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Evaluation of systolic and diastolic cardiac functions and heart rate variability in patients with juvenile myoclonic epilepsy

Vyhodnocení systolických a diastolických srdečních funkcí a variability srdeční frekvence u pacientů s juvenilní myoklonickou epilepsií

Abstract

Aim: To explore if patients with juvenile myoclonic epilepsy (JME) have differences in heart rate variability (HRV) associated with risk of arrhythmias and in systolic and diastolic functions. *Patients and methods:* This single-centre prospective study included 50 patients with JME followed up at the epilepsy outpatient clinic within the Antalya Training and Research Hospital's Neurology Department (34 women, mean age 26 ± 7.58 years) and 45 healthy controls (30 women, mean age 26.71 ± 5.14 years). Two patients were excluded since they had arterial hypertension, one patient was excluded due to diabetes mellitus and one patient was excluded due to rheumatic mitral stenosis. Finally, 46 patients were included in the study. All patients and controls were evaluated by conventional echocardiography and tissue Doppler imaging for systolic and diastolic functions (e.g. left ventricular ejection fraction, left ventricle diameters and volumes, deceleration time, pulmonary forward flows) and performing 24-h Holter monitoring to explore time domain (e.g. standard deviation of the normal-to-normal interval, the square root of the mean squared differences of successive normal-to-normal intervals) and frequency domain parameters of HRV. *Results:* There were no significant differences between the Holter parameters of the two groups with respect to HRV. Echocardiographic investigation did not reveal any significant differences except for the ratio of pulmonary venous systolic and diastolic (PVS/PVD) forward flows to one another (p = 0.008). *Conclusion:* In this study, we did not find anything else about cardiac involvement other than increased ratio of PVS/PVD and we did not find autonomic dysfunction in patients with JME. This may be due to good seizure control.

Souhrn

Cíl: Prozkoumat, zda u pacientů s juvenilní myoklonickou epilepsií (JME) existují rozdíly ve variabilitě srdeční frekvence (heart rate variability; HRV) spojené s rizikem arytmií a v systolických a diastolických funkcích. *Soubor a metodika:* Tato jednocentrická prospektivní studie zahrnovala 50 pacientů s JME, kteří byli sledováni na ambulanci pro epilepsii Neurologického oddělení nemocnice Antalya Training and Research Hospital (34 žen, průměrný věk 26 ± 7,58 let), a 45 zdravých kontrolních osob (30 žen, průměrný věk 26,71 ± 5,14 let). Dva pacienti byli ze studie vyloučeni z důvodu arteriální hypertenze, jeden pacient byl vyloučen kvůli diabetu mellitu a jeden pacient byl vyloučen kvůli revmatické mitrální stenóze. Nakonec bylo do studie zařazeno 46 pacientů. U všech pacientů a kontrolních osob byly konvenční echokardiografií a tkáňovým dopplerovským zobrazením vyšetřeny systolické a diastolické funkce (např. ejekční frakce levé komory, rozměry a objemy levé komory, decelerační čas, plicní dopředné toky) a provedl se 24h Holterův monitoring za účelem prozkoumání parametrů časové domény (např. směrodatná odchylka intervalů „normal-to-normal", druhá odmocnina průměru druhých mocnin rozdílů mezi po sobě jdoucími intervaly „normal-to-normal") a parametrů frekvenční domény HRV. *Výsledky:* Mezi oběma skupinami nebyly zjištěny žádné významné rozdíly v Holterovských parametrech, pokud jde o HRV. Echokardiografické vyšetření neodhalilo žádné významné rozdíly vyjma vzájemného poměru plicního venózního systolického a diastolického (PVS/PVD) dopředného toku (p = 0,008). *Závěr:* V této studii jsme u pacientů s JME kromě zvýšeného poměru PVS/PVD nenalezli nic jiného, co by se týkalo srdečního postižení, a rovněž jsme u nich nepozorovali autonomní dysfunkci. Tato skutečnost může být důsledkem dobré kontroly záchvatů.

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Introduction

Epilepsy often affects the autonomic functions during ictal, inter-ictal and post-ictal periods. Epileptic discharges are inculpated for impairing or altering the central autonomic pathway and normal autonomic cardiac functions in patients having seizures. Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with epilepsy and accounts for about 17% of these deaths [1]. However, the mechanisms involved in SUDEP are not well understood; fatal cardiac arrhythmias caused by the activation of the autonomic nervous system (ANS) are also inculpated. Measurement of heart rate variability (HRV) is one of the ways to measure the effects of ANS on the heart. The intervals between the heart beats in the sinus rhythm are different in healthy individuals, which is a normal physiological process [2]. HRV refers to the mathematical formulation of the fluctuations in heart rate around the average heart rate within a certain time [2]. Physical and metabolic factors lead to variations in the heart rate associated with autonomic tonus. HRV seems to be very promising for the investigation of cardiovascular response to the variations in the autonomic tonus [2,3]. Increased activation of the sympathetic system and suppression of the parasympathetic system leads to a decline in the HRV [2]. HRV is evaluated in two ways: time and frequency analysis. The intervals between the normal pulses in the 24-h electrocardiography (ECG) records are analyzed during the time domain measurement, while the heart rate signals are grouped according to frequencies and intensities and information is obtained about the amount of heart rate variation on the basis of the periodical cardiac oscillations at different frequencies during the frequency domain spectral analysis [2,4]. In our study, we investigated autonomic dysfunction through time domain and frequency domain HRV analysis in patients diagnosed with juvenile myoclonic epilepsy (JME) and healthy controls. Recent studies found that epilepsy patients had cardiac systolic and diastolic dysfunctions, while the effect of ANS on the heart are inculpated for such abnormalities [5].

Increased sympathetic cardiac stimulation may lead to cardiac arrhythmias but also repetitive sympathetic stimulation may cause structural damage in the heart, which means that there is a high predisposition to arrhythmia and ischaemia. Myocardial fibrosis may also lead to left ventricular systolic and diastolic dysfunction. We evaluated the presence of such dysfunction through conventional echocardiographic investigation and tissue Doppler imaging (TDI).

Patients and methods

This single-centre prospective study enrolled 50 patients with JME followed up at the epilepsy outpatient clinic within the Antalya Training and Research Hospital's Neurology Department (34 women, mean age 26 ± 7.58 years) and 45 healthy controls (30 women, mean age 26.71 ± 5.14 years). Patients were diagnosed by three neurologists who were specialized in epilepsy. The neurological examination of the patients and controls was performed by that team of neurologists and their cardiologic examination was performed by a cardiologist.

Exclusion criteria included pregnancy, known coronary artery disease, hepatic and renal dysfunction, arterial hypertension, valvular heart disease, left ventricular systolic dysfunction (ejection fraction <50%), restrictive, hypertrophic or dilated cardiomyopathy, congenital cardiac disease, pulmonary pathologies, diabetes mellitus, malignancies, severe alcohol consumption, hyperlipidaemia, previous cardiac surgery, severe mitral annular calcification, atrial fibrillation or other severe arrhythmias, use of pacemaker or implantable cardioverter defibrillator, poor echocardiographic image quality. Two patients were excluded since they had arterial hypertension, one patient was excluded due to diabetes mellitus and one patient was excluded due to rheumatic mitral stenosis and thus 46 patients were included in the study and 40 of them were seizure-free.

The epilepsy diagnosis was established on the basis of the Guidelines of the International League Against Epilepsy, and the patients were diagnosed according to the medical history of the patients and their relatives, physical and neurological examination, as well as the EEG and neuroradiological findings [6].

Blood pressure of both groups was measured in sitting position after 5-min rest. Height, weight and waist circumference of both groups were measured and their body mass index and body surface area were calculated. Potential SUDEP risk in patients was estimated using an inventory of seven validated SUDEP risk factors (SUDEP-7), which was assembled from a large prospective cohort study of SUDEP reported by Walczak et al. [7]. Based on this study, Di Giorgo et al. validated a SUDEP-7 inventory [8]. This inventory consists of seven items in which scores were based on the log of the odds ratio of the main risk factors [7,8]. The score on the SUDEP-7 ranged from 1 to 7, out of a maximum possible score of 10.

Electrocardiographic study

Standard 12-lead ECG was recorded in all participants to study the following variables: heart rate, PR interval (the time between the beginning of P-wave and the beginning of QRS complex), QRS complex duration, QT interval (the time between the beginning of QRS complex and the end of T-wave), QTc interval (the QT interval after correction for heart rate, which is the QT interval divided by the square root of RR interval [Bazett's formula]).

Echocardiography study

The echocardiographic investigation of all patients and the control group was performed using Philips IE33 xMatric (Philips, Andover, MA, USA) with 5-1MHz matrix transducer using transthoracic approach. The images of the patients were obtained in left lateral decubitus position, while measurements were performed in 2D, M Mode, continuous-wave Doppler, pulse-wave Doppler and TDI echocardiography using parasternal long and short axis, apical four-chamber and five-chamber views. Left ventricular and right atrium diameters as well as interventricular septum and posterior wall thickness were measured using M mode technique in line with the recommendations of the American Society of Echocardiography [9]. The early (E) and late (A) peak velocities of diastolic filling, deceleration time (DT) and isovolumetric relaxation time (IVRT) were obtained from mitral inflow and aortic outflow Doppler records [10]. The filter setting was reduced and Nyquist limit was adjusted for TDI measurement (range 15–20 cm/s). The gain of the device was reduced in order to decrease the noise in the background and obtain a clear tissue signal. For TDI measurements to be performed from the apical window, 5-mm sample volume was placed lateral to the mitral valvular annulus on 4-chamber view [10]. Measurements

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were performed simultaneously with ECG at a rate of 50–100 mm/s. Peak systolic velocity (s'), early (e') and late (a') diastolic velocities and ratio of e'/a' were measured. For recording pulmonary venous flow velocities, right superior pulmonary venous flow in the apical four-chamber view was used and sample volume was placed 1–2 cm into the orifice. Here, pulmonary venous systolic forward flow (PVS) and pulmonary venous diastolic forward flow (PVD) were recorded. The ratio of E/e' was obtained by dividing transmitral E peak to e'. The diagnosis and staging of left ventricular diastolic dysfunction (LVDD) were done according to the recommendations of the European Society of Echocardiography [11]. LVDD was diagnosed when lateral mitral annular e' velocity was lower than 10 cm/s or left atrium volume index was greater than 34 mL/m^2. LVDD has 3 stages (I, II and III). When LVDD was diagnosed, Doppler parameters such as E/A ratio, DT, IVRT, E/e' ratio and PVS/PVD ratio were used for staging [11]. Ejection fraction was quantified according to Teicholz formula [12]. All echocardiographic investigations were recorded digitally so that they could be examined off-line later. All measurements were performed by calculating the average of three cardiac cycles in order to decrease the respiratory variation.

Heart rate variability

In order to evaluate HRV of the patients and controls, 24-h ECG records were performed using 3-channel digital Holter recording device DMS300-3A (DM Software Inc., Stateline, NV, USA). Holter records were analyzed using the software Cardioscan 12,0 (DM Software Inc., Stateline, NV, US) and the records were evaluated manually in order to rule out the artifacts (ectopic beats, arrhythmic events, missing data and noise effects).

During HRV evaluation, standard deviation (SD) of the normal-to-normal (NN) interval (SDNN), the square root of the mean squared differences of successive NN intervals (RMSSD), the division of the number of interval differences of successive NN intervals of more than 50 ms by the total number of NN intervals (pNN50) were analyzed for the time domain parameters. SDNN represents a global measure of HRV. RMSSD is considered a powerful measure of high frequency (HF) variations in short-term recording, as it provides a useful evaluation of HF and vagal tone [2]. The fast Fourier transformation (FFT) has been used to calculate the power spectrum density. Total power (S POWER) in the range 0.0033–0.4 Hz, power in very low frequency (VLF) in the range 0.0033–0.04 Hz, power in low frequency (LF) in the range 0.04–0.15 Hz and power in high frequency (HF) in the range 0.15–0.4 Hz. were analyzed for frequency domain parameters. VLF was evaluated although this component does not have a well-defined physiological explanation [2]. The HF was regarded as a measure of solely parasympathetic activity. The LF was considered to be a measure of mainly sympathetic activity that was modulated by the influence of the parasympathetic system. LF/HF ratio expresses the balance between sympathetic and parasympathetic nervous system activity. All analyses were performed according to the standards set by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [2].

This study was conducted upon the local approval no 46/12 and dated September 11, 2014 of the ethics board of Antalya Training and Research Hospital, and written consent forms were obtained from everyone included in the study. This study was conducted in compliance with the Declaration of Helsinki.

Statistical analysis

All of the statistical analyses were performed using the SPSS software package, version 21.0 (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as mean ± SD and the categorical variables as numbers and percentages. The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. The Mann-Whitney U test was used for variables that were not normally distributed. Statistical significance was defined as $p < 0.05$.

Tab. 1. Demographic characteristics in JME patients and control group.

Parameters	JME (N = 46) mean ± SD	Control group (N = 45) mean ± SD	P
age (year)	25.30 ± 6.18	26.71 ± 5.14	0.117
female (n, %)	32 (69.56)	30 (66.66)	ns
height (cm)	165.22 ± 8.82	167.18 ± 9.22	0.304
weight (kg)	65.84 ± 13.55	66.69 ± 14.85	0.772
BMI (kg/m^2)	24.19 ± 5.02	23.87 ± 5.28	0.598
BSA (m^2)	1.72 ± 0.18	1.74 ± 0.20	0.570
waist circumference (cm)	84.24 ± 12.98	82.36 ± 11.83	0.424
SBP (mmHg)	107.74 ± 12.67	108.67 ± 11.61	0.650
DBP (mmHg)	65.15 ± 9.37	65.22 ± 9.85	0.835
HR (bpm)	81.48 ± 10.23	82.91 ± 8.62	0.278

BMI – body mass index; BSA – body surface area; DBP – diastolic blood pressure; HR – heart rate; JME – juvenile myoclonic epilepsy; ns – not significant; SBP – systolic blood pressure; SD – standard deviation

Results

All participants were Caucasians. Thirty-two patients (69.56%) out of 46 included in the study were female and the mean age was 25.30 ± 6.18 years. In the control group, 30 individuals (66.66%) were female and the mean age was 26.71 ± 5.14 years while the control group included 45 healthy individuals. There was no difference between the two groups with respect to height, weight, body mass index, body surface area, waist circumference, systolic and diastolic blood pressure and resting heart rate (Tab. 1).

In JME group, 24 patients did not have any issues in their history; however, 6 patients had a history of febrile convulsion, one had a history of hypoxic delivery, one had a history of CNS infection, 11 had a head trauma and three had a history of febrile convulsion and head trauma. Thirty-two patients did not have any issues in their family history, whereas 13 patients had a family history of epilepsy and the parents of one patient had consanguineous marriage.

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Tab. 2. The SUDEP risk inventory (SUDEP-7, version 2.0) with each risk factor, weighting, and scoring convention [35].

SUDEP-7 parameters (scores)	Odds ratio	Points assigned if positive (weighting loge × odds ratio)	Number of patients with each risk factor
1. more than 3 GTCs in the past year	8.1	2	1
2. one or more GTCs in the past year	2.4	1	5
3. one or more seizures of any type over the last 12 months	2.2, 3.8, 4.6	1	0
4. > 50 seizures of any type per month over the last 12 months	11.5	2	0
5. duration of epilepsy ≥ 30 years	13.9	3	0
6. current use of ≥ 3 AEDs	4.0	1	2
7. developmental intellectual disability, IQ < 70 or too impaired to test	5.0	2	0

AEDs – antiepileptic drugs; GTCs – generalised tonic clonic seizures; IQ – intelligence quotient; SUDEP – sudden unexpected death in epilepsy

The mean epilepsy duration was 10.43 ± ± 6.67 years while the mean duration of drug use was 8.43 (max. 27, min. 1) years, the average frequency of seizures was 0.25 ± 0.7 (max. 4, min. 0) per month. For the epileptic treatment, 20 patients were taking valproic acid, 10 patients were taking lamotrigine, 7 patients were taking levetiracetam, 1 patient was taking topiramate, 6 patients were taking dual combination of these medications while 2 patients were on triple combination, mean SUDEP-7 inventory score of patients was 0.19 (max. 2, min. 0). Tab. 2 shows the components of the SUDEP-7 inventory and the number of subjects with each factor.

Echocardiography records of both groups and 24-h rhythm Holter were analyzed and registered. There was no significant difference between the JME group and control group with respect to time domain (SDNN, RMSSD, pNN50) and frequency domain (S POWER, VLF, LF, HF, LF/HF) parameters of HRV. No statistically significant difference was found with respect to left atrium diameter, area and volume index ($p = 0.374$, $p = 0.256$ and $p = 0.398$, resp.); likewise, interventricular septum and posterior wall thickness were similar in both groups ($p = 0.703$ and $p = 0.554$, resp.); moreover, there was no statistical difference between the other anatomic echocardiographic values. Furthermore, there was no difference between the Doppler and TDI parameters such as E wave velocity, E/A ratio, DT, IVRT, e'/a' ratio, E/e' ratio except PVS/PVD ($p = 0.008$). Analysis showed that JME patients had a significantly lower mean of heart rate, QRS duration, QT and QTc interval ($p = 0.007$, $p = 0.032$, $p = 0.027$, $p = 0.021$ resp.). Tab. 3 presents the HRV, echocardiographic and ECG data of the patient and control groups.

Discussion

Sinus arrhythmia refers to the respiratory cyclic changes in the heart rate and is associated with the cardio-respiratory connection in the brain stem. Physiological HRV is the indication of cardiac health while its absence or reduction may be a sign of a disease or aging process [13]. HRV analysis is a strong tool that gives semi-quantitative information about the relationship between the cardiovascular sympathetic and parasympathetic modulation under several physiological and pathophysiological conditions [14].

Compared to the healthy controls, patients with chronic temporal lobe epilepsy were found to have declined HRV. Although the results suggest that there is a decrease in the parasympathetic tonus and/or increase in the sympathetic tonus, the data about the relationship between epilepsy and the variations in the sympathetic and parasympathetic tonus are still insufficient [15]. We did not find HRV changes in our JME group which may be due to differences in anti-epileptic drugs (AEDs) such as classical sodium blockers that are used in temporal lobe epilepsy but are not used in JME. Increased sympathetic tone of the heart rate may play an important role in the development of ventricular tachycardia that may be associated with the high incidence of SUDEP in generalized tonic clonic seizure (GTCS) patients compared to the control group. Recently, a meta-analysis of HRV in epilepsy reported a lack of significant alterations of LF in epilepsy patients compared to controls; however, this parameter was found to be lower in patients with AEDs when compared to drug-free subjects [16]. As mentioned in the SUDEP-7 inventory that was designed to analyze risk factors identified by Walczak et al., seizure frequency is a well-known risk factor for SUDEP, but recent studies reported that seizure frequency of GTCS is much more important than for patients with any other type of seizure [7,17]. In the SUDEP-7 inventory, results indicated that older age, longer duration of epilepsy, and presence of developmental disability had direct influence on vagus-mediated HRV and thus increased SUDEP risk. The higher the SUDEP-7 inventory score, the higher the risk of SUDEP. Lower RMSSD values were associated with higher risk scores on the new SUDEP risk inventory. This provides new evidence that HRV (specifically RMSSD) is a marker of SUDEP risk [8].

Heart rate variability is observed to vary across the treated and untreated patients. Haliloğlu et al. found in their study that children taking valproic acid, oxcarbazepine or phenobarbital had better HRV results compared to the untreated ones [18]. Contrary to this finding, we did not find any difference with respect to heart rate and HRV parameters, which might be due to the fact that the seizures were controlled well. In a recent trial, comparison of changes in HRV parameters in the peri-apnea / hypopnea period of patients with JME and healthy controls did not show any significant difference except for SDNN [19]. However we did not find any significant difference between JME patients and healthy controls in none of HRV parameters. Further studies using a larger sample size and in patients with newly diagnosed and/or drug-resistant epilepsy may prove beneficial in understanding the mechanism.

Mechanisms underlying SUDEP may lead to fatal arrhythmia or ischaemia in pa-

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Tab. 3. Heart rate variability, echocardiographic and ECG parameters.

Parameters	JME (N = 46) mean ± SD	Control group (N = 45) mean ± SD	P
Heart rate variability			
RMSSD (ms)	33.70 ± 12.42	33.19 ± 12.03	0.767
SDNN (ms)	145.48 ± 34.60	150.78 ± 41.92	0.740
pNN50 (%)	11.48 ± 8.34	10.81 ± 7.75	0.791
SPOWER (ms^2)	3648.10 ± 1676.94	3836.09 ± 1996.47	0.886
VLF (ms^2)	2412.24 ± 1214.98	2548.42 ± 1452.87	0.827
LF (ms^2)	819.57 ± 330.61	896.79 ± 420.17	0.647
HF (ms^2)	390.26 ± 284.74	407.07 ± 290.48	0.716
LF/HF (ratio)	2.80 ± 1.39	2.75 ± 1.30	0.942
Echocardiography			
LV end diastolic diameter (mm)	44.91 ± 3.91	44.54 ± 3.75	0.662
LV end systolic diameter (mm)	27.82 ± 3.76	27.15 ± 2.91	0.502
IVS thickness (mm)	8.14 ± 0.98	8.14 ± 1.22	0.703
PW thickness (mm)	8.28 ± 1.18	8.42 ± 1.13	0.554
LA diameter (mm)	31.09 ± 3.30	31.87 ± 2.55	0.374
LA area (cm^2)	14.39 ± 2.61	15.03 ± 2.22	0.256
LA volume (mL)	37.99 ± 10.88	39.80 ± 9.54	0.395
E (cm/s)	87.05 ± 14.68	85.85 ± 13.68	0.949
A (cm/s)	59.40 ± 11.77	58.95 ± 11.83	0.683
LV end diastolic volume (mL)	63.07 ± 16.39	65.49 ± 15.95	0.472
LV end systolic volume (mL)	20.09 ± 7.39	19.07 ± 5.01	0.753
LV mass (gr)	140.40 ± 22.29	138.60 ± 28.95	0.453
lateral e' (cm/s)	18.01 ± 3.20	17.76 ± 3.25	0.986
lateral a' (cm/s)	9.87 ± 1.82	11.44 ± 10.07	0.893
A wave duration (ms)	130.43 ± 18.26	138.58 ± 15.24	0.050
s (cm/s)	12.77 ± 2.48	11.84 ± 2.12	0.063
PAP (mmHg)	21.87 ± 4.11	22.01 ± 4.68	0.543
ejection fraction (%)	67.89 ± 5.03	69.74 ± 4.20	0.111
LV mass index (g/m^2)	81.76 ± 10.97	79.23 ± 12.61	0.155
E deceleration time (ms)	167.00 ± 27.90	171.56 ± 21.59	0.265
isovolumetric relaxation time (ms)	86.13 ± 13.07	88.52 ± 10.23	0.125
Vp (cm/s)	75.40 ± 16.61	75.39 ± 10.77	0.850
PVS (cm/s)	59.30 ± 9.66	57.35 ± 11.09	0.368
PVD (cm/s)	49.98 ± 6.80	53.33 ± 12.22	0.262
LVDD index (mm/m^2)	26.24 ± 2.23	25.74 ± 2.57	0.396
LVDS index (mm/m^2)	16.22 ± 1.88	15.66 ± 1.67	0.175
IVS index (mm/m^2)	4.74 ± 0.48	4.71 ± 0.75	0.614
PW index (mm/m^2)	4.81 ± 0.48	4.85 ± 0.62	0.570
LA diameter index (mm/m^2)	18.15 ± 1.76	18.43 ± 1.96	0.368
LA area index (cm^2/m^2)	8.32 ± 1.41	8.83 ± 1.71	0.272
LA volume index (mL/m^2)	22.05 ± 5.76	22.88 ± 5.19	0.398
LV end diastolic volume index (mL/m^2)	36.59 ± 8.25	37.53 ± 7.90	0.748
LV end systolic volume index (mL/m^2)	11.65 ± 4.03	10.96 ± 2.65	0.654
E/A	1.50 ± 0.34	1.49 ± 0.28	0.480
e'/a'	1.88 ± 0.46	1.84 ± 0.57	0.657
E/e'	4.94 ± 1.00	4.93 ± 0.89	0.855
PVS/PVD	1.20 ± 0.19	1.10 ± 0.22	0.008
ECG			
heart rate (beat/minute)	75.80 ± 13.05	83.02 ± 12.31	0.007
QRS duration (msec)	84.10 ± 9.1	88.22 ± 9.52	0.032
PR interval (msec)	144.91 ± 18.18	141.20 ± 15.74	0.301
QT interval (msec)	349.50 ± 24.63	365.46 ± 36.07	0.027
QTc interval (msec)	390.13 ± 30.59	406.17 ± 31.31	0.021

A – peak mitral inflow late velocity; a' – peak late diastolic annular velocity; E – peak mitral inflow early velocity; e' – peak early diastolic annular velocity; HF – high frequency; IVS – interventricular septum; JME – juvenile myoclonic epilepsy; LA – left atrium; LF – low frequency; LV – left ventricle; LVDD – left ventricular diastolic diameter; LVSD – left ventricular end-systolic diameter; NN – normal-to-normal; PAP – pulmonary arterial systolic pressure; pNN50 – the division of the number of interval differences of successive NN intervals of more than 50 ms by the total number of NN intervals; PVD – diastolic pulmonary vein wave velocity; PVS – systolic pulmonary vein wave velocity; PW – posterior wall; s – peak systolic annular velocity; RMSSD – root mean square successive difference; SD – standard deviation; SDNN – SD of the NN interval; SPOWER – power spectrum density total power; VLF – very low frequency; Vp – propagation velocity of mitral inflow

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tients with or without predisposing functional or structural cardiac abnormalities. However, malignant cardiac arrhythmias have rarely been seen during recorded SUDEP cases [20]. Increased sympathetic cardiac stimulation may lead to cardiac arrhythmias but also repetitive stimulation may cause structural damage in the heart, which means that there is a high predisposition to arrhythmia and ischaemia. It was found previously that patients with SUDEP had myocardial fibrosis [21]. Myocardial fibrosis may lead to left ventricular systolic and diastolic dysfunction. Troponin does not rise in the post-ictal period in patients with non-complicated seizures, while ischaemia findings on ECG and elevated cardiac enzymes suggest that epileptic patients may have secondary cardiac damage [22,23]. Alehan et al. showed that brain natriuretic peptide (BMP) and creatine kinase-muscle/brain (CK-MB) were elevated in postictal period in patients with seizures and they obtained the evidence proving that epileptic patients may had mild cardiac dysfunction which was difficult to detect [24]. Elevated sympathetic activity may lead to left ventricular dilatation which may result in Takotsubo and stress-induced cardiomyopathy reported in GTCS. This may affect the cardiac output and lead to insufficient peri-ictal oxygen supply [25,26]. Two studies reporting that recurrent Takotsubo cardiomyopathy developed due to GTCS and convulsive status epilepticus were published [27,28]. The cited authors stated that this occurred due to the sympathetic fluctuations. Bilgi et al. reported that patients with GTCS had not only systolic and diastolic dysfunction but had also impaired end-systolic left ventricular diameter and volume [5]. In a recently published study, increased left atrial diameter was reported in patients with GTCS compared to the control group. The authors argued that this might be caused by the increased left ventricular end-systolic pressure due to the sympathetic activity [29]. Pulmonary vein Doppler method contains load-dependent parameters and thus can be used for the estimation of left ventricular filling pressures [30]. Kuecherer et al. thought that increased left atrial pressure was negatively correlated with PVS and PVS2/PVD ratio in patients with pseudo normal or restrictive pattern [31]. In our study, we did not find a negative change in PVS/PVD either, similar to other echocardiographic parameters.

Cardiac ion channels are subdivided as depolarizing and repolarizing ones. Prolonged repolarization can cause triggered activity, while rapid repolarization may lead to reentrant excitation. Eric et al. reported decreased heart rate from 80 to 67 and increased QRS intervals in Lamotrigine users [32]. In our study, we could have detected decreased heart rate in the patient group because 10 of our patients were using LTG but decreased QRS intervals could be due to other AEDs effects. In the line of our study, Ramadan et al. reported shortening of QT and QTc intervals in newly diagnosed GTCS patients without medication [29]. There are, however, conflicting data on whether QTc intervals in epileptic patients differ from controls [33,34]. A potential confounder in these studies could be, at least partly, the use of different AEDs.

Further studies are needed using a larger sample size and in patients with newly diagnosed and/or drug-resistant JME.

Conclusion

Epilepsy patients may be predisposed to autonomic dysfunctions which may be associated with cardiac arrhythmias due to the effects of recurrent seizures on the cardiac microstructure. There are several studies demonstrating the effect of epilepsy on cardiac and autonomic functions. However, studies on JME patients, which represents a specific patient group, are very limited. Our study did not show any finding within echocardiographic and HRV parameters suggesting cardiac involvement or autonomic dysfunction in patients with JME who were undergoing treatment.

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