Clinical Research

Heart Rate Variability in Childhood Epilepsy

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ABSTRACT

Objective: Heart rate variability (HRV) is a non-invasive method used to assess the status of autonomic function of the heart. The aim of this prospective study was to assess HRV and cardiac function in children with epilepsy. In addition, the effects over HRV of epilepsy type, therapy regimens, refractory and well controlled epilepsy were investigated.
Material and Method: Between September 2013 and March 2014, 61 epileptic children and 53 healthy children were included in the study. All subjects were evaluated by electrocardiography, echocardiography, and 24 hours rhythm holter.
Results: In the children with epilepsy, it was determined a significant reduction in all the time domain (SDNN, SDNN index, SDANN, RMSSD, pNN50 p-values 0.011, 0.001, 0.021, 0.001, 0.001, respectively) and frequency domain (LF, HF, VLF p-values 0.001, 0.001, 0.001 respectively) parameters. There were not statistically significant differences in both time and frequency domain parameters between children with partial and generalized epilepsy. There was a significant reduction in SDNN, SDNN index, SDANN, RMSSD, LF, HF, VLF (p-values 0.009, 0.008, 0.015, 0.039, 0.004, 0.010, 0.005, respectively) values in the children who underwent polytherapy regimen.
Conclusion: Epilepsy is associated with suppressed HRV values indicating decreased vagal activity. Having pathological EEG findings, and polytherapy regimen associated with refractory epilepsy are effective on suppressed HRV. In addition, cardiac systolic functions may be affected in patients with epilepsy under drug therapy.

Keywords: *Epilepsy, Heart Rate Variability, Electrocardiography, Echocardiography.*

ÖZ

Çocukluk Çağı Epilepsisinde Kalp Hızı Değişkenliği
Amaç: Kalp hızı değişkenliği (KHD), kalbin otonom fonksiyonunun durumunu değerlendirmek için kullanılan noninvaziv yöntemdir. Bu prospektif çalışmanın amacı, epilepsili çocuklarda KHD ve kardiyak fonksiyonu değerlendirmekti. Ayrıca epilepsi tipi, tedavi rejimleri, dirençli ve iyi kontrol edilen epilepsinin KHD üzerindeki etkileri araştırıldı.
Gereç ve Yöntem: Eylül 2013 Mart 2014 tarihleri arasında 61 epileptik çocuk ve 53 sağlıklı çocuk çalışmaya dahil edildi. Tüm denekler elektrokardiyografi, ekokardiyografi ve 24 saatlik ritim holter ile değerlendirildi.
Bulgular: Epilepsili çocuklarda tüm zaman alanı (SDNN, SDNN indeksi, SDANN, RMSSD, pNN50 p değerleri sırasıyla 0.011, 0.001, 0.021, 0.001, 0.001) ve frekans alanı (LF, HF, VLF p değerleri sırasıyla 0.001, 0.001, 0.001) parametrelerinde anlamlı azalma tespit edildi. Parsiyel ve jeneralize epilepsili çocuklar arasında hem zaman hem de frekans alanı parametrelerinde istatistiksel olarak anlamlı fark yoktu. Çoklu terapi uygulanan çocuklarda SDNN, SDNN indeksi, SDANN, RMSSD, LF, HF, VLF (p değerleri sırasıyla 0.009, 0.008, 0.015, 0.039, 0.004, 0.010, 0.005) değerlerinde anlamlı azalma oldu.
Sonuç: Epilepsi, azalmış vagal aktiviteyi gösteren baskılanmış KHD değerleri ile ilişkilidir. Patolojik EEG bulgularının olması ve dirençli epilepsi ile ilişkili politerapi rejimi baskılanmış KHD üzerinde etkilidir. Ayrıca ilaç tedavisi gören epilepsili hastalarda kardiyak sistolik fonksiyonlar da etkilenebilmektedir.
Anahtar Sözcükler: *Epilepsi, Kalp Hızı Değişkenliği, Elektrokardiyografi, Ekokardiyografi.*

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Heart rate variability (HRV) is a non-invasive method used to assess the status of autonomic function of the heart. Normal heart rate variation is dependent on the balance between sympathetic and parasympathetic systems (1). Low HRV is indicative of increased sympathetic activity and decreased parasympathetic activity. Excessive sympathetic or inadequate parasympathetic tone is associated with the pathogenesis of ventricular dysrhythmias and sudden cardiac death. In short, decreased HRV may be a reflection of electrically unstable myocardium, and associated with some disorders (2).

The mortality rate of people with epilepsy is two to three times higher than in the general population (1). Sudden unexpected death in epilepsy (SUDEP) is the most common cause of deaths in epilepsy, and is responsible for up to 17 % of mortality in people with epilepsy (3). The etiology of SUDEP is unknown. However, recent researches have indicated to be an association between SUDEP and suppressed parasym-

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pathetic control of the heart (4).
According to the report of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (5), variations in heart rate may be evaluated using time and frequency domain measures as the simplest methods. Time domain measures include standard deviation of all RR intervals (SDNN), mean of the standard deviations of all NN intervals in 5-minute recordings (SDNN index), standard deviation of mean NN intervals in 5-minute recordings (SDANN), root mean squares of successive differences (RMSSD), NN50 count (number of pairs of adjacent NN intervals differing more than 50 ms) divided by the total number of all NN intervals (pNN50). These measurements predominantly display the magnitude of parasympathetic modulation of heart rate. Frequency domain measures of HRV include total power (TP), the very low frequency band (VLF), the low frequency band (LF), high frequency band (HF) and LF/HF ratio. HF component is predominantly under the influence of the parasympathetic system. The LF component has controversial interpretation, which is considered by some authors as a parameter of sympathetic modulation or as a marker that includes both sympathetic and parasympathetic influences. The LF/HF ratio can be considered as an indicator of sympathovagal balance. The VLF segment accounts for most of the staying power, but its physiological properties are still not fully known. HRV analysis, especially HF and LF/HF ratio, has been widely used for the analysis of autonomic nerve activity for cardiovascular diseases, epilepsy and stroke (6).
The aim of this study was to investigate whether HRV is reduced in children with epilepsy. For this purpose, the effects of epilepsy type, treatment regimens, and resistant and well-controlled epilepsies on HRV were investigated. In addition, cardiac functions were evaluated in children with epilepsy.

MATERIAL AND METHOD

Study population

This prospective study was conducted in the Department of Pediatric Cardiology and Department of Pediatric Neurology of Fırat University, Medical Faculty, between September 2013 and March 2014. Patients aged 1-18 years, who had been under follow-up and treatment with the diagnosis of epilepsy for at least 1 year, were included in the study. These patients were divided groups as generalized and partial according to the epilepsy type. The patients were divided into subgroups according to their antiepileptic treatment response as well-controlled and refractory (≥1 seizure/month and failed ≥ 2 drugs) epilepsy. In addition, patients were grouped according to whether their EEG findings were pathological or normal. The healthy group was selected from children who applied to the pediatric cardiology unit for sports approval and had no known history of seizures, epilepsy, and no signs of heart disease on examination. The epilepsy and healthy groups were matched with respect to age, gender, and body mass index (BMI). Children with chronic systemic diseases other than epilepsy were excluded from the study. The study was approved by the Fırat University Ethical Committee.

Study protocol

All children underwent physical examination, blood cell count, blood electrolyte measurement, electrocardiography (ECG), echocardiography and 24-hour rhythm holter. The transthoracic echocardiographic examination (Vivid S5, GE Vingmed, Horten, Norway) was performed in all children. Interventricular septum at end-diastole dimension (IVSD), the end-diastolic left ventricular posterior wall thickness (LVPWd), left atrial to aortic root ratio (LA/Ao), left ventricular ejection fraction (EF) and fractional shortening (FS), and cardiac mass were measured by using the M-mode echocardiography. Mitral pulsed-wave Doppler evaluation was performed to obtain the following parameters of the mitral inflow early diastolic wave (E), mitral inflow late diastolic wave (A), ratio of early to late diastolic mitral inflow velocity (E/A), deceleration time (DT), isovolumic relaxation time (IVRT), isovolumetric contraction time (ICT), the ejection time (ET). In addition, QT, PR and QRS times were measured in all children's ECG examinations. The corrected QT (QTc) interval values of the participants were calculated with the Bazett formula (7).
HRV was analysed using a four-lead ECG Holter recording (DMS 300-4A, MTM Multitechmed GmbH, Hunfelden-Dauborn, Germany) for 24 hours. The recordings were analysed automatically by software (Cardioscan II premier). All holter recordings were visually checked. Recordings of low technical quality were rejected. Measurement of heart rate variability was evaluated by time and frequency domain methods. Minimal heart rate, maximal heart rate, mean heart rate, mean RR interval (NN), SDNN, SDNN index, SDANN, RMSSD, pNN50 were computed as time domain measures. Frequency domain analysis of HRV was performed using the Fast Fourier transformation method. The power in the heart rate spectrum between 0 and 0.5 Hz was defined as total power, and it was classified into three frequency bands: VLF, LF and HF. LF/HF ratio was used as a measure of sympathovagal balance.

Statistical analyses

The sample size was 16 with a 95% confidence level and a 5% margin of error. Statistical analyses were performed using the SSPS 21 (SPSS Inc, Chicago, IL, USA). The visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) were used to test the normality of distributions of continuous variables. The Independent Student T-Test or the Mann-Whitney U test was used to compare parameters between the groups normally or non-normally distributed, respectively. The Pearson or Fisher's exact chi square tests, where appropriate, was

used for categorical comparisons of nominal values in different groups. $p<0.05$ was considered statistically significant.

RESULTS

Sixty-one epileptic patients (29 girls, 32 boys) and 53 (26 girls, 27 boys) healthy children were included in the study. The median ages of healthy and epileptic children were 9 years (age ranges were 1-17 and 0.8-17 years, respectively). There was no significant difference between the children in terms of gender and body mass index. Demographic characteristics of the patients, median age at first seizure, epilepsy type, disease duration, treatment regimens and laboratory parameters are summarized in table 1.

Table 1. *Demographic, clinical and laboratory parameters of children with epilepsy and healthy.*

	Children with epilepsy (n: 61)	**Healthy Controls (n: 53)**	**p**
Age (year), median (min-max)	9 (0.8-17)	9 (1-17)	0.500[a]
Gender (Female/male)	29 / 32	26/27	0.872[c]
BMI (kg/m^2), median (min-max)	16.67 (5.57-31.32)	15.80 (13.46-26.02)	0.880[a]
Age of first seizure, median (min-max)	3 (0-15)		
Type of epilepsy (Generalized/Partial)	25 / 36		
Illness duration, year, median (min-max)	3 (0-13)		
EEG findings (normal/pathological/ unknown)	14/38/9		
Treatment regimen (mono/polytherapy/no drug)	35 / 24/ 2		
Sodium (mmol/l), median (min-max)	141 (135-148)	141 (136-148)	0.670[a]
Potassium (meq/l), mean±SD	4.38 ± 0.39	4.43 ± 0.35	0.582[b]
Calcium (mg/dl), mean±SD	9.47 ± 0.55	9.68 ± 0.43	***0.025[b]***
Phosphorus (mg/dl), median (min-max)	4.70 (3.3-6)	4.86 (3.3-6.3)	0.636[a]
Magnesium (mg/dl), median (min-max)	1.94 (1.1-3.6)	2.09 (1.20-2.90)	0.454[a]
Hemoglobin (g/dl), mean±SD	12.98 ± 1.20	13.41 ± 0.97	***0.039[b]***
Leukocytes (x100/µl), mean±SD	7.66 ± 2.75	7.58 ± 1.75	0.858[b]
Platelet count (x100/µl), median (min-max)	306 (98-563)	330 (189-537)	0.061[a]

Body mass index (BMI). [a] Mann Whitney U Test, [b] Independent Student T Test, [c] Pearson Chi-Square Test were used.

Calcium and haemoglobin measurements from laboratory parameters were found to be significantly lower in the patient group (p= 0.025 and p= 0.039, respectively).

There was no significant difference between the ECG parameters of the children in the patient and healthy groups. QTc was detected as 390 ± 25 ms in epileptic patients and 381 ± 21 ms in healthy children, and there was no statistically significant difference (p = 0.066). The only fractional shortening of echocardiographic parameters in epileptic children was detected statistically lower compared healthy group (p = 0.045) (Table 2).

Table 2. *Echocardiographic and ECG parameters of children with epilepsy and healthy controls.*

	Children with epilepsy (n: 61)	**Healthy Controls (n: 53)**	**p**
Echocardiography			
EF, mean±SD	69.23 ± 6.44	71.40 ± 5.88	0.065[b]
FS, mean±SD	38.48 ± 5.41	40.45 ± 4.94	***0.045[b]***
Cardiac mass(g), median (min-max)	60.07 (6.46-219.5)	68.72 (23.74-211.97)	0.149[a]
IVSDd (mm), median (min-max)	6.02 (3.07-13.14)	6.64 (4.38-12.04)	0.154[a]
LVPWd (mm), mean±SD	6.57 ± 4.83	6.14 ± 1.40	0.530[b]
LA/Ao, median (min-max)	1.25 (0.92-1.89)	1.24 (0.83-1.83)	0.521[a]
E/A, mean±SD	1.66 ± 0.30	1.73 ± 0.29	0.209[b]
DT (ms), median (min-max)	104 (52-170)	102 (52-170)	0.270[a]
IVRT (ms), median (min-max)	89 (52-155)	81 (52-155)	0.589[a]
ET (ms), median (min-max)	201.50 (104-318)	207 (148-296)	0.682[a]
ICT (ms), median (min-max)	74 (26-348)	74 (10-222)	0.751[a]
ECG			
PR (ms), median (min-max)	120 (100-160)	120 (100-160)	0.864[a]
QRS (ms), median (min-max)	80 (80-120)	80 (70-100)	0.923[a]
QTc (ms), mean±SD	390.4 ± 25.7	381.8 ± 21.6	0.066[b]

Left ventricular ejection fraction (EF), fractional shortening (FS), Interventricular septum at end-diastole dimension (IVSD), the end-diastolic left ventricular posterior wall thickness (LVPWd), left atrial to aortic root ratio (LA/Ao), ratio of early to late diastolic mitral inflow velocity (E/A), deceleration time (DT), isovolumic relaxation time (IVRT), the ejection time (ET), isovolumetric contraction time (ICT). [a] Mann Whitney U Test, [b] Independent Student T Test were used.

The results of the time and frequency domain analysis of HRV in children with epilepsy and healthy control were presented in table 3.

Table 3. *Heart rate variability of children with epilepsy and healthy controls.*

	Children with epilepsy (n: 61)	Healthy Controls (n: 53)	p
Minimal heart rate (beats/min), median (min-max)	53 (38-87)	51 (37-73)	***0.023***[a]
Maximal heart rate (beats/min), mean±SD	164.79 ± 17.99	166.34 ± 16.02	0.630[b]
Mean heart rate (beats/min), median (min-max)	94 (68-147)	88 (61-128)	***0.020***[a]
Mean RR (ms), mean±SD	631.26 ± 87.90	676.80 ± 95.81	***0.010***[b]
SDNN (ms), mean±SD	115.87 ± 45.52	137.92 ± 45.01	***0.011***[b]
SDNN index, mean±SD	52.43 ± 20.76	68.94 ± 21.65	***<0.001***[b]
SDANN (ms), mean±SD	104.92 ± 44.26	123.25 ± 38.72	***0.021***[b]
RMSSD (ms), median (min-max)	33 (13-71)	45 (22-92)	***<0.001***[a]
pNN50 (%), mean±SD	13.34 ± 9.34	22.58 ± 10.42	***<0.001***[b]
Total power, median (min-max)	2307.4 (349.2-11428.80)	4235 (737-11518)	***<0.001***[a]
LF (ms^2), median (min-max)	505.7 (78.80-1898.70)	811.7 (182.3-2200)	***<0.001***[a]
HF (ms^2), median (min-max)	322 (28.70-1183.70)	561.8 (76.5-6269)	***<0.001***[a]
VLF (ms^2), median (min-max)	1349.6 (186.80-9060.20)	2600.6 (465.1-8420)	***<0.001***[a]
LF/H, median (min-max)	1.75 (0.55-5.66)	1.61 (0.13-2.88)	***0.038***[a]

Body mass index (BMI), standard deviation of all RR intervals (SDNN), mean of the standard deviations of all NN intervals in 5 minute recordings (SDNN index), standard deviation of mean NN intervals in 5 minute recordings (SDANN), root mean squares of successive differences (RMSSD), NN50 count (number of pairs of adjacent NN intervals differing more than 50 ms) divided by the total number of all NN intervals (pNN50), the low frequency band (LF), high frequency band (HF), the very low frequency band (VLF). [a] *Mann Whitney U Test,* [b] *Independent Student T Test were used.*

All time and frequency domain indices were significantly suppressed in the patient group. The LF/HF ratio, an indicator of sympathovagal balance, was higher in the children with epilepsy.

Children with epilepsy were divided into subgroups according to epilepsy type as partial and generalized. There were not statistically significant differences in both time and frequency domain parameters between children with partial and generalized epilepsy (Table 4).

Table 4. *Demographic, clinical characteristics and heart rate variability parameters of children with partial and generalized epilepsy.*

	Children with partial epilepsy (n: 36)	Children with generalized epilepsy (n: 25)	p
Age, mean±SD	9.00 ± 4.17	9.36 ± 5.21	0.772[b]
Gender (Female/male)	18/18	11/14	0.795[c]
BMI (kg/m^2), mean±SD	17.67 ± 4.32	16.29 ± 3.46	0.183[b]
Age at first seizure (year), median (min-max)	4 (0-15)	2.5 (0.25-14)	0.466[a]
Duration of disease (year), median (min-max)	2.5 (0-13)	5 (0.3-13)	0.144[a]
Minimal heart rate (beats/min), median (min-max)	53 (41-75)	53 (38-87)	0.936[a]
Maximal heart rate (beats/min), mean±SD	163.51 ± 16.73	166.50 ± 19.78	0.526[b]
Mean heart rate (beats/min), median (min-max)	94 (75-131)	95 (68-147)	0.930[a]
SDNN (ms), mean±SD	116.03 ± 39.06	115.65 ± 53.83	0.975[b]
SDNN index, mean±SD	51.94 ± 16.27	53.08 ± 25.95	0.846[b]
SDANN, mean±SD	104.54 ± 38.80	105.42 ± 51.51	0.940[b]
RMSSD (ms), mean±SD	36.57 ± 12.04	34.73 ± 15.82	0.608[b]
pNN50 (%), mean±SD	14.29 ± 9.04	12.08 ± 9.77	0.366[b]
Total power, median (min-max)	2422.45 (366.7-7306)	2254.50 (349.2-11428.8)	0.930[a]
LF (ms^2), median (min-max)	519.15 (112.2-1675.4)	486.40 (78.80-1898.70)	0.907[a]
HF (ms^2), median (min-max)	347.30 (48-799)	266.50 (28.7-1183.7)	0.660[a]
VLF (ms^2), median (min-max)	1456.80 (186.8-5007)	1284.40 (223.60-9060.2)	0.837[a]
LF/HF, median (min-max)	1.69 (0.55-4.70)	1.93 (0.81-5.66)	0.241[a]

Body mass index (BMI), standard deviation of all RR intervals (SDNN), mean of the standard deviations of all NN intervals in 5 minute recordings (SDNN index), standard deviation of mean NN intervals in 5 minute recordings (SDANN), root mean squares of successive differences (RMSSD), NN50 count (number of pairs of adjacent NN intervals differing more than 50 ms) divided by the total number of all NN intervals (pNN50), the low frequency band (LF), high frequency band (HF), the very low frequency band (VLF). [a] *Mann Whitney U Test,* [b] *Independent Student T Test,* [c] *Pearson Chi-Square Test were used.*

The study included 38 patients with well-controlled epilepsy and 23 patients with refractory epilepsy. In children with refractory epilepsy, SDNN, SDNN index and SDANN were significantly suppressed. Additionally, total power, LF and VLF were lower in patients with refractory epilepsy than in children with well-controlled epilepsy (Table 5).

Table 5. *Comparison of demographics and heart rate variability parameters of the children with well-controlled and refractory epilepsy.*

	Well-controlled epilepsy (n: 38)	Refractory epilepsy (n: 23)	p
Age, mean±SD	10.34 ± 4.03	7.19 ± 4.91	***0.008***[b]
Gender (Female/male)	21/17	8/15	0.186[c]
BMI (kg/m^2), mean±SD	18.12 ± 3.85	15.36 ± 3.73	***0.008***[b]
Age at first seizure (year), median (min-max)	4 (0-15)	0.5 (0-14)	***0.003***[a]
Duration of disease (year), median (min-max)	3 (0-13)	4.20 (0-12)	0.687[a]
Minimal heart rate (beats/min), median (min-max)	53 (38-75)	61 (41-87)	***0.050***[a]
Maximal heart rate (beats/min), mean±SD	165.39 ± 17.19	163.78 ± 19.60	0.738[b]
Mean heart rate (beats/min), median (min-max)	93 (68-113)	99 (72-147)	0.095[a]
SDNN (ms), mean±SD	127.45 ± 40.75	96.74 ± 47.38	***0.009***[b]
SDNN index, mean±SD	56.53 ± 19.46	45.65 ± 21.47	***0.046***[b]
SDANN, mean±SD	116.16 ± 39.54	86.35 ± 46.19	***0.010***[b]
RMSSD (ms), mean±SD	38.05 ± 12.96	32.04 ± 14.31	0.097[b]
pNN50 (%), mean±SD	14.68 ± 8.58	11.13 ± 10.29	0.152[b]
Total power, median (min-max)	2538.40 (803.7-11428)	1417.30 (349-8514)	***0.032***[a]
LF (ms^2), median (min-max)	575.85 (193.5-1898.7)	385.40 (78.8-1426.7)	***0.040***[a]
HF (ms^2), median (min-max)	354.10 (125.3-1183.7)	205.40 (28.7-859.8)	0.059[a]
VLF (ms^2), median (min-max)	1630.15 (459.1-9060)	891.90 (186.8-6182)	***0.023***[a]
LF/HF, median (min-max)	1.73 (0.81-4.02)	1.83 (0.55-5.66)	0.755[a]

Body mass index (BMI), standard deviation of all RR intervals (SDNN), mean of the standard deviations of all NN intervals in 5 minute recordings (SDNN index), standard deviation of mean NN intervals in 5 minute recordings (SDANN), root mean squares of successive differences (RMSSD), NN50 count (number of pairs of adjacent NN intervals differing more than 50 ms) divided by the total number of all NN intervals (pNN50), the low frequency band (LF), high frequency band (HF), the very low frequency band (VLF). [a] *Mann Whitney U Test,* [b] *Independent Student T Test,* [c] *Pearson Chi-Square Test were used.*

In the patient group, EEG reports of 14 patients were normal, and EEG reports of 38 patients were pathological. Nine patients, whose previous EEG reports could not be reached, refused to repeat EEG. The results of HRV analysis in the children with normal EEG and pathological EEG were presented in table 6.

Table 6. *Comparison of demographics and heart rate variability parameters of the children with normal EEG and pathological EEG.*

	Normal EEG (n: 14)	Pathological EEG (n: 38)	p
Age, mean±SD	11.40 ± 4.51	7.85 ± 4.28	***0.012***[b]
Gender (Female/male)	7/7	16/22	0.755[c]
BMI (kg/m^2), mean±SD	19.66 ± 4.36	16.16 ± 3.81	***0.007***[b]
Age at first seizure (year), median (min-max)	9.25 (0-15)	3 (0-14)	0.061[a]
Duration of disease (year), median (min-max)	3 (1-13)	2.50 (0-13)	0.605[a]
Minimal heart rate (beats/min), median (min-max)	48 (38-87)	55.50 (41-74)	0.069[a]
Maximal heart rate (beats/min), mean±SD	164.50 ± 16.37	166.55 ± 19.12	0.723[b]
Mean heart rate (beats/min), median (min-max)	86 (68-125)	98 (80-147)	***0.023***[a]
SDNN (ms), mean±SD	147.64 ± 54.64	105.63 ± 39.73	***0.004***[b]
SDNN index, mean±SD	65.21 ± 26.12	47.87 ± 16.96	***0.033***[b]
SDANN, mean±SD	136.50 ± 52.94	95.24 ± 39.32	***0.004***[b]
RMSSD (ms), mean±SD	41.50 ± 15.99	34.16 ± 13.06	0.097[b]
pNN50 (%), mean±SD	16.29 ± 9.58	12.55 ± 9.56	0.218[b]
Total power, median (min-max)	4595.90 (479.1-11428.8)	2088.40 (349.2-5818.3)	***0.026***[a]
LF (ms^2), median (min-max)	973.80 (105-1898.7)	467.70 (78.8-1379.1)	***0.030***[a]
HF (ms^2), median (min-max)	470.05 (70.9-1183.7)	321.95 (28.7-859.8)	0.257[a]
VLF (ms^2), median (min-max)	2898.35 (291.9-9060.2)	1274.80 (186.8-3849)	***0.011***[a]
LF/HF, median (min-max)	2.01 (0.98-4.02)	1.69 (0.55-5.66)	0.187[a]

Body mass index (BMI), standard deviation of all RR intervals (SDNN), mean of the standard deviations of all NN intervals in 5 minute recordings (SDNN index), standard deviation of mean NN intervals in 5 minute recordings (SDANN), root mean squares of successive differences (RMSSD), NN50 count (number of pairs of adjacent NN intervals differing more than 50 ms) divided by the total number of all NN intervals (pNN50), the low frequency band (LF), high frequency band (HF), the very low frequency band (VLF). [a] *Mann Whitney U Test,* [b] *Independent Student T Test,* [c] *Pearson Chi-Square Test were used.*

SDNN, SDNN index and SDANN were found to be decreased in the children with pathological EEG. In addition, there were significant reductions in frequency domain parameters (total power, LF and VLF) in the group with pathological EEG.

HRV parameters of the patients were analysed according to their treatment regimens. Children were categorized according to their monotherapy and polytherapy regimens. 35 and 24 patients have taken monotherapy and polytherapy medication, respectively. Two children were not included in this group. One of two children was finished his therapy before six months. The other child has not regularly taken his medication. The polytherapy regimen was found to be associated with suppressed HRV (reduced SDNN, SDNN index, SDANN, RMSSD, total power, LF, VLF, HF) when compared with monotherapy regimen (Table 7).

Table 7. *Comparison of demographics and heart rate variability parameters of the children receiving monotherapy and polytherapy regimens.*

	Monotherapy (n: 35)	**Polytherapy (n: 24)**	**p**
Age, mean±SD	10.17 ± 4.23	7.91 ± 4.96	0.066[b]
Gender (Female/male)	17/18	11/13	0.836[c]
BMI (kg/m^2), mean±SD	18.42 ± 3.79	15.34 ± 3.77	***0.003***[b]
Age at first seizure (year), median (min-max)	4.50 (0-15)	0.75 (0-11)	***0.001***[a]
Duration of disease (year), median (min-max)	3 (0-13)	5.25 (0-13)	0.417[a]
Minimal heart rate (beats/min), median (min-max)	51 (38-75)	61 (41-87)	***0.025***[a]
Maximal heart rate (beats/min), mean±SD	167.09 ± 16.90	160.63 ± 19.67	0.183[b]
Mean heart rate (beats/min), median (min-max)	93 (68-115)	97 (72-147)	0.158[a]
SDNN (ms), mean±SD	129.34 ± 43.41	98.17 ± 44.33	***0.009***[b]
SDNN index, mean±SD	58.66 ± 19.73	44.04 ± 20.17	***0.008***[b]
SDANN, mean±SD	117.26 ± 42.29	88.63 ± 43.79	***0.015***[b]
RMSSD (ms), mean±SD	39.00 ± 13.46	31.46 ± 13.54	***0.039***[b]
pNN50 (%), mean±SD	15.40 ± 9.07	10.58 ± 9.53	0.055[b]
Total power, median (min-max)	2899 (863.40-11428.8)	1540.75 (349.2-8514.2)	***0.005***[a]
LF (ms^2), median (min-max)	625.30 (188.4-1898.7)	381.15 (78.8-1426.7)	***0.004***[a]
HF (ms^2), median (min-max)	372 (103.1-1183.7)	186.65 (28.7-850)	***0.010***[a]
VLF (ms^2), median (min-max)	1775.40 (552.4-9060.2)	898.45 (186.8-6182)	***0.005***[a]
LF/HF, median (min-max)	1.75 (0.81-4.02)	1.79 (0.55-5.66)	0.926[a]

Body mass index (BMI), standard deviation of all RR intervals (SDNN), mean of the standard deviations of all NN intervals in 5 minute recordings (SDNN index), standard deviation of mean NN intervals in 5 minute recordings (SDANN), root mean squares of successive differences (RMSSD), NN50 count (number of pairs of adjacent NN intervals differing more than 50 ms) divided by the total number of all NN intervals (pNN50), the low frequency band (LF), high frequency band (HF), the very low frequency band (VLF). [a] *Mann Whitney U Test,* [b] *Independent Student T Test,* [c] *Pearson Chi-Square Test were used.*

DISCUSSION

Cardiovascular system, which is stimulated by the visceral autonomic system, is predominantly under the effect of the parasympathetic system (8). Several studies have reported that increased vagal activity provide the protective antifibrillatory effects (9). Additionally, recent studies have indicated that HRV has high predictive value for sudden cardiac death. Decreased HRV is a strong and independent prognostic indicator in patients with heart disease as well as in healthy subjects. It is well known that SUDEP is the most important cause of deaths in patients with epilepsy. The most important factors among multiple factors responsible for SUDEP etiology are autonomic dysfunction and ictal bradyarrhythmia (10).

In our study, no statistical difference was found between the patient and healthy groups in terms of QT, PR, and QRS durations. In many studies have investigated possible associations between SUDEP and cardiac arrhythmias. Although mostly pathological ECG changes were detected in the ictal period, resting ECG studies did not reveal any significant pathology except for QT prolongation (11-13).

In our study, in the echocardiographic evaluation of epilepsy patients, fractional shorting was significantly lower than the healthy group. Studies have shown that antiepileptic drugs (AEDs) may have negative effects on cardiac functions (14, 15). This situation in patients may be due to the direct negative effects of drugs on the myocardium, or indirectly to the negative effects of AEDs on Ca metabolism, which is effective in cardiac muscle functions (16). As we showed in our study, Ca values in epilepsy patients were significantly lower than in the healthy group. Hypocalcemia may occur as a result of the negative effects of AEDs on vitamin D metabolism (17). Severe hypocalcemia may impair systolic functions and cause reversible heart failure (18). In addition, loss of seizure control may occur in patients with epilepsy in Ca deficiency. Therefore, Ca is an important electrolyte whose values should be measured intermittently in epilepsy patients. Vitamin D supplementation is recommended prophylactically in chronic patients already receiving AEDs (17).

It is possible to separate the sympathetic and parasympathetic effect by the time and frequency dependent methods of HRV. In the time domain analysis of HRV, SDNN reflects a general measurement of autonomic nervous system balance, whereas the RMSSD and pNN50 predominantly represent parasympathetic activity (1). 19 case-control studies were evaluated in a meta-analysis conducted in 2011. This meta-analysis included 524 patients with epilepsy and 620 healthy control subjects covering a wide age range from infants to adults. In the result of this meta-analysis was determined that SDNN, RMSSD and HF parameters were lower in patients with epilepsy (3). In a case-control study, which included 30 children with epilepsy (age range 4-10 years), was detected no significant difference in the frequency domain parameters of HRV (19). In another study, which included 25 patients with idiopathic epilepsy and 50 control subjects, was found that SDNN was reduced in all age groups, while RMSSD and PNN50 were reduced only in the older age group (20). In a study conducted with 30 epileptic children was reported that HF and LF values were significantly lower in epileptic children compared to the control group (9). Hallioglu et al. (21) have compared 92 epileptic children and 83 healthy children in their study. In their study, a significant decrease was observed in children with epilepsy in SDNN, RMSSD parameters.

In this study, it was found that the time domain parameters of HRV (SDNN, SDNN index, SDANN, RMSSD, pNN50) and all parameters of frequency domain measures (LF, HF, VLF, total power) were significantly suppressed in children with epilepsy. Reduced RMSSD, pNN50 and HF parameters, which

are strong indicators of parasympathetic tone, display the suppression of parasympathetic tone in epileptic children. The LF that is affected by both sympathetic and parasympathetic systems was found low in our study. It was thought that low LF indicated the depression of all autonomic nervous system in epileptic children. In our study, the LF/HF ratio showing sympathovagal balance was found to increase in favor of sympathetic tone in children with epilepsy. According to this result, it was thought that the parasympathetic tone was due to the advanced level suppression rather than increased sympathetic tone. Increased heart rate and decreased HRV, have shown that the autonomic nervous system in epileptic children is under the influence of sympathetic tone. This situation may create potential cardiovascular risks for possible fatal arrhythmias in children with epilepsy.

In a study compared 25 patients with partial epilepsy and 12 patients with generalized epilepsy, in the time and frequency dependent parameters of HRV were no detected significant differences (22). Similarly, in our study, in the HRV parameters between children with partial and generalized epilepsy were no found significant differences. These data showed that epilepsy type had no effect on HRV parameters.

It has been reported that patients with refractory epilepsy are susceptible to autonomic nervous system dysfunction, and SUDEP is responsible for 50% of mortality in these patients (23, 24). In a study, it was compared the HRV parameters in children with refractory epilepsy and well-controlled, has been detected that pNN50 was significantly lower in children with refractory epilepsy, and has been suggested that the parasympathetic tone in these patients was suppressed (25). In a study conducted in adult patients with refractory epilepsy was determined the decreased parasympathetic tone and the increased sympathetic tone in patients with refractory epilepsy compared with well-controlled (22). In children with refractory epilepsy compared with well-controlled in this study were showed the low values in SDNN, SDNN index, SDANN, LF, VLF and total power parameters. According to these data, it was thought that this patient group had a general suppression of the autonomic nervous system, and that this suppression might primarily be due to the decrease in parasympathetic tone. Therefore, children with refractory epilepsy may be under a potential risk for cardiac arrhythmias.

When compared HRV parameters of the children with normal EEG and pathological EEG in this study; SDNN, SDNN index, SDANN, LF, VLF and total power were found to be significantly decreased in the children with pathological EEG. These data in this group of patients have shown to be the suppression of both two arms of the autonomic nervous system. As a result, it was thought that emitted electrical discharge continuously from an epileptic focus in children with pathological EEG also effect neurons provided the regulation the autonomic nervous system and may lead the autonomic dysregulation. Therefore, to have positive EEG findings in epileptic children may create a potential risk for cardiac arrhythmias

Several studies in the literature have shown that different antiepileptic drugs can have different effects on the autonomic nervous system (21). It has been reported that changes in the treatment regimen of patients may have also contributed to his sudden cardiac death (4). In a study has been identified that parasympathetic tone indicators were reduced in epileptic patients receiving polytherapy. In the same study has been revealed that polytherapy regimen was an independent variable associated with a serious decline in the value of SDNN (22). According to the results of our study, it was detected that there was a general suppression in the autonomic nervous system of the children who received polytherapy. This suppression may be a cumulative effect on the autonomic nervous system of drugs.

In our study, it was observed that the parasympathetic sympathetic balance changed in favor of the sympathetic in epilepsy patients. Studies have shown that beta-blocker drugs are anticonvulsive, especially on generalized tonic-clonic seizures. The suppression of increased sympathetic tone with beta-blocker therapy may play a role in this effect (26). The antiepileptic effects of beta blockers have been known for many years (27, 28). However, studies showing the antiepileptic effects of beta blockers are mostly animal experiments. In a study conducted in rats with artificial epileptic seizures with pentylenetetrazol, the antiepileptic effect of propranolol was found to be similar to that of diazepam (27). There are no comprehensive human studies on the use of beta-blockers in antiepileptic therapy in the literature. Cardiac events play an important role in the etiology of SUDEP. The protective effect of beta-blockers, which have been used safely for years in many cardiac diseases such as heart failure, arrhythmias, myocardial infarction, on SUDEP is still being discussed (29). Some authors have suggested to epileptiologists as a reasonable target the use of beta-blockers, especially in patients with persistent epilepsy, and with concomitant sympathetic overactivity (30).

This study has a limitation. The patients were using one or more of AEDs such as valproic acid, carbamazepine, lamotrigine, levetiracetam, topiramate, phenytoin, phenobarbital, clonazepam in combination. Therefore, the effects of drugs with different mechanisms of action used by patients on HRV could not be categorized.

Epilepsy is associated with suppressed HRV values indicating decreased vagal activity. In children with epilepsy, having pathological EEG findings and polytherapy regimen associated with refractory epilepsy are effective on suppressed HRV. In addition, it has been observed that cardiac systolic functions may be adversely affected in epilepsy patients due to the possible AED effect. Therefore, HRV and echocardiography can be used as a follow-up tool in the evaluation of autonomic dysfunction and cardiac functions in epilepsy patients, especially in refractory epilepsy patients.

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