Epilepsy & Behavior 90 (2019) 11–14

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Analysis of tissue Doppler parameters and 24-hour heart rate variations in children with newly diagnosed untreated idiopathic epilepsy in interictal period

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ARTICLE INFO

Article history:
Received 6 October 2018
Revised 26 October 2018
Accepted 28 October 2018
Available online 23 November 2018

Keywords:
Epilepsy
Pediatrics
Heart rate
Autonomic
Tissue Doppler

ABSTRACT

Introduction: Cardiac mortality has increased in patients with epilepsy. Although majority of cardiac autonomic and ventricular function abnormalities were detected in ictal and postictal period, interictal epileptogenic activity may induce the autonomic imbalance as well. In our study, we aimed to investigate the interictal, subclinical cardiac changes in terms of cardiac autonomic balance via 24-hour Holter electrocardiography (ECG) and ventricular functions by tissue Doppler echocardiography (TDI) in children with newly diagnosed untreated idiopathic epilepsy.

Material and methods: Thirty children with newly diagnosed untreated idiopathic epilepsy (12 males, 18 females; mean age: 125.13 ± 35.2 months) (patient group) and 40 healthy, age and body mass index (BMI)-matched children (18 males, 22 females; mean age: 129.43 ± 38.5 months) (control group) were enrolled. Included patients underwent 24-hour Holter electrocardiographic and tissue Doppler echocardiographic study.

Results: Time domain measures were found significantly lower in the patient group. Mean high frequency (HF) values were significantly lower, and mean low frequency (LF) and mean LF/HF parameters were significantly higher in the patient group. Mean isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT), and myocardial performance index (MPI) values were significantly higher, and mean ejection time (ET) values were significantly lower among the patients with untreated idiopathic epilepsy.

Conclusion: We found that patients with untreated newly diagnosed epilepsy have a significant subclinical deterioration of left ventricular functions, and they also showed changes in heart rate variability (HRV) regarding the sympathovagal imbalance in interictal period. These findings can be related with increased cardiac mortality.

1. Introduction

Epilepsy and seizure may have many effects on cardiac functions that increase cardiac mortality [1]. Mechanisms may involve epilepsy-related alternations of sympathetic–parasympathetic balance in the autonomic nervous system (ANS) and impaired ventricular functions [2–4]. Majority of cardiac autonomic and ventricular function abnormalities were detected in ictal and postictal period [5]. Abnormal interictal regional cortical blood flow in some areas, which can be responsible for autonomic modulation, has been shown by functional brain imaging studies in drug-naive patients with epilepsy [6]. Interictal epileptogenic activity may also induce the autonomic imbalance [7,8].

One of the best and noninvasive method that evaluates the sympathetic–parasympathetic balance in the ANS is the heart rate variability (HRV) measurements. Lower HRV values indicate insufficient adaptability of ANS [9,10]. Decrease in HRV is an indicator of increased cardiac mortality [11,12].

Tissue Doppler Imaging (TDI) is a preload independent technique that is currently used to evaluate ventricular functions at a preclinical stage [13]. Myocardial performance index (MPI-TEI index) is a tissue Doppler-derived time interval index, which shows both systolic and diastolic cardiac performance [14]. Right and left ventricular MPI assessed by TDI correlates with right and left ventricular ejection fraction as determined by magnetic resonance imaging (MRI) [15,16]. Current studies have shown that parameters evaluated by TDI provide diagnostic and prognostic information incremental to conventional echocardiography [17–19].

The effects of epileptic seizures and antiepileptic drugs have been investigated in adult and pediatric patients in the previous studies [2–4, 20]. But, there are no studies that investigated interictal alternations of both cardiac autonomic and ventricular functions in children with newly diagnosed untreated idiopathic epilepsy syndrome.

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https://doi.org/10.1016/j.yebeh.2018.10.039
1525-5050/

2. Objectives

In our study, we aimed to investigate the interictal subclinical cardiac changes in terms of cardiac autonomic balance via 24-hour Holter electrocardiography (ECG) and ventricular functions by TDI in children with newly diagnosed untreated idiopathic epilepsy syndromes.

3. Methods

3.1. Study population

The local ethical committee of our hospital approved this prospective study on 26.10.2017 with 2017/0315 report number. Informed consents of parents and subjects were obtained. Seventy patients who attended to outpatient clinic of pediatric cardiology and pediatric neurology between November 2017 and January 2018 were included. Thirty patients with newly diagnosed untreated idiopathic epilepsy (patient group) and 40 healthy, age and body mass index (BMI)-matched children (control group) were enrolled. Patients' medical history was taken, and neurological examinations were done by the same pediatric neurologist. The same blinded pediatric cardiologist performed the cardiac measurements of the patients after the diagnosis of epilepsy, before starting antiepileptic agent.

Exclusion criteria were the following: signs or symptoms of other diseases that are known to effect ANS and cardiac functions including smoking, arterial hypertension, diabetes, renal or cardiac failure, congenital or acquired heart disease, rhythm disorders, obesity, significant blood chemistry abnormalities, metabolic disorders, any medication usage, and poor echocardiographic images. Patients with symptomatic epilepsy and that had been receiving antiepileptic drug were excluded from the study.

Epilepsy was defined as two unprovoked seizures more than 24 h apart. Idiopathic epilepsy was diagnosed with electroencephalography (EEG), cranial MRI, and clinical findings. The type of epilepsy, the type of epileptic syndrome, and EEG findings were recorded. The type of epilepsy was classified according to the International League Against Epilepsy (ILAE) 2017 classification [21]. The type of epileptic syndromes was classified according to the ILAE 1989 criteria [22].

3.2. Echocardiography

All of the patients were examined during an at least 24-hour seizure-free period, and none of the patients reported seizure during the recording period. Samsung H60 Echocardiography Systems (Samsung Healthcare) S 5-1 probe was used for echocardiography. Echocardiography settings were as follows: gain and filter minimal, compress and reject maximum, velocity range −30 and +30 cm/min, and sampling volume width 5 mm. End expiration apnea period was used so that measurements were not affected by respiration.

Both the patient and control groups were assessed with echocardiography so as to determine tissue Doppler imaging. Pulse wave sampling volume was placed on the corner of the left ventricle, which is next to the mitral lateral leaflet in apical four-chamber view, in order to obtain left ventricle TDI. Doppler trace obtained by this method was used to record isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT), and ejection time (ET) by tissue Doppler imaging. Ejection time, IRT, and ICT were used to calculate MPI-TEI index (MPI = ICT + IRT / ET). Mitral inflow velocity (E) is derived from pulsed-wave (PW) Doppler from the apical 4-chamber view by using color flow imaging. A 1–3-mm sample volume is placed between the mitral leaflet tips during diastole. From the apical 4-chamber view, mitral annular PW tissue Doppler imaging is also performed to obtain mitral tissue Doppler inflow (E′) velocity. The E/E′ ratio was calculated to estimate left atrial filling pressure. All of the echocardiographic measurements were performed during the three heart cycles, and mean values were recorded. All data of the patient group and control group were recorded, and comparisons between the groups were performed.

3.3. Holter ECG recordings

A standard ambulatory ECG recording system (Cardioline Click Holter HRV Package System, version 1.4.1 Biomedical Systems, Italy) was used. All of the patients were examined during an at least 24-hour seizure-free period, and none of the patients reported seizure during the recording period and encouraged to perform their normal daily activities. Artifacts and ectopic complexes were excluded. Heart rate variability parameters used for the time domain analysis were the mean and the highest and lowest heart rates. Time domain analysis included the following: standard deviation (SD) of all normal RR intervals (SDNN, ms), SD of the average normal sinus intervals between successive heartbeats (RR intervals) for all 5 min segment of entire recording (SDANN, ms), the root mean squares successive differences RR intervals (RMSSD, ms), the average of the RR intervals (TINN, ms), the proportion of the adjacent RR intervals that differ by more than 50 ms in the 24-hour recording (PNN50, measured in percentage), and the mean of all of the five-minute SDs of the normal RR intervals during the 24-hour period (SDNN index, ms). Frequency domain measures of HRV included the following: high frequency (HF) power values (ms^2); low frequency power (LF) values (ms^2), and the ratio between LF and HF. For these analyses, the following LF and HF values were recorded: LF {0.050–0.150 Hz[Ln(ms^2)]}, HF {0.150–0.350 Hz[Ln(ms^2)]}. High frequency reflects the parasympathetic activity, LF reflects mixed sympathetic and parasympathetic activities, and LF/HF reflects the sympathetic and parasympathetic balance (sympathovagal balance) [23,24].

3.4. Statistical analysis

Statistical data were evaluated using the statistical package for social sciences (SPSS) for Windows software package (Version 15.0, SPSS Inc. Chicago, IL, USA). Descriptive statistical methods (mean ± standard deviation) were used for the assessment of data. We used Student's t-test for the comparison of dual groups, chi-square test for the comparison of qualitative data, and Pearson correlation test for the determination of the relationship between the variables. p values less than 0.05 were considered as statistically significant.

4. Results

Thirty newly diagnosed untreated idiopathic epilepsy (12 males, 18 females; mean age: 125.13 ± 35.2 months; range: 72 to 192 months) (study group) and 40 healthy, age and BMI-matched children (18 males, 22 females; mean age: 129.43 ± 38.5 months; range: 60 to 202 months) (control group) were included. The demographic characteristics of the study and control group are shown in Table 1. There were no differences in age, gender, or BMI between two groups ($p > 0.05$). The BMI for all the patients were in normal limits. According to the ILAE 2017 classification, 21 patients were diagnosed with focal

Table 1
The demographic characteristics of the patient and control groups.

	Patients	Control	p
Number	30	40	
Age (month)	125.1 ± 35.2	129.43 ± 38.5	0.31
BMI[a] (kg/m^2)[b]	17.050 ± 2.56	17.151 ± 3.44	0.44
Heart rate (/s[c])	83.63 ± 7.039	80.05 ± 18.5	0.53
Sex (male/female)	12/18	18/22	0.6

Values are presented as mean ± standard deviation.
The mean difference is significant at the 0.05 level.
[a] Body mass index.
[b] Kilogram/meter square.
[c] Second.

Table 2
Comparisons of time domain analysis measurements of control and patient groups.

	Patients	Control	p*
SDNN[a] (ms)[b]	91 ± 24.8	143.9 ± 44	<0.001
SDANN[c] (ms)[b]	81.7 ± 11.1	128.9 ± 37.3	<0.001
RMSSD[d] (ms)[b]	34.5 ± 9.6	70.2 ± 34.3	<0.001
PNN50[e] (ms)[b]	9.4 ± 2.9	21.1 ± 12.5	<0.001
SDNN index[f] (ms)[b]	46.1 ± 7.8	65.8 ± 8.4	<0.001

Values are presented as mean ± standard deviation.
* The mean difference is significant at the 0.05 level.
[a] The standard deviation of all the normal RR intervals.
[b] Millisecond.
[c] The standard deviation of the means of all the five-minute segment normal RR intervals.
[d] The square root of the mean of the sum of the squares of differences between adjacent RR intervals.
[e] The proportion of adjacent RR intervals that differ by more than 50 ms in the 24-hour recording.
[f] The mean of all the five-minute standard deviations of normal RR intervals during the 24-hour period.

onset seizures whereas 9 patients were diagnosed with generalized onset seizures. The type of epileptic syndromes was grouped as 15 patients with benign childhood epilepsy with centrotemporal spikes (BECTS), 5 with early onset childhood occipital epilepsy (Panayiotopoulos syndrome), 3 with juvenile myoclonic epilepsy (JME), 1 with juvenile absence epilepsy (JAE), and 6 were unclassified. According to interictal sleep EEG findings, focal epileptic activity was detected in 20 patients, generalized epileptic activity was detected in 9 patients, and normal EEG was detected in one patient. Cranial MRI was normal in all the patients. The mean time interval from their first seizure to enrollment in the study was 11.6 ± 1.379 months.

When compared with control group, time domain measures in the values of SDNN total, SDNN index, SDANN, RMSSD, and PNN50 were found significantly lower in the patient group ($p < 0.001$). Comparisons of time domain measurements are shown in Table 2.

Mean HF parameters were significantly lower in the patient group when compared with the control group ($p < 0.001$). Mean LF parameters were significantly higher in the patient group ($p = 0.001$). Mean LF/HF ratio was found significantly higher in the patient group ($p < 0.001$). Comparisons of frequency domain analysis measurements are shown in Table 3.

When compared with the control group, ICT (ms) and IRT (ms) values of the patient group were found significantly higher ($p < 0.001$). The mean ET (ms) values of patient group were significantly lower when compared with the control group ($p < 0.001$). The mean MPI values and mitral E/E′ values were significantly higher in the patient group ($p < 0.005$). Tissue Doppler parameters of study and control groups are shown in Table 4.

In the patient group, no significant correlations were found between the mean time domain parameters in the values of SDNN total, SDNN index, SDANN, RMSSD, and PNN50 (r: −0.203, −0.20, −0.207, −0.19, −0.079, $p > 0.05$, respectively), frequency domain measures in the values of LF, HF, and LF/HF (r: 0.16, −0.12, 0.109, $p > 0.05$ respectively), and tissue Doppler parameters in the values of E/E′, ICT, IRT, ET, and MPI (r: 0.201, 0.13, 0.19, −0.09, 0.2, $p > 0.05$, respectively) from the first seizure to enrollment in the study.

Table 3
Comparisons of frequency domain analysis measurements of control and patient groups.

	Patients	Control	p*
HF[a] (ms)[b]	30.5 ± 5.94	47.11 ± 14.9	<0.001
LF[c] (ms)[b]	46.7 ± 15.5	31.5 ± 8.7	0.001
LF/HF[d]	1.61 ± 0.65	0.77 ± 0.51	<0.001

Values are presented as mean ± standard deviation.
The mean difference is significant at the 0.05 level.
[a] High frequency.
[b] Millisecond.
[c] Low frequency.
[d] Low frequency/High frequency.

Table 4
Tissue Doppler parameters of the patient and control groups.

	Patients	Control	p*
E/E′[a]	0.5 ± 0.2	0.4 ± 0.1	<0.005
ICT[b] (ms)[c]	63. 27 ± 12.06	35.5 ± 6.3	<0.001
IRT[d] (ms)[c]	63. 37 ± 18.6	34.7 ± 6.2	<0.001
ET[e] (ms)[c]	197 ± 21.7	219.3 ± 22.7	<0.001
MPI[f]	0.7 ± 1.1	0.3 ± 0.8	0.001

Values are presented as mean ± standard deviation.
* The mean difference is significant at the 0.05 level.
[a] Early peak velocity of mitral valve to e′: tissue Doppler early peak velocity of mitral valve ratio.
[b] Isovolumetric contraction time.
[c] Millisecond.
[d] Isovolumetric relaxation time.
[e] Ejection time.
[f] Myocardial performance index.

5. Discussion

The majority of cardiac autonomic and ventricular function abnormalities have been detected in ictal and postictal periods [5]. Abnormal interictal regional cortical blood flow and interictal epileptogenic activity can also induce autonomic imbalance and ventricular dysfunction as well [6–8]. One of the best and noninvasive method that evaluates the sympathetic–parasympathetic balance in the ANS is the HRV measurements, and subclinical cardiac dysfunction at a preclinical stage can be detected by MPI [9–13].

El-Rashidy et al. have reported a significant reduction in the mean values of all time domain measures of HRV and frequency domain measures in terms of HF and increase in the mean values of LF and LF/HF ratios in the children with epilepsy. Parameters were similar both in patients not taking antiepileptic drug and patients taking antiepileptic drugs, but they were unable to find any statistically significant difference between the groups because dividing their patients into subgroup made the sample size too small [2].

El-Sayed et al. have evaluated 25 children with idiopathic epilepsy who were using antiepileptic drug for at least 6 months. They have showed that all frequency domain measurements were reduced in the epilepsy group as a result of autonomic dysfunction [3]. Similar results were shown by Lotufo et al. and Ferri et al. regarding higher sympathetic and lower parasympathetic regulation in the patients with chronic epilepsy [25,26].

In the study of Hallioğlu et al., they have compared children with epilepsy without treatment (n: 14) with children receiving treatment (n: 78). In this study, only 6 of the untreated ones have idiopathic epilepsy, and the sample size was too small to make a statement about autonomic balance in untreated children [20]. Evrengül et al. have reported an increase in sympathetic activity in untreated adults with generalized epilepsy [4].

In our study, similar with the previous studies, all of the time domain parameters including SDNN, SDNNday, SDANNindex, mean intervals between normal R-peaks (NN) and HF parameters were significantly lower in the patient group. These results reflect a reduced parasympathetic nervous system activity. Low frequency parameters, reflecting mostly sympathetic activity, were higher in the patient group. The LF/HF ratio was significantly higher in the patient group regarding sympathovagal imbalance. Since most of these studies were carried out in patients who are using antiepileptic drugs, we thought that it is difficult to make a conclusion about whether the epilepsy itself or the antiepileptic drugs affected the autonomic function in the interictal period. Similarly, structural brain lesions could affect the ANS function, so including patients with epilepsy with symptomatic or cryptogenic etiology might alter the results. Therefore, we conducted our study with patients

with newly diagnosed untreated idiopathic epilepsy in order to evaluate the subclinical autonomic nervous alternations in the interictal period.

Myocardial performance index is a preload independent Doppler-derived time interval index that shows both systolic and diastolic cardiac performance [13,14]. Right and left ventricular MPI assessed by TDI correlates with right and left ventricular ejection fraction as determined by MRI [15,16]. Compared with MRI, it is an easy and cheaper technique. It can be used to detect subclinical cardiac dysfunctions.

Similar with our study, Bilgi et al. have showed subclinical myocardial systolic and diastolic dysfunction of left ventricle in 30 adult patients with newly diagnosed epilepsy, and they have found high mitral E/E′ ratio regarding left ventricular diastolic dysfunction [27]. Our study differentiates from this study by including MPI values that reflect both systolic and diastolic ventricular functions.

Kibar et al. have investigated 52 children with epilepsy treated with antiepileptic drugs [28]. They have showed high E/E′ ratio and increased ICT and MPI values regarding subclinical left ventricle systolic and diastolic dysfunction in their study group. They have contributed these findings to antiepileptic drug therapy, but they haven't evaluated the TDI parameters before treatment, so in this study, we could not have any idea if the TDI values worsen after treatment or get better. But, different from Kibar's study, we evaluated patients before treatment, and we found high mean ICT, IRT, mitral E/E′, and MPI values and low ET values. High E/E′ ratios showed increased left atrial filling pressure; high MPI values showed impaired systolic and diastolic functions in our patients.

In our study, different from the previous pediatric studies, we compared the HRV and TDI measurements with the time interval from the first seizure to enrollment in the study. We did not find any correlation. Since our patients were patients with idiopathic epilepsy, the time interval from the first seizure to involvement in our study was short to show correlation.

6. Conclusion

We found that patients with untreated newly diagnosed epilepsy have a significant subclinical deterioration of left ventricular functions, and they also showed changes in HRV regarding the autonomic sympathovagal imbalance in interictal period. These findings can be related with increased cardiac mortality. We thought that these patients can be evaluated with these noninvasive techniques at diagnosis, after giving treatment, and in the follow-up period regularly. So, if necessary, we can provide additional care for these patients like more detailed cardiovascular system examinations.

Further studies with more patients and evaluating the same patients after giving antiepileptic treatment and long term follow-up are needed.

Grant support & financial disclosures

None.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the author and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

References

[1] Freeman R. Cardiovascular manifestations of autonomic epilepsy. Clin Auton Res 2006;16:12–7.
[2] El-Rashidy OF, Shatla HR, Youssef OI, Samir E. Cardiac autonomic balance in children with epilepsy: value of antiepileptic drugs. Pediatr Neurol 2015;52:419–23.
[3] El-Sayed HL, Kotby AA, Tomoum HY, El-Hadidi ES, El Behery SE, El-Ganzory AM. Non-invasive assessment of cardioregulatory autonomic functions in children with epilepsy. Acta Neurol Scand 2007;115:377–84.
[4] Evrengul H, Tanriverdi H, Dursunoglu D, Kaftan A, Kuru O, Unlu U, et al. Time and frequency domain analyses of heart rate variability in patients with epilepsy. Epilepsy Res 2005;63:131–9.
[5] Devinsky O, Joo EY, Tae WS, Hong SB. Effects of seizures on autonomic and cardiovascular function. Epilepsy Curr 2004;4:43–6.
[6] Cerebral blood flow abnormality in patients with idiopathic generalized epilepsy, J Neurol 2008;255:520–5.
[7] Lathers CM, Schraeder PL, Weiner FL. Synchronisation of cardiac autonomic neural discharge with epileptogenic activity: the lockstep phenomenon. Electroencephalogr Clin Neurophysiol 1987;67:247–59.
[8] Lathers CM, Schraeder PL. Autonomic dysfunction in epilepsy: characterization of autonomic cardinal neural discharge associated with pentylenetetrazol induced epileptogenic activity. Epilepsia 1982;23:633–47.
[9] Sharma P, Makharia GK, Ahuja V, Dwivedi SN, Deepak KK. Autonomic dysfunctions in patients with inflammatory bowel disease in clinical remission. Dig Dis Sci 2009;54:853–61.
[10] Furlan R, Guzzetti S, Crivellaro W, Dassi S, Tinelli M, Baselli G, et al. Continuous 24 hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. Circulation 1990;81:537–47.
[11] Kleiger RE, Miller JP, Bigger Jr JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256–62.
[12] Ansakorpi H, Korpelainen JT, Huikuri HV, Tolonen U, Myllyla W, Isojarvi JI. Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2002;72:26–30.
[13] Tei C, Nishimura RA, Seward JB, Tajik AJ. Noninvasive Doppler-derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr 1997;10:169–78.
[14] Waggoner AD, Bierig SM. Tissue Doppler imaging: a useful echocardiographic method for cardiac sonographer to assess systolic and diastolic ventricular function. J Am Soc Echocardiogr 2001;4:143–52.
[15] Pavlicek M, Wahl A, Rutz T, de Marchi SF, Hille R, Wustmann K, et al. Right ventricular systolic function assessment: rank of echocardiographic methods vs. cardiac magnetic resonance imaging. Eur J Echocardiogr 2011;12:871–80.
[16] Maceira AM, Prasad SK, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. Eur Heart J 2006;27:2879–88.
[17] Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, et al. Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. J Am Coll Cardiol 2003;41:820–6.
[18] Yamamoto T, Oki T, Yamada H, Tanaka H, Ishimoto T, Wakatsuki T, et al. Prognostic value of atrial systolic mitral annular motion velocity in patients with left ventricular dysfunction. J Am Soc Echocardiogr 2003;16:333–9.
[19] Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, et al. Tissue Doppler imaging provides incremental prognostic value in patients with systemic hypertension and left ventricular hypertrophy. J Hypertens 2005;23:183–91.
[20] Hallioglu O, Okuyaz C, Mert E, Makharoblidze K. Effects of antiepileptic drug therapy on heart rate variability in children with epilepsy. Epilepsy Res 2008;79:49–54.
[21] ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology, Epilepsia 2017;58:512–21.
[22] Proposal for revised classification of epilepsies and epileptic syndromes Commission on Classification and Terminology of the International League Against Epilepsy, Epilepsia 1989;30:389–99.
[23] Massin M, von Bernuth G. Clinical and haemodynamic correlates of heart rate variability in children with congenital heart disease. Eur J Pediatr 1998;157:967–71.
[24] Ori Z, Monir G, Weiss J, Sayhouni X, Singer DH. Heart rate variability. Frequency domain analysis. Cardiol Clin 1992;10:499–537.
[25] Lotufo PA, Valiengo L, Benseñor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia 2012;53:272–82.
[26] Ferri R, Curzi-Dascalova L, Arzimanoglou A, Bourgeois M, Beaud C, Nunes ML, et al. Heart rate variability during sleep in children with partial epilepsy. J Sleep Res 2002;11:153–60.
[27] Bilgi M, Yerdelen D, Çölkesen Y, Müderrisoğlu H. Evaluation of left ventricular function by tissue Doppler imaging in patients with newly diagnosed and untreated primary generalized epilepsy. Seizure 2013;22:537–41.
[28] Kibar EA, Unver O, Oflaz MB, Güven AS, Balli S, Ece I, et al. Effect of antiepilepsy drug therapy on ventricular function in children with epilepsy: a tissue Doppler imaging study. Pediatr Cardiol 2014;35:280–8.