathetic activity. Triangular index measurement is the integral of the density distribution (that is, the number of all NN intervals) divided by maximum of the density distribution. It can be used as estimate the overall HRV.

We analysed the HRV parameter for 24 h. Also parameters were evaluated again in two different time periods as daytime (between 7:00–12:00 am), and nighttime (between 12:00–7:00 am).

Holter monitorization of the study group was done simultaneously during the video EEG monitorization. Therefore we could also evaluate the HRV parameters during the seizure.

Fourteen refractory epilepsy patients had seizures during Holter monitoring. In total, 17 seizures were observed, for which heart rate variability data were collected 15 min before, during, and 30 min after the seizure. This periictal period lasted about a hour. These data from the seizure time periods were compared with the all-day mean values.

Data are expressed as proportions or the means $\pm$ the S.D. Student's *t*-tests were used for the evaluation of continuous variables. Chi-square analysis and Student's unpaired *t*-tests were used to compare variables between groups in univariate analyses. *P*-values lower than 0.1 were considered as statistically significant. All statistics were calculated with the SPSS 16.0 program.

3. Results

This study involved 60 children under the age of 18 years old. The demographic data, seizure semiology and antiepileptic drug therapy of the subjects are summarised in Table 1. There were no significant differences in the demographic data between the three groups (Table 1).

Corrected QT dispersions were calculated for groups 1 and 2. Ten patients in group 1 and five patients in group 2 exhibited QTc dispersions greater than 50 ms. Statistically significant lengthening was found in group 1 (Table 2).

All groups were evaluated with echocardiography, and no functional cardiac disorders were found.

Holter monitoring was performed in all groups and revealed that three patients in group 1 exhibited sinus tachycardia during seizure and that one patient exhibited T wave inversion.

All groups were evaluated for time- and frequency-domain heart rate variability. Statistical analyses were performed with student's *t*-tests (Table 3).

Table 1
Demographic data of the groups.

	Group I (refractory epilepsy)	Group II (controlled epilepsy)	Group III (healthy children)
Number of subjects	20	20	20
Age (years mean $\pm$ SD)	9.55 $\pm$ 5.02	10.1 $\pm$ 4.18	10.35 $\pm$ 4.39
Gender (female/male)	8/12	8/12	8/12
Partial/generalised seizure	15/5	9/11	No seizure
Median number of AED	3.25	1	0

Table 2
Patients' QTc dispersion values.

Groups	<50 ms	>50 ms	Total
Group 1	10	10	20
Group 2	15	5	20
Total	25	15	40

p < 0.1 (difference between groups' QTc dispersion values).

Table 3

Heart rate variability values of the groups.

	HF (Hz)	LF (Hz)	LF/HF	Triangular index	RMSSD (ms)	SDNN (ms)	PNN50 (%)	nHF	nLF
Group 1 all day	827 ± 257	721.9 ± 188.6	1.4 ± 0.2	11.9 ± 1.4	37.2 ± 6.08	51.8 ± 7.1	14.7 ± 3.7	45.2 ± 2.8	41.2 ± 3.2
Group 2 all day	1675.8 ± 389.3	1188.6 ± 127.9	1.3 ± 0.2	15.7 ± 0.7	55.6 ± 5.7	72.6 ± 4.3	24.2 ± 3.1	45.4 ± 3.9	46.3 ± 3.8
Group 3 all day	2569 ± 684.8	1847.3 ± 279.6	0.9 ± 0.08	17.1 ± 0.8	68.9 ± 8.9	76.8 ± 5.8	23.3 ± 3.5	48.9 ± 2.1	44.2 ± 2.2
Group 1 day time	624.4 ± 206.3	666.8 ± 179	1.6 ± 0.2	11.9 ± 1.4	34.3 ± 5.7	49.9 ± 6.8	12.5 ± 3.3	37.2 ± 2.8	48 ± 2.8
Group 2 day time	1092 ± 213	1078.2 ± 105.3	1.6 ± 0.2	15.2 ± 0.6	46.2 ± 4.1	67.5 ± 3.2	18.8 ± 2.4	38.7 ± 3.2	50.7 ± 3.5
Group 3 day time	1849 ± 575.3	1544.4 ± 231.8	1.3 ± 0.1	16.3 ± 0.9	57.8 ± 8.2	76.8 ± 5.8	23.3 ± 3.5	41.6 ± 2.4	49.5 ± 2.6
Group 1 night time	1263.2 ± 402	836.2 ± 215.1	1.2 ± 0.2	11.9 ± 1.5	44.4 ± 7.9	55.2 ± 8.6	19.3 ± 4.8	46.8 ± 4.1	41.3 ± 3.3
Group 2 night time	3199.4 ± 782.2	1427 ± 204.8	1.03 ± 0.2	16.4 ± 1.2	77.1 ± 9.9	83.9 ± 7.6	36.6 ± 5	53.9 ± 4.4	40 ± 4.1
Group 3 night time	4290.2 ± 973.9	2573.5 ± 457.3	0.75 ± 0.09	18.9 ± 1	95.5 ± 11.3	106.1 ± 8.2	42.6 ± 4.2	56.7 ± 2.5	38.7 ± 2.4
Group 1 preictal	306 ± 132.9	506.2 ± 123.6	2.6 ± 0.5	13.1 ± 1.6	26.7 ± 2.3	62.1 ± 7.9	7.1 ± 1.5	35.4 ± 1.3	41.6 ± 2.1
Group 1 ictal	237.4 ± 50.5	586.5 ± 126.2	2.9 ± 0.5	13.2 ± 1.7	27.9 ± 2.6	61.9 ± 8.8	7.2 ± 1.7	30.9 ± 4.1	56.5 ± 5.1

The all-day low frequency band (LF) values were significantly lower in group 1 and the controlled epilepsy group than in the healthy subjects (Fig. 1).

The all-day high frequency band (HF) values were significantly greater in the healthy group than in the refractory epilepsy group. Although HF values were greater in the healthy group than the well-controlled epilepsy group, this difference did not reach significance (Fig. 1).

There were no statistically significant differences between groups in all-day, nHF, nLF or LF/HF values.

Time domain parameters of heart rate variability were also evaluated. pNN50 values were statistically significant lower in the refractory epilepsy group than in the healthy controls. But there was no statistical difference between the controlled epilepsy group and the healthy controls (Fig. 2).

The RMSSD and SDNN values were significantly lower in group 1 ($p < 0.05$), but there was no significant difference between groups 2 and 3 ($p > 0.1$) (Fig. 2).

Differences in heart rate variability during the day and night between groups were also evaluated. Daytime LF values were significantly lower in the refractory epilepsy group than in the healthy controls (Fig. 1).

There were no significant differences between groups in any other daytime frequency domain parameters.

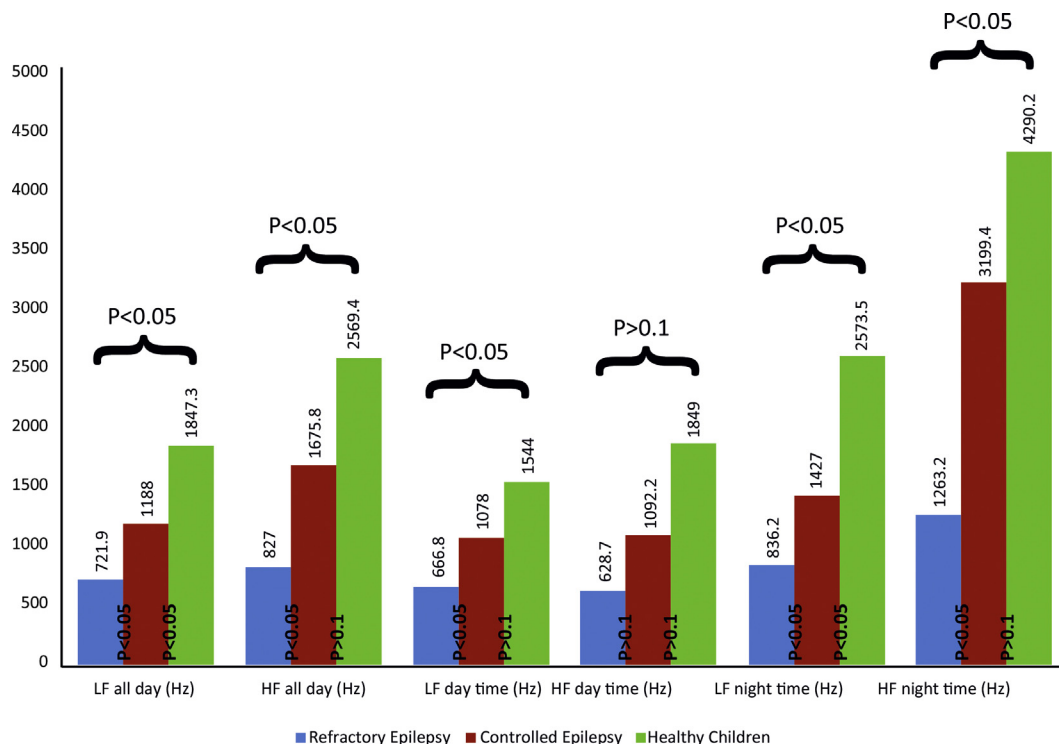
Daytime pNN50 and RMSSD values were significantly differed between the healthy controls and the patients with intractable epilepsy, while the SDNN values were significantly differed between the two control groups and the patients with intractable epilepsy (Fig. 2).

Nighttime LF values were significantly lower in groups 1 and 2 than in the healthy controls. Nighttime HF levels were significantly lower in group 1 than in the other two groups. Moreover, nHF levels were significantly lower in patients with refractory epilepsy than in the healthy controls ($p < 0.05$).

Nighttime pNN50, RMSSD and SDNN values were significantly lower in the refractory epilepsy group than in the other two groups. There was no significant difference between groups 2 and 3 (Fig. 2).

Triangular index values were evaluated over nighttime daytime and across entire days; for all time periods, group 1 yielded significantly lower values than the other groups ($p < 0.05$), and no difference was found between groups 2 and 3 ($p > 0.1$) (Fig. 2).

During the seizures, the nHF values were reduced, and the nLF values and LF/HF ratios increased relative to the all-day mean values (Fig. 3).

**Fig. 1.** Mean values of the frequency domain variables of the groups according to time period.

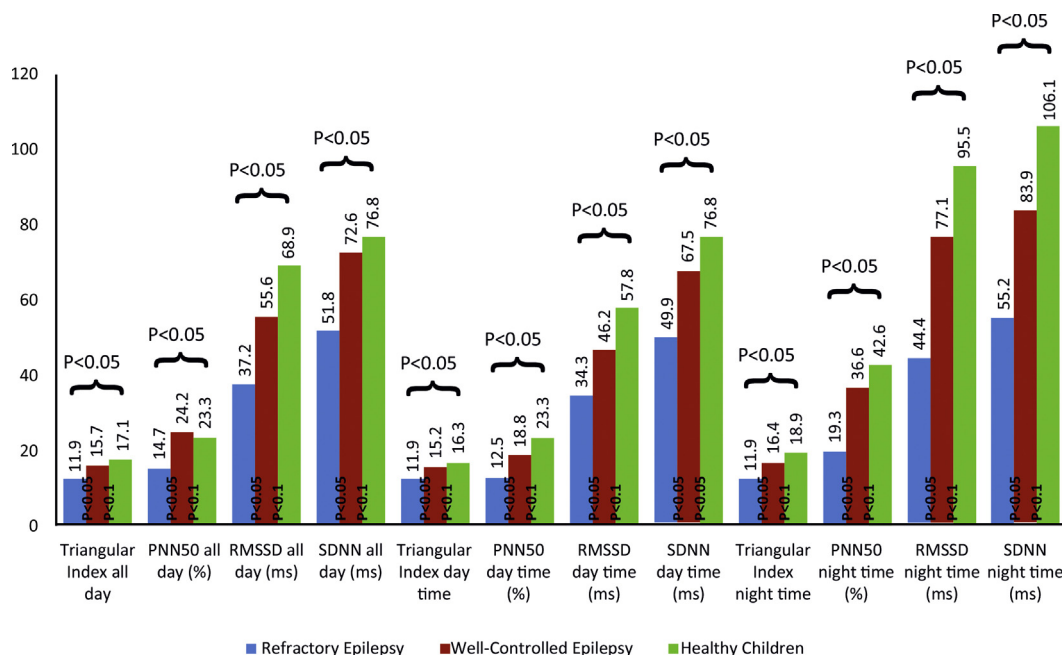


Fig. 2. Mean values of the time domain variables of the groups according to time period.

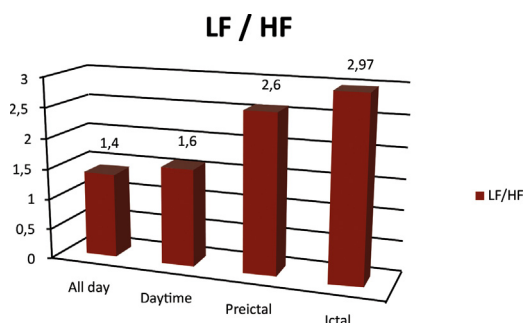


Fig. 3. Comparison of LF/HF ratio all day, day time, 1 h before and during seizure.

Time domain heart rate variability parameters were also compared, but no significant differences were found.

Heart rate variability parameters in one-hour period prior to seizure were compared with heart rate variability parameters from appropriate time periods. Heart rate variability parameters before the seizure which were evaluated in nighttime compared with nighttime HRV parameters, and HRV parameters before the seizure which were evaluated in day time compared with day time HRV parameters. Fourteen seizures were observed during the daytime, and the nLF and LF/HF values were statistically greater than the daytime mean values before the seizures. No significant differences were found in other parameters (Fig. 3).

4. Discussion

It is well-known that epilepsy and seizures affect cardiac rhythms. The autonomic dysfunctions that accompany epilepsy affect heart rhythms. It is thought that the insula and the prefrontal cortex control the autonomic system. Oppenheimer et al. used deep brain electrodes to demonstrate that the right and left hemispheres have excitatory and inhibitory effects on the heart, respectively.¹⁹

Ictal tachycardia had been reported in many previous studies.^{20,21} However, we observed sinus tachycardia during seizure in only three patients. Two of the three seizures were complex partial seizure; one with right hemisphere and one with

left temporal lobe originated. The other seizure with ictal tachycardia was a generalised seizure.

Nei et al. showed that patients with intractable epilepsy have cardiac conduction disorders during seizure.²² Atrial fibrillation, supraventricular tachycardia, atrial and early ventricular repolarisation have been observed during seizures. ECG changes, such as ST-segment depression and T-wave inversion, are more common in generalised seizures and are more dangerous.²³ T-wave inversion was observed in only one patient who had a generalised seizure in our study.

QT and QTc dispersion have been used as indicators of the repolarisation of the ventricles. Prolonged QTc has been shown to cause susceptibility to arrhythmias.²⁴ It has been shown that regardless of drug use, patients with epilepsy have prolonged QTd.²⁵ This finding is also supported by our study, as we observed 10 patients with refractory epilepsy that had QTds of more than 50 ms, which was a significant greater proportion than that found in the controlled epilepsy group.

There are many studies which have suggested that autonomic dysfunction with disturbed heart rate variability might be responsible for SUDEP.

Heart rate variability is evaluated by time and frequency domain variables. While the low frequency band (LF) reflects parasympathetic and sympathetic activity, the high frequency band (HF) reflects only parasympathetic activity. Evrengül et al. reported that 43 newly diagnosed generalised epilepsy patients without drug therapy exhibited lower HF and higher LF levels than a group of healthy controls. Moreover, the SDANN, SDNN and triangular index values were significantly higher in the epilepsy group than in the normal group. These authors suggested that the sympathetic activity of the patients with epilepsy was more dominant than the parasympathetic activity.²⁶ Yildiz et al. compared the heart rate variabilities of partial and generalised epilepsy patients and healthy controls. These authors determined that the time and frequency domain variables exhibited sympathetic dominance and that there were differences between the epilepsy groups.²⁷ Furthermore, several studies have reported dominance of sympathetic system, while other studies have reported suppression of both the sympathetic and parasympathetic systems. Persson et al. evaluated adult patients with

refractory epilepsy and found suppression of both LF and HF values.²⁸ Harnod et al. reported decreases in both LF and HF values in children with refractory epilepsy and suggested that these decreases may have been the result of inhibition of the parasympathetic system, which may be different in children.¹²

In our study, we observed that the all-day HF and LF levels were significantly lower in the refractory epilepsy group than in the patients with well-controlled epilepsy and the healthy subjects. Moreover, the all-day LF values of the controlled epilepsy group were significantly lower than those of the healthy group. These results may be the results of decreased parasympathetic activity. Furthermore, the unchanged LF/HF ratios of these patients suggest that they were affected by a co-acting mechanism. In a study of a large sample of patients with chronic heart failure, reductions in LF values have been reported to be an independent predictor of sudden death; thus, suggesting that that autonomic control is important in sudden death.²⁹

The time domain heart rate variability variables of (PNN50, RMSSD, SDNN and triangular index) of the patients with refractory epilepsy were significantly lower than those of the other two groups. Although there were no significant differences between the other two groups, the time domain values were lower in the controlled epilepsy group than in the healthy group. These findings suggest that epilepsy itself causes deteriorations in heart rate variability. Furthermore, these findings suggest that deterioration increases with increasing disease severity. Similarly Ponnusamy et al. found suppressed HRV parameters in both patients with refractory epilepsy and patients with psychogenic nonepileptic seizures. HRV parameters were more suppressed in the epilepsy group.³⁰ Significantly increased sympathetic activity during the ictal period in epilepsy group was demonstrated in an other study.³¹

DeGiorgio et al. found an inverse correlation between SUDEP 7 scale scores and RMSSD values.³² RMSSD values are an indicator of cardiac vagal activity. These authors suggested that the decreases in RMSSD values are due to the loss of control of sympathetic activity that occurs during seizure.

The LF values observed during the daytime in the refractory epilepsy group were significantly lower than those of the other two groups. LF values are particularly high during the daytime. Thus, it is thought that decreases in parasympathetic activity during the daytime are more predominant in LF values. Although HF levels were lower in the refractory epilepsy group, no significant difference was found between the other groups. The time domain variables of RMSSD and pNN50 were significantly lower in refractory epilepsy group than in the healthy group. Moreover, SDNN values and triangular indices were significantly lower in the refractory epilepsy group than in either of the other two groups. Although there was no significant difference between group 2 and the healthy subjects, these values tended to be lower in the controlled epilepsy group. However, at that time, the effects of the drugs were controversial. Lossius et al. showed that withdrawal of controlled epilepsy drugs increases heart rate variability values.³³

Nighttime LF and HF values were significantly lower in the refractory epilepsy group than in either of the control groups, but the LF/HF ratios did not differ between each group. These findings could be the result of suppression of the vagal system, which attracts both LF and HF values to decrease. Moreover, the nighttime LF values of the controlled epilepsy group were significantly lower than those of the healthy controls. The nighttime time domain variables of the refractory epilepsy group were also significantly lower than the other two groups. Together, these results suggested that the patients with refractory epilepsy had severe impairments of heart rate variability due to deterioration of the parasympathetic system. Moderate deterioration of heart rate variability was also observed in patients with controlled epilepsy. We did not

include subjects who are free of medication in our study; therefore, it was not possible to determine whether these impairments were due to drug use or illness. Evrengül et al. showed that patients with epilepsy who do not use drugs exhibit impairments in heart rate variability.²⁶ Haliloğlu et al. reported impairments in heart rate variability in patients with epilepsy both with and without drug use. Moreover, these authors reported greater suppression of the parasympathetic systems of patients who were using multiple drugs.¹⁴ However, the patients with refractory epilepsy in our study were also using multiple drugs; thus, the findings of Haliloğlu et al. are compatible with ours.

Peri-ictal heart rate variability has been investigated in limited number of studies. Toth et al. assessed the heart rate variabilities of 31 patients 30 and 5 min before seizure and 10 min and 6 h after seizure. These authors demonstrated decreases in HF values in the early post-ictal period and decreases in LF values in the late post-ictal period. SDNN and RMSSD values both decrease in the early and late post-ictal periods.³⁴ Surges et al. retrospectively investigated the records of the patients who had died due to SUDEP. These authors showed that patients' heart rate variabilities decreased to greater extents than those of a control group during seizure.³⁵ Adjei et al. reported decreases in heart rate variability, especially among patients with left temporal lobe seizures.³⁶ We also evaluated peri-ictal heart rate variability 15 min before and 30 min after seizure. Our patients experienced a total of 17 seizures, and we observed a predominance of the sympathetic system at these time points. nHF values decreased during the seizures compared to the all-day nHF mean values. nLF values significantly increased relative to all-day nLF values, and LF/HF ratios also increased. These findings also supported the supposition that sympathetic activity dominates during seizure. We did not find any differences in the time domain variables. However, we propose that the frequency domain variables are useful as short-term measures. The frequency domain variables were more important in the peri-ictal period.

There are several studies that have suggested that heart rate variability can be used as a predictor of seizures. Based on six seizures in three patients, Jeppesen et al. observed that reciprocal HF values increase 2.96- to 93.6-fold between 10 s before and 24 s after seizure. This suggested suppressed parasympathetic activity just around the seizure onset.³⁷ We compared the frequency domain variables 1 h before seizure with the exact time period. Fourteen seizures were observed during the day. We observed significant increases in nLF and LF/HF values before the seizure relative to the daytime values. These findings suggest that the sympathetic system begins to predominate before the seizure.

Although there were suppressions in the parasympathetic system during the seizures, the sympathetic system began to predominate 1 h before the seizure. Consequently, epilepsy-induced autonomic dysfunction and deterioration became more significant during seizures. The heart rate variability of patients prior to seizures should be studied in larger groups. Heart rate variability may be useful as a predictor of seizures in the future.

Conflict of interest statement

None of the authors have any conflicts of interest to disclose.

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