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ORIGINAL ARTICLE

# Effect of Antiepilepsy Drug Therapy on Ventricular Function in Children With Epilepsy: A Tissue Doppler Imaging Study

**Ayse Esin Kibar · Olcay Unver · Mehmet Burhan Oflaz · Ahmet Sami Güven · Sevket Balli · İbrahim Ece · Sevcan Erdem · Fusun Dilara İçağasıoğlu**

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**Abstract** Impaired cardiac myocardial function may contribute to the risk for sudden unexpected death of a patient with epilepsy. This study aimed to investigate the effect of antiepilepsy drugs (AEDs) on cardiac function in pediatric epileptic patients using standard and tissue Doppler imaging (TDI) echocardiography. This hospital-based, prospective cross-sectional study investigated 52 epileptic children (mean age 9.3 ± 3.1 years) treated with AEDs (duration 2.4–10.0 years) and 36 healthy children (mean age 9.5 ± 4.0 years). In the epilepsy group, standard echocardiography showed increased left ventricular (LV) end-diastolic and end-systolic diameters, an increased LV mass index, and preserved ejection fraction. The patients also exhibited increased mitral peak A-wave velocity and mitral E-wave deceleration time as well as a decreased mitral E/A ratio. The E/Em ratio was significantly higher in the epilepsy group (5.6 ± 1.2) than in the control group (5.2 ± 1.1) ($p = 0.016$). In the epilepsy group, TDI showed an increased isovolumetric relaxation time and myocardial performance index (MPI). It also exhibited decreased early diastolic velocity (Em) and a decreased mitral annular displacement index in these patients. There were positive correlations between the LV lateral wall MPI ($r = 0.231$), septal MPI ($r = 0.223$), and LV mass index ($p < 0.05$) but no correlation with the duration of AED treatment. The authors detected subclinical ventricular dysfunction associated with AEDs at a preclinical stage. They suggest that TDI can be useful for determining the short- and long-term cardiac effects of AEDs.

**Keywords** Antiepilepsy drugs · Echocardiography · Epilepsy · Tissue Doppler imaging · Ventricular dysfunction

**Abbreviations**

| | |
|---|---|
| VPA | Valproic acid |
| CBZ | Carbamazepine |
| TPM | Topiramate |
| LTG | Lamotrigine |
| LEV | Levetiracetam |
| TDI | Tissue Doppler imaging |
| AED's | Antiepileptic drugs |

## Introduction

Antiepilepsy drugs (AEDs) produce different types and severity of adverse effects, which occur mainly during drug initiation and early treatment [2]. Clinically significant cardiovascular dysfunction rarely occurs in patients with

A. E. Kibar (✉) · S. Erdem
Department of Pediatric Cardiology, Mersin Women's and Children's Hospital, Güneykent, Mersin, Turkey
e-mail: dreseresin@yahoo.com

O. Unver
Department of Pediatric Neurology, Mersin Women's and Children's Hospital, Mersin, Turkey

M. B. Oflaz
Department of Pediatric Cardiology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey

A. S. Güven · F. D. İçağasıoğlu
Department of Neurology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey

S. Balli
Department of Pediatric Cardiology, Balikkesir Hospital, Balıkesir, Turkey

İ. Ece
Department of Pediatric Cardiology, Faculty of Medicine, Yüzüncü Yıl University, Van, Turkey

AEDs [1, 2, 7]. Studies in the literature investigating AEDs among epileptic patients report hypertension or hypotension, bradycardia, arrhythmia, atrioventricular block with syncope, circulatory collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, and thromboembolism, primarily during their initiation and early treatment [14, 16, 21, 23, 28]. Other well-known cardiovascular effects are PR and QT prolongations on the electrocardiogram, higher basal heart rate, tachycardia, sinus bradycardia, and congestive heart failure, which may contribute to the occurrence of sudden unexpected death in children with epilepsy [12, 16, 33]. These cardiac effects, which have been reported mostly in case reports of older patients receiving therapeutic doses for epilepsy, have been associated with carbamazepine (CBZ), valproic acid (VPA), and fenitoin [6, 14, 23]. The cardiac side effect profiles of the newer AEDs, such as lamotrigine (LTG) and levetiracetam (LEV), among others, indicate that they have better tolerability than the older traditional antiepilepsy drugs [31].

The best practices for monitoring the subclinical myocardial adverse effects of AEDs have not been carefully studied for children. Recently, tissue Doppler imaging (TDI) was reported to be appropriate for evaluating early changes in systolic and diastolic myocardial dysfunction [20, 26]. The results of TDI are less affected by age, cardiac rate, or preload than those of conventional echocardiography [22, 26]. These parameters are known to be associated with mortality and morbidity in individuals with cardiovascular disease. Thus, TDI is shown to be a useful tool for detecting subclinical dysfunction that is not typical in epileptic children.

This study aimed to determine the late-appearing adverse effects of AEDs on right and left ventricular myocardial function, as determined by standard echocardiography and TDI, in a group of children with epilepsy and no previously diagnosed cardiovascular disease. We evaluated whether AEDs cause subclinical ventricular dysfunction at therapeutic doses during the preclinical stage. To the best of our knowledge, this study is the first to evaluate the effects that therapeutic doses of AEDs have on biventricular regional myocardial functions using TDI in pediatric epileptic patients without prior cardiac disease.

## Materials and Methods

### Study Groups and the Patient Population

This prospective cross-sectional study included 52 children with epilepsy who were randomly selected at the pediatric neurology outpatient clinic of Sivas Cumhuriyet University Hospital and Mersin Women's and Children's Hospital between July 2012 and September 2012. The study participants were 88 children ages 4–16 years, including 52 children who had been treated for epilepsy without convulsions during the past year and 36 healthy children (control group).

The epilepsy diagnosis was based on electroencephalography (EEG), cranial imaging, and clinical findings. The epileptic syndromes were classified in accordance with International League Against Epilepsy (ILAE) 1989 criteria [19].

The 52 patients with epilepsy had been given various antiepileptic drugs (VPA, CBZ, LEV, LTG, and topiramate [TPM]). A detailed history was obtained, and a physical examination was conducted to exclude atherosclerosis and cardiovascular comorbidities. All the patients in the epilepsy group underwent standard blood analyses (complete blood count, biochemistry, thyroid function tests, serum AED level), blood pressure measurement, electrocardiography, and echocardiography. Arterial pressure was measured at least two times after the subjects had rested more than 10 min in supine position in a quiet room. Pediatric epileptic patients were examined for age-and gender-standardized systolic and diastolic blood pressure values against dose of the Turkish pediatric population of $<$90th percentile [29]. The control subjects were recruited from a group of healthy children who had an innocent murmur.

The Medical Ethics Committee of the hospital approved the protocol, and all the families of the patients gave informed consent.

### Exclusion Criteria

The study excluded children with a structural or functional cardiac abnormality, hypertension, sleep apnea, recurrent epileptic seizures, a systemic disease that had received medical treatment, clinically significant blood chemistry abnormalities, or any secondary causes of obesity. The participants who refused blood sampling or echocardiography measurement and those whose images were of poor quality also were excluded from the study.

### Echocardiographic Measurements

The left and right ventricular functions were investigated in a silent setting at the pediatric cardiology echocardiography outpatient clinic. All the subjects were examined in the left lateral position after 10 min of rest in the lateral decubitus position. Echocardiographic assessments were performed using the ViVid 7 dimension echocardiography device (GE Medical Systems, Carrollton, TX, USA), a 4-MHz probe (GE Vingmed Ultrasound AS, Horten, Norway), and simultaneous electrocardiography.

A complete echocardiographic study was performed using standard views and techniques. All Doppler echocardiographic and TDI recordings were obtained during normal respiration. The left and right ventricular functions were evaluated using standard pulsed-wave Doppler echocardiography and TDI in the obese and control groups. All measurements were performed based on American Echocardiography Society standards [17]. Imaging windows obtained from the parasternal long axis, and the apical four chambers were used.

All echocardiographic assessments were digitally recorded (DVD-CD) to enable later investigation. The analyses were performed using commercially available computer software programs (Echopac 2008; GE Vingmed). The mean values of three consecutive measurements were recorded.

### Standard Echocardiography

Using standard echocardiography, we measured the left ventricular end-diastolic diameter (LVEDD) and the left atrium and aortic diameters at the parasternal long axis in M-mode. The end-diastolic volumes, percentage of fractional shortening, and ejection fraction measurements were obtained by echocardiography. The left ventricular mass (LVM) was calculated using the predefined Devereux and Reishek formula [17]. To obtain the left ventricular mass index (LVMI, $g/m^2$), the LVM was divided by the body surface area.

To determine the tricuspid annular plane systolic excursion (TAPSE), the apical four-chamber view was used, and an M-mode cursor was placed through the lateral tricuspid annulus in real time. The brightness was adjusted offline to maximize the contrast between the M-mode signal arising from the tricuspid annulus and the background. In this study, TAPSE was measured as the total displacement of the tricuspid annulus (cm) from end-diastole to end-systole, with values of three to five beats representing the average TAPSE [15].

For measurement of mitral annular plane systolic excursion, M-mode echocardiography across the mitral annulus was acquired using the apical four-chamber view. The vector was adjusted to be as parallel to the walls as possible using the anatomic M-mode when necessary [32].

### Standard Doppler Echocardiography

Pulsed-wave (PW) Doppler analysis measurements were used to evaluate the left ventricular (LV) systolic and diastolic functions. Transmitral flow velocities were recorded by placing the PW Doppler sample volume (1–3 mm) at the tip of the mitral valve parallel to the blood flow on the apical four-chamber view during diastole. Similar measurements were made for tricuspid flow velocities.

The early diastolic velocity (mitral E-wave) and the late diastolic velocity (A-wave) were measured as previously reported [26]. We determined the aortic flow velocity using PW Doppler over the apical five-chamber axis. Pulmonary velocity was measured from the short axis.

Tricuspid regurgitation (TR) was detected by continuous-wave Doppler echocardiography. The maximum systolic pressure gradient between the right atrium and left ventricle was calculated from the maximum velocity of the TR flow using the Bernoulli equation ($P = 4\ V^2$). The systolic pulmonary artery pressure was calculated by adding the mean right atrial pressure to this pressure [11]. All pulmonary artery pressures were within normal limits.

### Myocardial Tissue Doppler Measurements

The PW tissue Doppler technique was performed using spectral PW Doppler signal filters, adjusting the Nyquist limit to 15–20 cm/s (close to myocardial velocities), and using the minimal optimal gain. High frame-rate images (>120 frames) were acquired in TDI mode. For apical four-chamber images, a 2- to 5-mm pulsed Doppler sample volume was placed at the septum, the LV lateral wall, and the RV free wall by placing the sample volume at the basal segment (tricuspid and lateral mitral annulus level) and the mid-segment (between the annular junction and the apex at the midpoint). The angle between the Doppler beams and the ventricular longitudinal movements was kept as low as possible.

For calculation of the myocardial performance index (MPI), we used TDI to measure the systolic myocardial velocity (SM), the ejection time (ET), and the isovolumetric contraction time (IVCT) as systolic parameters. The early (Em) and late (Am) diastolic velocities (Em/Am ratio) and the isovolumetric relaxation time (IVRT) were the diastolic parameters. The ratio between the mitral E-wave deceleration time and the Em (E/Em) was calculated as a preload independent index of LV filling pressures.

We also measured the IVRT from the end of the S-wave to the beginning of the E-wave and the IVCT from the beginning of the first positive deflection after the Q-wave to the onset of the S-wave. The ET was measured from the beginning to the end of the S-wave. The MPI (IVRT + IVCT/ET) was calculated to assess the left ventricular global (systolic + diastolic) function [26]. The resulting velocities were recorded for three cardiac cycles. The mean measurement values were used for statistical analysis.

The S-wave was obtained during ventricular systole using TDI, with the sample volume positioned at the lateral mitral annulus. The velocity-time integral (VTI) was

measured by marking the peak systolic S-wave obtained using TDI [22]. The displacement index (DI) was calculated by dividing the VTI of the tissue Doppler systolic S-wave (S-VTI) by the end-diastolic distance from the mitral annulus to the left ventricular apex ($L_o$). Longitudinal DI was calculated by S-VTI/$L_o$.

### Statistical Analysis

Statistical evaluation was performed using SPSS software version 12.5 (SPSS, Chicago, IL, USA). The Kolmogorov–Smirnov test was applied to check the distribution of parameters. Data were expressed as mean ± standard deviation (SD). Descriptive statistics are presented as mean ± SD. We used *t* tests for independent samples to compare the continuous variables between the epilepsy and control groups. Categorical variables, shown as frequencies, were compared using the $\chi^2$ test.

Mono- and polytherapy AED groups were analyzed with the Mann–Whitney *U* test. Pearson's linear correlation coefficient analysis was used to assess the relation between TDI-derived indexes for the left and right ventricles (MPI, Em-wave, Em/Am ratio, S-VTI, DI) and other clinical parameters (LVM, body mass index [BMI]). A *p* value lower than 0.05 was considered statistically significant.

## Results

### Clinical and Demographic Characteristics

This study included 52 patients with a diagnosis of epilepsy (32 boys and 20 girls; mean age 9.3 ± 3.1 years; range 4–16 years) and 36 healthy control subjects (22 boys and 14 girls; mean age 9.5 ± 4.0 years). The characteristics of the patients are shown in Table 1. There were no differences in age or sex between the groups. The BMI for all the patients were within normal limits.

The study groups were evaluated as pubertal in 69.2 % of the cases. Systemic systolic blood pressure was within the normal range (70–110 mmHg). The mean systolic and diastolic blood pressures were respectively 87.7 ± 15.0 and 93.1 ± 13.5 mmHg in the epilepsy group ($p = 0.089$) and 56.3 ± 9.5 and 58.8 ± 9.4 mmHg in the control group ($p = 0.237$). However, the cardiac rate was significantly higher in epileptic group (mean, 85.6 ± 13.1 beats/min) than in the control group (mean, 78.6 ± 8.3 beats/min) ($p = 0.006$).

In all, 7 (13.5 %) of the 52 epilepsy patients had no pathologic EEG findings. Among the others, 31 (59.6 %) showed focal epileptic activity, and 14 (26.9 %) displayed generalized epileptic activity. Cranial imaging (magnetic resonance or computed tomography) was performed for all the patients before treatment, with 46 (88.5 %) showing normal scans, and 6 (11.5 %) exhibiting pathologic findings.

Among the study group patients, the duration of antiepilepsy medication use ranged from 2.4 to 10.0 years. A total of 42 patients were receiving monotherapy: VPA ($n = 33$, 63.4 %), CBZ ($n = 7$, 10.7 %), or LTG ($n = 2$, 3.8 %). The remaining patients ($n = 10$, 22.1 %) were receiving polytherapy: VPA + CBZ ($n = 6$), VPA + LEV ($n = 2$), VPA + LTG ($n = 1$), or LEV + TPM ($n = 1$). The serum CBZ and VPA levels of our patients were within normal therapeutic ranges. The serum levels of the other AEDs were not measured.

### Effect of Antiepilepsy Drug Therapy on Standard and Tissue Doppler Echocardiographic Parameters

The standard and tissue Doppler echocardiography findings are shown in Table 2. The epilepsy and control groups exhibited similar ejection fractions. The epileptic children, however, had significantly higher left ventricular end-diastolic and end-systolic diameters, LVM, and LVMI than the control subjects ($p < 0.05$). There was a significant positive correlation of BMI with LVM ($r = 0.561$; $p < 0.001$) and LVMI ($r = 0.244$; $p = 0.022$) but not with the duration of epilepsy. Compared with the control group, the epileptic subjects showed a significant increase in the peak late mitral A-wave and mitral E-wave deceleration time and a decreased mitral E/A ratio.

The systolic myocardial velocities of the right and left ventricles (Sm) were similar in the two groups. As shown by TDI, the epileptic children and the control group differed significantly in regional myocardial deformation properties (IVRT, Em, Em/Am ratio, MPI, DI) at the septum, LV lateral wall, and RV lateral wall (Table 3). The E/Em was significantly higher in the patients with epilepsy (5.6 ± 1.2 vs 5.2 ± 1.1; $p = 0.016$). The mono- and polytherapy AED groups did not differ significantly in terms of the biventricular standard echocardiography and TDI findings.

### Correlation Between Antiepilepsy Drug Therapy and the Tissue Doppler Imaging Parameters

The results of the exploratory correlation analysis are shown in Table 4. The major tissue Doppler correlates included the LV IVRT, Em, MPI, and LV mass/index of the LV lateral wall and septum in the pediatric epileptic patients. The correlates did not include the duration of AED treatment. In addition, the DI, indicating LV systolic function, was significantly correlated with the MPI at the basal-mid septum ($r = -0.567$; $r = -0.495$) and at the basal-mid right ventricular lateral wall ($r = -0.445$; $r = -0.548$) and basal-

**Table 1** Clinical and demographic features of the epilepsy and control groups

| Parameters | Epileptic group ($n = 52$) | Control group ($n = 36$) | $p$ value |
|---|---|---|---|
| Sex (M:F) | 32:20 | 22:14 | 0.188 |
| Age (years) | 9.36 ± 3.1 | 9.5 ± 4.0 | 0.775 |
| BMI (kg/m$^2$) | 17.3 ± 2.5 | 17.3 ± 1.3 | 0.963 |
| Heart rate (beats/min) | 85.6 ± 13.1 | 78.6 ± 8.3 | 0.006* |
| Systolic blood pressure (mmHg) | 87.7 ± 15.0 | 93.1 ± 13.5 | 0.089 |
| Diastolic blood pressure (mmHg) | 56.3 ± 9.5 | 58.8 ± 9.4 | 0.237 |
| Types of seizure: % ($n$) | | | |
| Partial | 65.3 (33) | – | |
| Generalized | 36.5 (19) | | |
| Etiology | | | |
| Symptomatic | 13.4 (7) | – | |
| İdiopathic | 71.2 (37) | | |
| Criptogenic | 15.4 (8) | | |
| Median duration of AED treatment (years) | 3.6 ± 2.7 (2.4–10) | – | |
| AEDs (monotherapy/polytherapy) | 42/10 | – | |
| Older-generation/new AEDs | 46/6 | – | |
| Range of dose (mg/kg) | 2.7–48 | – | |

Values are expressed as mean ± standard deviation and range

*AEDs* antiepileptic drugs

* $p < 0.05$ was accepted as statistically significant

mid left ventricular lateral wall (r = −0.301; r = −0.347) (respectively, $p < 0.05$).

## Discussion

The interactions of epilepsy and antiepileptic therapy an one hand and cardiovascular system on the other hand are multiple and complex [9]. Detection of myocardial dysfunction by TDI during the preclinical stage in otherwise healthy epileptic children is important for clinical follow-up care and for determining the prognosis. We detected subclinical ventricular dysfunction at a preclinical stage that was associated with AEDs.

Most of the cardiac effects reported as resulting from AEDs were in adults. These effects included documented cardiac conduction disturbances and reduced LV function after overdoses [1, 23, 25]. Elderly patients with coronary heart disease appear to be most frequently affected at therapeutic doses [23].

The literature has limited information on myocardial dysfunction due to AED treatment over time in children [2, 4, 9]. The mechanism is relatively unknown. Some concerns are related to pharmacodynamic tolerance, which often is affected by the dose and rate of initiation. Other concerns are idiosyncratic responses to the drug. Combination therapy can result in additive and sometimes supra-additive adverse effects [2, 6, 16, 21, 23, 27]. The most probable mechanism is myocardial injury and a chronically disturbed sympathetic tone [7].

Direct effects of AEDs on ventricular function have received less attention [2]. Community-based studies have corroborated a higher incidence of myocardial infarction, peripheral vascular diseases, hypercholesterolemia, LV hypertrophy, and stroke among patients with epilepsy [9]. Patients have presented with LV hypertrophy, hypotension, and congestive heart failure (reduced systolic function).

The exact mechanism by which AEDs cause LV dysfunction is unknown, but AEDs are thought to have a direct toxic effect on myocardial fibers, causing deterioration in ventricular function [1]. Some studies have indicated that enzyme-inducing AEDs increase the levels of both lipoprotein A and homocysteine (CBZ, VPA) and reduce the concentration of C-reactive protein (CBZ, fenitoin, LEV, LTG) [18, 24]. The influence of AEDs on serum lipids, lipid metabolism, and changes in the microcirculation usually are the focus of possible explanations for these findings in patients with epilepsy [9, 13].

Bilgi et al. [4], in a TDI study, reported subclinical myocardial systolic and diastolic dysfunction of the left ventricle in cases of newly diagnosed adult epilepsy. They found no significant differences regarding the LVEDD or LV end-diastolic volume. However, they did find a higher LV end-systolic diameter and mitral E/Em ratio, an indicator of LV filling pressure, in epileptic patients.

We found that increased LV end-diastolic and end-systolic diameters and LVMI were associated with the use of AEDs. We also demonstrated a significant increase in the MPI and mitral E/Em ratio and a decrease in DI in epileptic patients. Although TDI parameters (IVRT, Em, MPI) were

**Table 2** Comparison of right and left ventricular standard and pulsed-wave Doppler echocardiographic parameters in both the epileptic and control groups

| Parameters | Control group ($n = 36$) | Epileptic group ($n = 52$) | $p$ value |
|---|---|---|---|
| Left ventricular end diastolic diameter (mm) | 32.6 ± 4.4 | 35 ± 4.6 | **0.019** |
| Left atrium/aortic ratio | 1.1 ± 0.17 | 1.06 ± 0.08 | 0.306 |
| Posterior wall thickness (mm) | 7.2 ± 0.9 | 7.3 ± 1.0 | 0.938 |
| Left ventricular end diastolic volume | 47 ± 9.1 | 50.4 ± 12.4 | 0.156 |
| Septal wall thickness (mm) | 7.1 ± 1.4 | 7.4 ± 1.2 | 0.341 |
| LVM (g) | 63.3 ± 26.2 | 75.6 ± 24.2 | **0.042** |
| LVM index (g/m$^2$) | 61.5 ± 14.6 | 71.3 ± 13.8 | **0.002** |
| Left ventricular systolic diameter (mm) | 17.9 ± 1.8 | 21.0 ± 3.3 | **<0.001** |
| Ejection fraction (%) | 71.5 ± 3.2 | 70.9 ± 4.5 | 0.496 |
| Fractional shortening (%) | 40.1 ± 4.1 | 39.4 ± 3.8 | 0.414 |
| Early mitral inflow (mitral E) (cm/s) | 94 ± 10 | 88 ± 10 | 0.056 |
| Late mitral inflow (mitral A) (cm/s) | 51 ± 7 | 60 ± 9 | **<0.001** |
| Mitral E/A ratio | 1.86 ± 0.1 | 1.47 ± 0.1 | **<0.001** |
| Mitral E deceleration time | 106.8 ± 5.2 | 120.8 ± 11.3 | **<0.001** |
| Early tricuspid inflow (tricuspid E) (cm/s) | 63 ± 8 | 58 ± 9 | 0.018 |
| Late tricuspid inflow (tricuspid A) (cm/s) | 76 ± 9 | 49 ± 10 | 0.055 |
| Tricuspid E/A ratio | 1.26 ± 0.4 | 1.12 ± 0.2 | 0.272 |
| Pulmonary velocity (cm/s) | 91 ± 10 | 90 ± 10 | 0.781 |
| Aortic velocity (cm/s) | 93 ± 10 | 110 ± 13 | 0.363 |
| Systolic pulmonary artery pressure (mmHg) | 19.1 ± 2.7 | 18.0 ± 3.0 | 0.088 |
| TAPSE (cm) | 2.09 ± 0.2 | 2.16 ± 0.35 | 0.304 |
| MAPSE (cm) | 1.5 ± 0.1 | 1.45 ± 0.1 | 0.053 |

Groups were compared by independent $t$ test. Values are expressed as mean ± standard deviation. $p$ value lower than 0.05 was accepted as statistically significant, and $p$ values lower than 0.05 are in bold

*LVM* left ventricular mass, *TAPSE* tricuspid annular plane systolic excursion, *MAPSE* mitral annular plane systolic excursion

not associated with the duration of AED treatment, they were correlated with increased LVM and LVMI in the children with epilepsy (Table 4).

This study showed potentially drug-induced abnormalities in myocardial function parameters in epileptic children who had been treated chronically by monotherapy with one of the two most often used antiepileptic drugs (VPA, CBZ). In previously reported studies, ventricular dysfunction occurred due to overdoses of CBZ [2, 14, 25]. Marked coronary atherosclerosis and myocardial infarction may have already occurred in children treated with CBZ [9]. The negative chronotropic and inotropic effects of CBZ are due to its effect on sodium channels. It can cause clinical hypotension, impaired LV function, severe hypotension, and arrhythmias [2, 5, 8, 10, 23].

Arhan et al. [2], using M-mode and two-dimensional echocardiography, demonstrated that LV function was within normal limits before treatment as well as 3 and 12 months after the start of CBZ treatment in 40 epileptic pediatric patients. Woodruff et al. [33] measured serial cardiac troponin levels after monitored seizures. They found no myocardial injury during uncomplicated seizures.

We took measurements reflecting the morphologic structure of the heart in our pediatric epileptic patients using standard echocardiography. The measurements indicated that the cardiac structure was within the normal limits. The ejection and shortening fractions (systolic myocardial velocity values indicating LV function) also were within normal limits. However, although our epileptic subjects did not have hypertension or obesity, the TDI parameters demonstrated subclinical significantly impaired systolic and diastolic myocardial function (Table 3). We also found negative correlations between the DI (indicating LV systolic function) and the MPI of the basal and mid-segments of the LV lateral wall and septum.

Bratton et al. [5] reported a child with VPA-associated carnitine deficiency who experienced severe cardiac dysfunction that resolved with carnitine replacement therapy. Metabolic syndrome occurred in 41 % of women treated with VPA compared with 5.3 % of those treated with CBZ. None of them had been treated with lamotrigine or topiramate. This syndrome appears to occur exclusively in those who become obese during valproate therapy [30, 31]. Thus, VPA-associated weight gain probably is due to hyperinsulinemia with relative insulin resistance. Elevated levels of cortisol, leptin, and neuropeptide Y also may be contributory [3].

Our study suggests that LV structural (LVEDD, LVM, LVMI, mitral E/Em ratio) and regional myocardial functional parameters differed significantly between the epilepsy and control groups (Table 2).

**Table 3** Evaluation of left and right ventricular function by tissue Doppler imaging-derived parameters in patients with epileptic subjects and controls

| Parameters | Control group ($n = 36$) | Epileptic group ($n = 52$) | $p$ value |
|---|---|---|---|
| Lateral mitral annulus (basal segment) | | | |
| Peak systolic velocity (Sm) (cm/s) | 11.2 ± 1.2 | 10.9 ± 1.2 | 0.192 |
| Early diastolic velocity (Em) (cm/s) | 17.6 ± 1.9 | 16.4 ± 2.5 | 0.011 |
| Late diastolic velocity (Am) (cm/s) | 8.4 ± 1.5 | 7.9 ± 1.8 | 0.165 |
| Em/Am ratio | 2.1 ± 0.3 | 2.0 ± 0.4 | 0.294 |
| IVRT (ms) | 43.5 ± 2.9 | 51.1 ± 6.1 | **<0.001** |
| Mitral E/Em ratio | 5.2 ± 1.1 | 5.6 ± 1.2 | **0.016** |
| MPI | 0.35 ± 0.03 | 0.42 ± 0.04 | **<0.001** |
| DI (%) | 26.9 ± 2.4 | 22.9 ± 2.1 | **<0.001** |
| Left ventricular lateral wall (mid-segment) | | | |
| Sm (cm/s) | 8.3 ± 1.3 | 8.1 ± 0.8 | 0.464 |
| Em (cm/s) | 16.6 ± 2.8 | 14.7 ± 2.5 | **0.001** |
| Am (cm/s) | 7.7 ± 1.5 | 7.6 ± 1.7 | 0.549 |
| Em/Am ratio | 2.19 ± 0.4 | 2.0 ± 0.4 | 0.074 |
| IVRT (ms) | 47.1 ± 4.9 | 52.2 ± 6.0 | **<0.001** |
| MPI | 0.36 ± 0.03 | 0.43 ± 0.04 | **<0.001** |
| Lateral tricuspid annulus (basal segment) | | | |
| Sm (cm/s) | 14.1 ± 1.1 | 14.0 ± 1.4 | 0.676 |
| Em (cm/s) | 18.5 ± 2.0 | 17.3 ± 2.2 | **0.012** |
| Am (cm/s) | 11.1 ± 1.8 | 12.5 ± 2.2 | **0.003** |
| Em/Am ratio | 1.7 ± 0.3 | 1.4 ± 0.3 | **<0.001** |
| IVRT (ms) | 47.2 ± 4.5 | 51.9 ± 5.9 | 0.001 |
| MPI | 0.36 ± 0.03 | 0.41 ± 0.03 | **<0.001** |
| Right ventricular free wall (mid-segment) | | | |
| Sm (cm/s) | 13.0 ± 1.1 | 12.8 ± 1.5 | 0.576 |
| Em (cm/s) | 17.0 ± 2.1 | 15.6 ± 2.0 | **0.001** |
| Am (cm/s) | 10.7 ± 2.1 | 11.6 ± 2.2 | **0.07** |
| Em/Am ratio | 1.6 ± 0.3 | 1.3 ± 0.3 | **<0.001** |
| IVRT (ms) | 46.0 ± 4.5 | 53.0 ± 6.4 | **<0.001** |
| MPI | 0.35 ± 0.02 | 0.43 ± 0.03 | **<0.001** |
| Interventricular septum (basal segment) | | | |
| Sm (cm/s) | 9.2 ± 1.1 | 8.9 ± 1.1 | 0.376 |
| Em (cm/s) | 14.5 ± 1.8 | 13.1 ± 1.8 | **0.01** |
| Am (cm/s) | 7.6 ± 1.1 | 7.8 ± 2.1 | 0.68 |
| Em/Am ratio | 1.9 ± 0.2 | 1.7 ± 0.4 | 0.067 |
| IVRT (ms) | 46.9 ± 4.3 | 54.0 ± 6.6 | **<0.001** |
| MPI | 0.35 ± 0.02 | 0.44 ± 0.04 | **<0.001** |
| Interventricular septum (mid-segment) | | | |
| Sm (cm/s) | 8.1 ± 2.0 | 7.8 ± 1.1 | 0.474 |
| Em (cm/s) | 14.1 ± 2.6 | 12.6 ± 1.8 | **0.01** |
| Am (cm/s) | 7.0 ± 1.6 | 6.7 ± 1.4 | 0.417 |
| Em/Am ratio | 2.0 ± 0.2 | 1.8 ± 0.4 | **0.009** |
| IVRT (ms) | 48.9 ± 3.9 | 52.7 ± 6.7 | 0.003 |
| MPI | 0.34 ± 0.02 | 0.42 ± 0.04 | **<0.001** |

Groups were compared by independent $t$ test. Values are expressed as mean ± standard deviation. $p$ value lower than 0.05 was accepted as statistically significant, and $p$ values lower than 0.05 are in bold

*IVRT* isovolumetric relaxation time, *MPI* myocardial performance index, *DI* displacement index

## Clinical Implications

Overall, our data indicate that follow-up evaluation regarding cardiac function is necessary in the pediatric epileptic population when treatment is initiated. Examinations to detect subclinical myocardial dysfunction at an early stage can prevent AED-associated complications. We suggest that the influence of AEDs on myocardial function

**Table 4** Pearson's correlations of tissue Doppler echocardiographic parameters, LV mass, LV mass index, and duration of AED treatment in epileptic subjects

| | LV mass (g) ($r$ value) | LV mass index (g/m$^2$) ($r$ value) | Duration of AED treatment ($r$ value) |
|---|---|---|---|
| Left ventricular lateral wall | | | |
| IVRT | **0.298*** | **0.325*** | 0.180 |
| Em | −0.016 | −0.023 | −0.129 |
| MPI | 0.003 | **0.213*** | 0.218 |
| Interventricular septum | | | |
| IVRT | **0.351*** | **0.267*** | 0.180 |
| Em | **−0.280*** | **−0.314*** | −0.183 |
| MPI | **0.288*** | **0.223*** | 0.124 |
| Right ventricular free wall | | | |
| IVRT | **0.218*** | 0.189 | 0.029 |
| Em | −0.104 | −0.065 | −0.095 |
| MPI | 0.123 | 0.157 | 0.191 |

Em/Am, ratio of early to late diastolic myocardial velocity

*LV* left ventricular, *AED* antiepileptic drug, *IVRT* isovolumetric relaxation time, *MPI* myocardial performance index

* $p$ values lower than 0.05 are in bold

should be considered in further studies using TDI to detect subclinical cardiac changes in patients taking antiepilepsy medication for the long term. This review is an attempt to describe the features and incidences of some of the side effects associated with the AEDs.

## Study Limitations

This study had limitations that need to be considered. It was a relatively small cross-sectional study of otherwise healthy epileptic young patients. Our results were limited to determining long-term outcomes related to myocardial changes after the start of AED therapy.

Another limitation was that we did not obtain recordings of echocardiographic and 24-h Holter monitoring for our patients before treatment. Therefore, we may have missed possible conduction anomalies. Our study population consisted of epileptic children without any underlying cardiac disease, hypertension, or obesity. Elderly patients and patients with known heart diseases can be expected to have more frequent cardiac toxicity from AEDs.

Another important point in our study was that most of the epileptic patients were treated with monotherapy and older-generation AEDs. Hence, the mono- and polytherapy AEDs did not differ significantly regarding biventricular function on standard and tissue Doppler echocardiography findings.

The main limitations of this study included the dependence of the method on the angle and the difficulty of providing a good echocardiographic window due to the difficulty of obtaining normal respiration.

## Conclusions

Our study showed that AED therapy is associated with subclinical regional ventricular myocardial deformation in epileptic patients without preexisting cardiac disease at the preclinical stage. We found increased LV end-diastolic and end-systolic diameters and LVMI as well as a preserved ejection fraction in epileptic children using standard echocardiography. The TDI results showed increased MPI and mitral E/Em and decreased DI. We believe that the subclinical ventricular dysfunction is associated with the severity of the increased LVM and LVMI. According to this study, TDI may be useful for determining short- and long-term cardiac effects of AEDs.

**Conflict of interest** The authors report no conflicts of interest in this work.

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