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Assessment of Time and Frequency Domain Parameters of Heart Rate Variability and Interictal Cardiac Rhythm Abnormalities in Drug-naïve Patients with Idiopathic Generalized Epilepsy

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Background and Purpose: Epilepsy is a disease known to occur with autonomous phenomenons. Earlier studies indicate decreased heart rate variability (HRV) during ictal and interictal periods among epilepsy patients. In this study, we aim to investigate cardiac rhythm abnormalities and HRV during interictal period between drug-naïve patients with idiopathic generalized epilepsy (IGE) and healthy control group.

Methods: Twenty-six patients with IGE and 26 healthy individuals included in the study. In order to eliminate any structural cardiac pathology, transthoracic echocardiography was performed in all subjects and time and frequency domain parameters of HRV were evaluated after 24-hour rhythm holter monitoring.

Results: Between two groups, no significant difference was detected in terms of mean heart rate and maximum duration between the start of the Q waves and the end of the T waves (QT intervals). In the time domain analysis of HRV, no statically significant difference was detected for standard deviation of all R - R intervals and root-mean-square of successive differences between patient and control group (p = 0,070 and p = 0,104 respectively). In the frequency domain analysis of HRV, patients tended to display lower total power and very low frequency power than did healthy subjects, but the differences were not statistically significant.

Conclusions: Our results suggest that there is no major effect of the epilepsy on HRV in patients with IGE. It should be emphasized that, in this study, HRV was evaluated only in patients with IGE and that the results are not proper to be generalized for patients with partial seizures. **(2016;6:22-27)**

Key words: Heart rate/physiology, Epilepsy, Cardiac rhythm, Autonomic control

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Introduction

Sudden unexpected death in epilepsy (SUDEP) is one of the most important causes of death in patients with epilepsy. Although the exact mechanism of SUDEP is still controversial, autonomic dysfunction has been considered to play a significant role. The theories proposed on the mechanism of SUDEP have focused on autonomic instability and contain possible cardiac arrhythmias.[1] Interictal epileptogenic activity may also induce an autonomic imbalance and that such altered autonomic neural discharges may be related to cardiac arrhythmias in the mechanism of SUDEP.[2,3] In several studies designed to understand the etiopathogenesis of SUDEP, decreased heart rate variability (HRV) was observed in patients with chronic epilepsy and under antiepileptic treatment compared to healty populations.[4,5]

The HRV reflects the balance of sympathetic and parasympathetic activities on the heart. While parasympathetic stimulation slows the heart rate, on the contrary, heart rate is accelerated by sympathetic stimuli. Autonomic control of the heart is generally regulated by parasympathetic system at rest.[6] The HRV measurement can be performed through a short 5-minute or 24-hour long-term ECG recordings and cardiac autonomic control can be evaluated by this practical and noninvasive method.[7,8] Higher HRV indicates well-functioning autonomic control mechanisms; lower HRV values are generally a sign of an insufficient adaptability of the autonomic nervous system.[9] The decrease in HRV is a strong indicator of fatal arrhythmias and increased mortality related to sudden cardiac death and it is also considered to be an indicator of risk related adverse events in a wide range of diseases.[10-13] In recent years, there have been increasing evidences of that decrease in HRV is a significant risk factor for SUDEP.[14,15] However, there are very few studies evaluating HRV in

drug-naïve patients with idiopathic generalized epilepsy (IGE) as isolated.[9,16,17] In a study using conventional autonomic tests to evaluate cardiac autonomic parameters in drug-naïve patients with epilepsy, no autonomic dysfunction was observed in patient group.[18] Abnormal interictal regional cortical blood flow in areas responsible for autonomic modulation has been shown by functional imaging studies in drug-naïve patients with epilepsy.[19] In a Turkish study, increased sympathetic control of HRV was shown in young patients with generalized tonic-clonic seizures (GTCSs).[9] In another study conducted in Sweden, HRV was compared between patients with localized and generalized epileptic seizures and control group but no significant difference was detected.[16] The aim of this study was to investigate the presence of cardiac autonomic dysfunction by analysing time and frequency domain parameters of HRV and possible cardiac rhythm abnormalities in drug-naïve patients with IGE.

Methods

Patients and controls

The drug-naïve patients with IGE applied to the Marmara University, Department of Neurology outpatient clinic were evaluated prospectively. Patients in the 15-45 age range and diagnosed with IGE according to the International League Against Epilepsy (ILAE) 1989 classification were included in the study. Patients with a history of any disease that can lead to the cardiac autonomic dysfunction and/or patients receiving any medication other than antiepileptics known to affect the blood pressure and/or heart rate were excluded from the study. Magnetic resonance imaging was performed in all patients to exclude any structural pathology and interictal activated electroencephalography (EEG) was performed to confirm the clinical diagnosis. Patients who were clinically diagnosed with IGE with normal imaging were subjected to further evaluation. Patients who had a seizure during the previous 24-hour period of recordings were excluded from the study. None of the patients had any cardiopulmonary disease, diabetes mellitus and/or a history of substance abuse. Healthy volunteers with normal physical and neurological examinations were chosen from amongst hospital staff as a control group.

Fourteen female and 12 male, a total of 26 patients meeting the inclusion criteria and 26 gender matched (14 female and 12 male) healthy volunteers were included in the study. The mean age of patient group was 26,15 ± 5,97 and that of control group was 28,69 ± 4,76. There was no age difference between groups ($p = 0,09$).

For each patient, first seizure date, frequency of seizures and history of febrile convulsion were questioned. In all cases, routine physical and neurological examinations were performed, liver and renal function tests and serum electrolytes were obtained and no pathological result was detected. Transthoracic echocardiography (TTE) was performed in all patients and healthy volunteers with General Electric Vivid 7, USA echocardiography device. Diastolic and systolic diameters of the cardiac chambers were measured by 2D, M-mode, Doppler and tissue Doppler echocardiographic examination and left ventricular ejection fractions (EF) were measured by Simpson's method. The study protocol was in accordance with the Helsinki Declaration on Human Rights and was approved by the local ethics committee.

Heart rate variability

The 24-hour rhythm holter monitorings of the patients and control subjects were performed by using miniature holter device, "DMS 9800, USA". During the recordings, patients were asked to continue their routine daily activities and night sleeps, no special activity was required. Electrocardiographic raw data recorded in three channels were digitalised with 128-Hz sampling rate. Evaluation of electrocardiographic data and HRV were performed by a physician blinded to clinical informations of the patients via using the software "Cardioscan 12.0, DMS, USA". Holter recordings were obtained at least 24 hours after seizure attacks and none of the patients had any seizure during the recordings.

The HRV was evaluated by both time domain and frequency domain analysis. Mean heart rate, standard deviation of all R–R intervals (SDNN) and root-mean-square of successive differences (RMSSD) were measured in the time domain analysis of HRV. The misclassified drop beats deviating more than three standard deviations (SD) from the mean normal RR-interval of each epoch were detected and epochs with more than 4% of non-normal RR-intervals were excluded from further analysis. At least 50% analyzable data of 24-hour recording was seeked to be analyzed. For frequency domain parameters, spectral analysis was performed by using fast-Fourier transform method. The power in the heart rate spectrum between 0.003 and 0.40 Hz was defined as total power (TP). The power in the heart rate spectrum was divided into four different frequency bands including TP, very low frequency power (VLF), low frequency power (LF) and high frequency power (HF). From these parameters, LF/HF ratio was calculated.

Statistical Method

Data recording and statistical analysis were performed by using SPSS for Mac, version 20, (SPSS Inc., Chicago, IL, USA). All continuous variables were expressed as mean ± SD. The normal distribution of the data was determined by Kolmogorov-Smirnov test. Student's *t*-test as a parametric test and Mann-Whitney *U*-test as non-parametric test were used to compare data. Significance was set at $p < 0.05$.

Results

The mean age of the patients was 26.15 ± 5.97 years, and the median time from their first seizure to enrolment in the study was 93 months. There was no history of febrile convulsion in any of the patients. While 17 patients have not received any medical assistance in the past, the other 9 patients did not use recommended anti-epileptic treatments since they were diagnosed with epilepsy. All patients had been seizure free at least 24 hours before the recordings and none of the patients reported any seizure during the recording. There was no significant difference between patients and controls in terms of demographic data including age and sex. The following parameters were evaluated by TTE; left ventricular ejection fraction (EF), left ventricular mass (LVM), left ventricular end-diastolic capacity (LVDC), left ventricular end-systolic capacity (LVSC) and E/A ratio; left ventricular diastolic function marker. All of these parameters were within normal limits in patients and controls and there was no significant difference between two groups. The demographic data, clinical charasteristics and TTE findings of the subjects are summarized in Table 1.

In terms of mean, minimum and maximum heart rates and maximum duration of QT intervals, no significant difference was detected between two groups. In the time domain analysis of HRV, no statically significant difference was detected for SDNN and RMSSD parameters between patient and control groups ($p = 0{,}070$ and $p = 0{,}104$ respectively). In the frequency domain analysis of HRV, patients tended to display lower TP and VLF values, but the differences

Table 1. Demographic data, clinical charasteristics and TTE findings of the subjects

	Patients	Controls	*p*-value
Female/male	14/12	14/12	NA
Age (years)	26.15 ± 5.97	28.69 ± 4.76	0.09
Age at onset (years)	18.26 ± 8.91	NA	NA
Duration of illness (years)	7.88 ± 8.64	NA	NA
Seizure frequency (per year)	1.50 ± 0.92	NA	NA
Interictal EEG findings			
Generalized spike and waves	N: 19	NA	NA
Normal	N: 7	NA	NA
EF (%)	68.45 ± 5.70	68.22 ± 5.22	0.89
LVM (gram)	127.22 ± 17.13	141.31 ± 33.39	0.06
LVDC (mm)	43.92 ± 4.12	45.95 ± 4.02	0.09
LVSC (mm)	26.65 ± 3.45	27.81 ± 4.01	0.28
E/A ratio	1.50 ± 0.36	1.45 ± 0.36	0.65

Values are presented as mean ± standard deviation unless otherwise indicated.
TTE, transthoracic echocardiography; NA, not applicable; EEG, electroencephalography; EF, ejection fraction; LVM, left ventricular mass; LVDC, left ventricular end-diastolic capacity; LVSC, left ventricular end-systolic capacity; E/A, left ventricular diastolic function marker; mm, millimeter; N, number of patients.

Table 2. Time domain analysis of heart rate variability in patients with epilepsy and controls

	Patients	Controls	*p*-value
Mean heart rate (beats/min)	78.23 ± 7.80	74.50 ± 6.94	0.075
SDNN (ms)	150.38 ± 26.39	165.76 ± 33.21	0.070
RMSSD (ms)	38.19 ± 10.31	42.96 ± 10.42	0.104

Values are presented as mean ± standard deviation unless otherwise indicated.
SDNN, standard deviation of R-R intervals; RMSSD, root mean square successive difference of intervals.

Table 3. Frequency domain analysis of heart rate variability in patients with epilepsy and controls

	Patients	Controls	*p*-value
TP (ms^2)	4,028.0 ± 1,259.2	4,801.2 ± 1,604.0	0.059
HF (ms^2)	410.5 ± 283.4	497.1 ± 266.2	0.261
LF (ms^2)	985.1 ± 327.4	1,090.7 ± 277.8	0.216
VLF (ms^2)	2,605.4 ± 853.5	3,217.0 ± 1,301.7	0.051
LF/HF	3.06 ± 1.56	2.65 ± 1.09	0.277

Values are presented as mean ± standard deviation unless otherwise indicated.
TP, total power; HF, high frequency absolute power; LF, low frequency absolute power; VLF, very low frequency absolute power; LF/HF, low frequency to high frequency ratio.

were not statistically significant. Time domain analysis of HRV is summarized in Table 2 and frequency domain analysis in Table 3.

Discussion

In this study, we aimed to investigate the presence of interictal cardiac rhythm abnormalities and extent of HRV in drug-naïve patients with IGE. The heart rhythm of all patients during interictal period was sinus rhythm and in terms of mean heart rate, there was no difference in patients when compared to control group. In studies investigating cardiac rhythm abnormalities in patients with epilepsy, although the majority of detected abnormalities are in ictal and postictal period, it has been reported that these abnormalities can also be detected in interictal period.[20] While seizure-induced sympathetic nervous system activity increases blood pressure and heart rate, in partial seizures, parasympathetic system activation and/or inhibition of the sympathetic system can be seen and as a result, seizure related arrhythmias such as tachycardia, bradycardia and asystole can be detected in patients with epilepsy.[20]

Strzelczyk et al. reported an increase in T wave variability during GTCSs and Lanz et al. reported ictal asystole in patients with epilepsy.[21,22] Since none of the patients in our study had epileptic seizure during 24-hour rhythm holter recordings, no cardiac rhythm abnormality associated with ictal period was noted. In a study investigating cardiac rhythm abnormalities during interictal period in epilepsy patients, QT dispersion was detected in one-third of patients and ventricular late potentials were observed in some of the patients as well.[23] None of our patients had ventricular late potentials and maximum QT intervals were within normal limits in all patients.

In our study, we could not demonstrate any statistically significant difference in any of the analysed parameters between two groups. In the frequency domain analysis of HRV, an increase in HF values shows more dominant parasympathetic effect, on the other hand, higher LF values indicate the dominance of sympathetic effect. But, studies in recent years have shown that parasympathetic activity may also affect the value of LF.[24,25] In healthy individuals, LF/HF ratio shows the balance between sympathetic and vagal tone.[26] While higher LF/HF rates show an increase in sympathetic activity, lower rates indicate increased vagal activation. However, recently, Reyes del Paso et al. stated that fundamentally, the LF is a marker of parasympathetic nervous system.[27] The HF has been reported to be associated with respiratory effects, LF with blood pressure control mechanisms such as modulation of vasomotor tone, VLF with renal functions and thermoregulation by Reyes del Paso et al.[27]

In 2005, Evrengül et al. reported statically significant decrease in HF values, an increase in LF values and increase in LF/HF ratio in 42 young military recuits with newly diagnosed GTCSs compared to healthy controls.[9] We could not confirm these findings from the study of Evrengul et al. In another study, Persson et al. detected that there was no difference in the time and frequency-dependent parameters of HRV in newly diagnosed and untreated epilepsy patients compared to healthy controls.[16] In this study, all analyses were first performed for the full 24-hour period. Thereafter, separate analyses were performed for nighttime and daytime respectively. In all measurements of both time and frequency dependent HRV parameters, none of the results created statistically significant difference between groups. However, in the study of Persson et al. patient group was heterogeneous, both patients with localization-related complex partial seizures and the patients with GTCSs were included in the study.[16] Despite the dissimilar inclusion criteria, our results are consistent with the study of Persson et al.[16]

In a recent study carried out by Mativo et al.,[17] time domain HRV measurements showed significant decrease in RMSSD values in patients with idiopathic generalized tonic-clonic epilepsy when compared to controls, frequency domain parameters showed decreased TP and HF values in patients when compared to controls as well.

Patients also had an increased LF/HF ratio in the study of Mativo et al.[17] In the study of Mativo et al., five-minute error-free Lead II electrocardiogram was recorded for all individuals and short-term resting HRV was evaluated. Dissimilar methodology may have contributed to the differences in findings between our study and that of Mativo et al.[17]

The HRV measures in our drug-naïve patients with IGE were not different in any respect from the results obtained from healthy controls but the trends in our study suggests lower TP and VLF in the frequency domain parameters of HRV. In their recent meta-analysis, Lofuto et al. confirmed the hypothesis of sympathovagal imbalance in epilepsy patients by showing lower HF, SDNN, and RMSSD values in patients with epilepsy when compared to controls and there was a trend for higher LF in patients receiving pharmacotherapy.[28] None of the patients in our study were receiving any antiepileptic treatment since some of the patients have not received any medical advice in the past and the others did not use recommended antiepileptic treatments.

In a study designed to determine SUDEP risk factors, De Giorgio et al. performed correlation analysis between HRV parameters and SUDEP-7 inventory scores and RMSSD values were determined positively correlated with the risk of SUDEP.[29] In our study, obtained statistically insignificant results may be associated with dissimilar inclusion criteria and small number of patients who can be considered as having refractory epilepsy in our study. Stefani et al. suggested that antiepileptic drug withdrawal or discontinuation has no significant contribution to the deterioration of cardiac physiology.[30] In addition, Sathyaprabha et al. and Berilgen et al. showed no significant association between autonomic dysfunction and the use of anticonvulsants.[31,32]

In conclusion, in our study we sought to investigate the presence of interictal cardiac rhythm abnormalities, extent of HRV and related factors in drug-naïve patients with IGE and we could not demonstrate any significant difference in any of the analyzed HRV parameters between our patients and healthy volunteers despite the non-significant trend towards lower values in TP and VLF among patients. Therefore, our results suggest that there is no remarkable effect of the epilepsy as such on HRV in patients with IGE. It should be emphasized that in this study, HRV was evaluated only in patients with IGE and that the results are not proper to be generalized for patients with partial seizures and other types of generalized seizures. Because of the limited number of included patients, further studies are needed to assess the effects of idiopathic generalized epilepsy on HRV in drug-naïve patients with IGE.

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