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Left ventricular myocardial deformation abnormalities in seizure-free children with epilepsy

Serkan Fazlı Çelik[a,*], Emre Baratalı[b], Ahmet Sami Güven[c], Yasemin Altuner Torun[b]

[a] Department of Pediatrics, Division of Pediatric Cardiology, Adnan Menderes University Medicine Faculty, Aydın, Turkey
[b] Department of Pediatrics, Kayseri Health Sciences University Hospital, Kayseri, Turkey
[c] Department of Pediatrics, Division of Pediatric Neurology, Necmettin Erbakan University, Meram Medicine School, Konya, Turkey

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ABSTRACT

Purpose: Although there is a higher risk of structural cardiac disease in people with epilepsy, there is no detailed advanced analysis of cardiac functions in patients with epilepsy. This study aimed to determine early echocardiographic findings of Left Ventricular (LV) dysfunction using cardiac strain technique in seizure-free children with epilepsy.

Method: The study investigated 60 children with epilepsy who had no seizures in the preceding 6 months, without any known cardiovascular disease and treated with one antiepileptic drug and 60 healthy subjects who underwent clinical evaluation including electrocardiography (ECG), standard echocardiography, tissue Doppler imaging (TDI) and two-dimensional Speckle Tracking Echocardiography (2DSTE).

Results: Despite the normal M-mode values, global longitudinal strain of the epilepsy of the control group was as follows: −16.86 ± 3.71, -18.95 ± 3.75, respectively (p = 0.001); global strain rates were determined as follows: -0.99 ± 0.23, -1.14 ± 0.31, respectively (p = 0003). The patients also had increased A-wave velocity, and decreased E/A ratio (p < 0.01). TDI results showed diastolic dysfunction as mirrored by significantly increased isovolemic relaxation time (IVRT), Early mitral inflow (E)/ Early diastolic velocity (E'), and Tei index (p < 0.01). There was no significant difference in LV torsion, Peak LV twist, and ECG parameters between the patients and the controls.

Conclusions: In seizure-free patients, cardiac systolic and diastolic functions were impaired when compared to healthy children. There was no difference in the patient group to explain the decline in cardiac functions and there may be unknown different factors besides the known risk factors.

1. Introduction

The most common chronic, recurrent neurological disease of childhood is epilepsy [1]. The association of epilepsy with Cardiovascular Disease (CVD) is widespread. Identified risk factors such as various arrhythmias, genetic risk factors like ion channel mutations, Antiepileptic Drugs (AEDs), structural cardiac conditions can explain the coexistence of epilepsy and CVD [2]. Also, among living epilepsy patients, transient left ventricular (LV) dysfunction was the most common postictal cardiac abnormality [3].

Left ventricular Ejection Fraction (EF) used with standard echocardiography is insufficient to identify the longitudinal function and to evaluate the endocardial layers which are affected firstly [3]. Moreover, EF measurement is highly dependent on operator experience and loading situations [4]. Two-Dimensional Speckle Tracking Echocardiography (2DSTE) is a newer echocardiographic technique which is useful in assessing the early changes in regional and global myocardial function in children [4]. In contrast to Tissue Doppler Imaging (TDI), STE is not angle-dependent and STE results correlate with Magnetic Resonance Imaging (MRI) results. [5]. Furthermore, STE has been related to the quantity of cardiac fibrosis [6,7].

Our aim in this study is to assess the ability of the subtle differences in LV strain models to characterize subclinical LV dysfunction in children with epilepsy.

2. Materials and methods

2.1. Study sample

The Study Group included 60 consecutive children with epilepsy

* Corresponding author.
E-mail address: docser2003@yahoo.com (S.F. Çelik).

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aged < 18 years who were selected at the pediatric neurology clinic of University Hospital. The epileptic syndromes were classified in accordance with International League Against Epilepsy (ILAE) 2001 criteria [8]. Patients who had previous status epilepticus, a central nervous system disease, neonatal convulsion, infections, tumors, degenerative diseases, neuro-metabolic syndromes, received polytherapy AEDs, obesity, diabetes mellitus, known coronary artery disease, EF < 60%, significant valvular insufficiency, hypertension or hypotension, dysrhythmia and acquired cardiac disease were excluded from the study. Healthy children were recruited from the local population. They were referred to our hospital because of a cardiac murmur without obvious cause. All participants in the control group were examined by the same pediatric cardiologist; and the participants who had normal ECG and normal standard echocardiography findings were included in the study.

Height-weight, ECG, Body Mass Index (BMI), routine blood biochemical values, whole blood count and blood pressures of the patients were recorded. Blood Pressures (BP) were measured three times with intervals of 1–2 minutes on the right arm, resting and seated using oscillometric Omron devices. Casual BP z-score was calculated based on the 95th percentile for age, sex, and height [9]. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Ethical Approval Number: 2017/51). The detailed consent forms were signed by the parents of all subjects before participating in the study.

2.2. Electrocardiography

Each participant was subjected to ECG investigation. Specifications of the ECG machine were: 12 standard leads, the sensitivity was 10 mm/mV, and the recording speed was 25 mm/s. The ECG records of the patients who were in sinus rhythm were obtained. Then the ECG record strips were scanned, and the scanned picture was magnified by PC Windows photo viewer. From each ECG record strips, the following data were obtained: Heart rate (beats/min); RR interval (s); PR interval (s); QRS wave duration (s); QT corrected (QTc) interval (s); S wave amplitude (mV); and summation of S (v1) and R (v5). QTc interval (s): It was calculated using the Bazett's formula.

2.3. Standard 2-Dimensional and doppler echocardiography

The patient and control group received standard transthoracic echocardiography (Vivid E7, GE Healthcare, Norway) in standard positions [10]. The results were recorded (EchoPAC software products 12.1; GE Vingmed Ultrasound AS) and digital images were analyzed offline by an author who was blinded to the medical diagnosis, BP, and medical therapy. The modified Simpson method was used to measure the LV volumes and the LVEF. The Left Ventricular Mass Index (LVMI) was calculated by dividing the LVM(g) by the height in meters. The Left Ventricular Hypertrophy (LVH) was diagnosed based on LVMI $\geq 95^{th}$ percentile according to the age- and gender-appropriate reference LVM indices [11]. The Tricuspid Annular Plane Systolic Excursion (TAPSE) and the Mitral Annular Plane Systolic Excursion (MAPSE) were also measured [12]. Late diastolic flow (A-wave), Early diastolic flow (E-wave) velocities, the deceleration time of the E-wave and the E:A ratio were measured as previously reported [13].

2.4. Tissue doppler imaging

Pulsed-wave Doppler was used to evaluate the LV filling patterns on the apical four-chamber view and between the tips of the mitral valve leaflets during diastole. The late diastolic (A'-wave) and early diastolic (E'-wave) velocities were measured at the lateral parts of the mitral annuli on the apical four-chamber views. Tei index was used for the LV systolic and diastolic performance, which was proposed before [14].

2.5. 2D speckle tracking, twist and torsion analysis

Gray images were obtained from apical four-chamber (A4C), three-chamber (A3C), two-chamber (A2C) and parasternal short-axis (level of the papillary muscle) views [15]. All the images which were obtained at the left lateral decubitus position and under ECG monitoring were stored for offline analysis. The endo-myocardial borders of the LV were marked manually at the end of systole. Epicardial marking was performed by the computer automatically. Longitudinal, transverse, and radial strain and strain rates were evaluated from 6 basal and 6 mid-ventricular segments of the LV including apical, mid, basal segments at the four-chamber, two-chamber and three-chamber view of the LV; and anterior, septal and inferior segments at the short-axis view of the LV. Peak basal and apical rotation, peak LV twist, and peak LV torsion were automatically calculated.

2.6. Statistical analysis

The Kolmogorov-Smirnov test was applied to check the distribution of parameters. Parameters with normal distribution were expressed as mean ± SD, and parameters which had abnormal distribution were expressed as median (25^{th} percentile-75^{th} percentile). The histogram, q-q graphs and Shapiro-Wilk normality test were used to examine whether the data showed normal distribution. Kruskal Wallis test was used for the quantitative variables and Mann-Whitney U tests were used for the comparison between the two groups in nonparametric variables. Pearson's linear correlation coefficient analysis was used to assess the relation between the strain for LV and AEDs and the duration of AEDs treatment. Statistical evaluation was performed using the IBM SPSS Statistics 22.0 package program. Values of $p < 0.05$ were considered statistically significant in all statistical analyses.

3. Results

3.1. Study population

Study population included 60 patients with a diagnosis of epilepsy (33 male, 27 female ; mean age 11.3 ± 3.1 years) and 60 healthy control subjects (34 male, 26 female ; mean age 12.1 ± 2.9 years). Among the initial sample of 78 patients, 6 patients had technically inadequate STE records, 8 patients had uncontrolled epilepsy and 4 patients had significant valvular insufficiency (Fig.1). There was no difference in age or sex between the groups. The BMI for two groups were within normal limits. The mean systolic and diastolic blood pressures were within the normal range (84–110 mmHg) (Table 1).

Ten (16.6%) of the epilepsy patients had no pathologic EEG

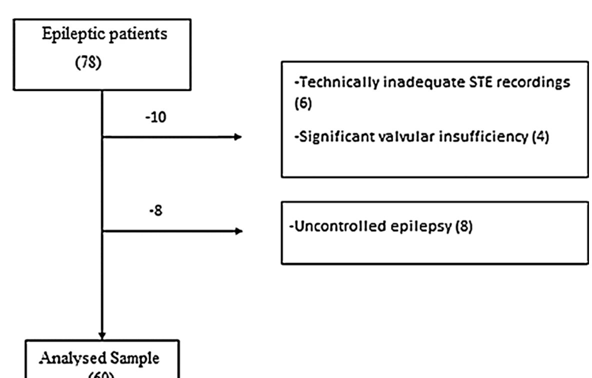

Fig. 1. Patient selection flow chart. The ultimate study population consisted of selected patients who did not require combination therapy, who had no epileptic seizures for at least 6 months; and who had no significant valvular insufficiency or EF lower than 60%.