

Effect of Sodium Valproate on Cardiac Function in Epileptic Children by Tissue Doppler Echocardiography

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Abstract- The antiepileptic Valproic acid (VPA) changes the oxidative/ anti-oxidative balance that results in oxidative stress and maybe an increased risk of cardiac dysfunction. The aim of this study was to investigate the effect of VPA on ventricular function in epileptic children. We designed a study to evaluate ventricular function in epileptic children who had received VPA for at least one year. All subjects were evaluated using standard echocardiography, pulsed wave Doppler (PWD), and tissue Doppler imaging (TDI). This study consisted of 60 patients with epilepsy (mean age 10.30±3.21 years) and 60 healthy subjects in the control group (mean age 10.28±3.18 years). The duration of antiepilepsy medication ranged from 1.4 to 10 years, and the dose of VPA was 5-30 mg/kg. The ejection fraction and fractional shortening ($P=0.841$ and 0.064 , respectively) were not significantly different between the two groups. The present study reports subclinical right and left ventricular systolic and diastolic dysfunction along with longitudinal ventricular motion disorder. It is recommended the evaluation of subclinical cardiac dysfunction in children treated by VPA.

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Introduction

Antiepilepsy drugs (AEDs) can be divided into two major groups: old and new drugs. Phenytoin, carbamazepine, and valproic acid (VPA) falls in the category of traditional antiepilepsy drugs. The adverse cardiovascular effects with clinical significance occur in patients with AEDs (1,2). Cardiac arrhythmias may occur in short- and long-term treatment with AEDs (3). Some of these complications, such as PR and QT prolongations or ventricular tachycardia, can be life-threatening, inducing unexpected death in patients with epilepsy (4). Other reported side effects of AEDs include syncope, sinus bradycardia, atrioventricular block, and arrhythmia (2), which mostly depend on phenytoin, CBZ, and VPA (5).

Another study reported that the VPA caused increase oxidative stress in both humans and animal models, especially in the liver (6,7). Therapy with antiepileptic drugs may change the oxidative/anti-oxidative balance that may be associated with an increase in the risk of

atherosclerosis (8). Ebru Emekli-Alturfan *et al.*, shown that VPA increases Lipid peroxidation and decreases the activity of Glutathione peroxidase in the cardiac myocyte in comparison with the control group (9).

Ebru Arhan *et al.*, demonstrated that epilepsy per se does not seem to cause an increase of lipid peroxidation but provides evidence that Nitric oxide (NO) related oxidative damage may be involved in epilepsy. Their results also indicate decreased lipid peroxidation with an antiepileptic drug (10). We hypothesis that it may be the VPA interferes with oxidative metabolism in the left and right ventricular function. We designed a study that assesses the effect of VPA and its therapeutic range on ventricular myocardial function in epileptic children who had no history of cardiac disease. Tissue Doppler imaging (TDI) is a useful method for detecting subclinical systolic and diastolic dysfunction, which is less dependent on preload, post-load, heart rate, and age. TDI is useful for discovering early systolic and diastolic myocardial dysfunction (11,12).

We aim of our study was to evaluate the effect of

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sodium valproate on the left and right ventricular function in epileptic children.

Materials and Methods

This cross-sectional study consisted of 60 epileptic pediatric aged 5-15 years who were randomly selected from pediatric neurology clinics in the period from 2015 to 2018. The protocol was approved by the Research Ethics Committee of the University of Medical Sciences (IR.ARAKMU.REC.1394.240). All of the patients were under treatment with VPA and seizure-free over the past year (one year). Sixty healthy children who matched the patients were selected from other pediatric clinics and assigned to the control group. The epilepsy was diagnosed based on the history of this medical condition and findings of electroencephalography. The blood pressure was measured by a pediatric cardiologist. Arterial blood pressure was measured after 15 minutes of rest in the supine position. Systolic and diastolic blood pressure values were standardized based on age and gender. Exclusion criteria included a history of sleep apnea, systemic disease, hypertension, obesity, pulmonary hypertension, recurrent epileptic seizures, or treatment duration of less than a year.

Echocardiography

In the epileptic and control groups, ventricular functions were evaluated using standard echocardiography, pulsed wave Doppler (PWD), and tissue Doppler imaging (TDI). The echocardiography was performed according to the guidelines of the American Echocardiography Society for all subjects (12). We utilized echocardiography parameters in three consecutive cardiac cycles to confirm the analysis. Echocardiographic assessments were performed using a 3-8 MHz probe by ViVid 3 (GE Medical Systems, General Electric, and the USA).

Standard echocardiography

In both groups, standard echocardiography was performed in the parasternal view. The ejection fraction (EF) and fractional shortening (FS) were calculated along with other parameters such as the left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrium and aortic diameters ratio (LA/AO), left ventricular end-diastolic volumes (LVEDV), left ventricular end-systolic (LVESV), volumes posterior wall thickness (PWT), septal wall thickness (SWT), and left ventricular mass (LVM). In the apical four-chamber view, we assessed tricuspid annular

plane systolic excursion (TAPSE) and mitral annular plane systolic excursion (MAPSE).

Pulse wave doppler echocardiography

We used PWD echocardiography to evaluate RV and LV systolic, diastolic functions. The PWD was assessed by placing a sample of 3-5 mm above the tip of the tricuspid and mitral valve in accordance with the guidelines of the American Echocardiography Society. The tricuspid and mitral flow velocities were recorded to assess the early diastolic flow (E wave), late diastolic flow (A wave), E/A ratio, and E wave deceleration time (E-DT). Dysfunction in the diastolic phase was defined as any abnormality in one of the above parameters.

Tissue doppler imaging echocardiography

The TDI parameters were assessed by placing a sample volume at the basal segment of the RV free wall to assess tricuspid and the LV lateral wall mitral annulus. The LV function evaluated by measuring systolic myocardial velocity (S'), and diastolic function we assessed by the early (E') and late (A') diastolic velocities, E'/A' ratio, and the isovolumetric relaxation time (IVRT) at the basal segment of LV free wall. The myocardial performance index (MPI) (IVRT+IVCT/ET) was calculated to assess the left ventricular function as the systolic plus diastolic function. We calculated the E/A ratio as the index of LV filling pressure. The E/E' Raito was preload independent. At the basal segment of RV free wall, S', E', A', E'/A' ratio, IVRT, and MPI parameters were measured to assess right ventricular systolic and diastolic function.

Statistical analysis

Statistical analysis was performed using SPSS 20 (SPSS, Chicago, IL, USA). Descriptive statistics included mean±SD, and we used independent samples to test to compare the continuous variables between epilepsy and control groups. Pearson's correlation coefficient was used to assess the relationship between echocardiography indices, dose, and duration of VPA treatment. A *P* lower than 0.05 was considered as statistically significant.

Results

The clinical and demographic characteristics are depicted in table 1. Among 60 epileptic patients, 37 (66.61 %) had partial and 23 (33.38 %) had general seizures. The duration of antiepilepsy medication varied from 1.4 to 10 years, and the VPA dose was 5-30 mg/kg. There was no significant difference between the two

Sodium valproate and cardiac function in epileptic children

groups in terms of clinical and demographic evaluations.

Standard echocardiographic parameters are shown in table 2. The two groups were not significantly different from Standard Echocardiographic Parameters of left ventricular systolic and diastolic function.

The PWD of tricuspid and mitral flow parameters are

displayed in tables 3. There were no significant differences between the two groups. PWD revealed that the tricuspid flow was similar between two groups, also. The left ventricular systolic and diastolic functions were normal range and good function.

Table 1. Clinical and demographic characteristics

| Parameters | Epileptic group (N=60) | Control group (N=60) | P |
|--------------------------|---------------------------|-------------------------|-------|
| Gender (M/F) | 34/26 | 31/29 | 0.714 |
| Age (years) | 10.30 ± 3.21 | 10.28 ± 3.18 | 0.977 |
| BMI (kg/m ²) | 15.70 ± 0.90 | 15.92 ± 0.99 | 0.205 |
| HR (beats/min) | 86.93 ± 12.74 | 90.10 ± 11.75 | 0.160 |
| SBP (mmHg) | 94.18 ± 13.43 | 98.83 ± 14.81 | 0.074 |
| DBP (mmHg) | 62.81 ± 11.60 | 62.76 ± 11.37 | 0.981 |

BMI: body mass index, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure

Table 2. Standard echocardiographic parameters

| Echocardiographic parameters | Epileptic group (N=60) | Control group (N=60) | P |
|---------------------------------|---------------------------|-------------------------|-------|
| EF (%) | 65.66 ± 3.71 | 65.55 ± 2.53 | 0.841 |
| FS (%) | 35.00 ± 1.42 | 34.36 ± 2.30 | 0.064 |
| LA/AO ratio | 1.18 ± 0.20 | 1.12 ± 0.23 | 0.130 |
| LVESD (mm) | 20.00 ± 1.42 | 19.66 ± 1.61 | 0.233 |
| LVEDD (mm) | 37.56 ± 5.98 | 36.27 ± 5.69 | 0.228 |
| LVESV (mL) | 50.90 ± 5.31 | 51.45 ± 5.63 | 0.683 |
| LVEDV (mL) | 87.17 ± 1.61 | 88.02 ± 2.93 | 0.052 |
| PWT (mm) | 7.11 ± 0.41 | 7.01 ± 0.45 | 0.180 |
| SWT (mm) | 7.02 ± 0.84 | 7.13 ± 0.77 | 0.492 |
| LVM (g) | 63.50 ± 16.67 | 16.83 ± 16.79 | 0.578 |
| LV mass/BSA (g/m ²) | 41.13 ± 5.27 | 42.09 ± 4.98 | 0.307 |
| TAPSE (cm) | 1.85 ± 0.17 | 1.93 ± 0.28 | 0.061 |
| MAPSE (cm) | 1.39 ± 0.11 | 1.39 ± 0.10 | 0.836 |

EF: ejection fraction, FS: fractional shortening, LVEDD: left ventricular end-diastolic diameter, LA/AO: left atrium/aortic ratio, PWT: posterior wall thickness, LVEDV: left ventricular end-diastolic volume, LVM: left ventricular mass, BSA: body surface area, SWT: septal wall thickness, LVM: left ventricular mass, LVESD: left ventricular end-systolic diameter, TAPSE: tricuspid annular plane systolic excursion, MAPSE: mitral annular plane systolic excursion

Table 3. Comparison of right and left ventricular function based on the PWD of parameters

| Parameters | Epileptic group (N=60) | Control group (N=60) | P |
|--------------|---------------------------|-------------------------|-------|
| MIT E (cm/s) | 88.30 ± 7.73 | 89.55 ± 5.89 | 0.321 |
| MIT A (cm/s) | 59.66 ± 5.89 | 57.73 ± 5.71 | 0.071 |
| MIT E/A | 1.66 ± 1.31 | 1.71 ± 1.30 | 0.834 |
| MITE-DT(s) | 119.51 ± 8.75 | 117.75 ± 3.19 | 0.147 |
| TRI E (cm/s) | 58.13 ± 5.48 | 59.50 ± 6.41 | 0.211 |
| TRI A (cm/s) | 47.55 ± 5.89 | 47.50 ± 8.72 | 0.971 |
| TRI E/A | 1.20 ± 0.93 | 1.29 ± 0.66 | 0.087 |

MIT E: Mitral early diastolic flow, MIT A: Mitral late diastolic flow, MIT E/A: Mitral E/A ratio, E-DT: E -wave Deceleration time, TRI E: Tricuspid early diastolic flow, TRI A: Tricuspid late diastolic flow, TRI E/A: Tricuspid E/A ratio

The two groups were significantly different in TDI parameters at the mitral lateral wall, RV free wall, and interventricular septum basal segment (Table 4). Moreover, the regional myocardial deformation

properties at the lateral LV wall, Right ventricular free wall tricuspid annulus, and Interventricular septum (basal segment) were significantly different between the two groups (Table 4).

Table 4. Comparison of left and right ventricular function based on the TDI of Parameters

| | Epileptic group (N=60) | Control group (N=60) | P | |
|---|---------------------------|-------------------------|-------------|--------|
| Lateral wall mitral annulus | S' (cm/s) | 10.65 ± 0.87 | 11.59±0.94 | 0.001* |
| | E' (cm/s) | 15.87 ± 1.42 | 17.61±1.05 | 0.001* |
| | A' (cm/s) | 7.66 ±1.06 | 8.43±0.95 | 0.001* |
| | E'/A' ratio | 2.07 ± 1.33 | 2.08±1.10 | 0.964 |
| | E/E' ratio | 5.12 ± 5.44 | 5.08±5.60 | 0.968 |
| | IVRT (ms) | 50.03 ± 3.82 | 44.09±1.49 | 0.001* |
| | IVCT (ms) | 42.15±5.36 | 44.75±4.26 | 0.004 |
| | ET | 80.31±10.63 | 81.25±9.52 | 0.611 |
| | LVMPI | 0.43 ± 0.03 | 0.34±0.02 | 0.001* |
| | E/ E' | 4.79±2.45 | 5.72±2.97 | 0.064 |
| Right ventricular free wall tricuspid annulus | S' (cm/s) | 13.95 ± 1.01 | 14.20±1.17 | 0.213 |
| | E' (cm/s) | 17.43 ± 1.25 | 18.38±1.11 | 0.001* |
| | A' (cm/s) | 12.75 ± 1.44 | 10.95±1.00 | 0.001* |
| | E'/A' ratio | 1.36 ± 0.86 | 1.67±1.11 | 0.001* |
| | IVRT(ms) | 47.64± 4.54 | 46.75±3.19 | 0.215 |
| | IVCT (ms) | 46.84±5.27 | 45.36±5.82 | 0.134 |
| | ET | 79.34±11.49 | 80.12±11.13 | 0.706 |
| | RVMPI | 0.39 ±0.02 | 0.34±0.02 | 0.001* |
| | E/ E' | 4.23±1.98 | 4.65±1.14 | 0.158 |
| | S'(cm/s) | 8.54±0.88 | 8.85± 0.89 | 0.057 |
| Interventricular septum (basal segment) | E' (cm/s) | 12.83 ± 1.08 | 13.82± 1.05 | 0.001* |
| | A'(cm/s) | 7.70 ± 0.29 | 7.97±0.48 | 0.001* |
| | E'/A' ratio | 1.66 ± 3.72 | 1.73±2.18 | 0.001* |
| | IVRT(ms) | 52.10 ± 4.51 | 46.16±4.13 | 0.001* |
| | IVCT (ms) | 49.62± 3.98 | 48.57±4.98 | 0.205 |
| | ET | 81.01±10.13 | 80.63±10.09 | 0.837 |
| | MPI | 0.42 ± 0.03 | 0.33±0.02 | 0.001* |
| | E/ E' | 5.22±1.62 | 5.42±1.09 | 0.429 |

S': systolic myocardial velocity, E': early diastolic velocities, A': late diastolic velocities IVRT: isovolumetric relaxation time, IVCT: isovolumetric contraction time, ET: ejection time, MPI: myocardial performance index

We did not find any correlation between VPA dose and LV and RV systolic and diastolic dysfunction. Nevertheless, it was correlated among RVMPI and duration of use VPA ($P=0.001$, r -value =0.413), LVMPI in lateral wall mitral annulus ($P=0.001$, r -value=0.406), and LVMPI in the basal segment Interventricular septum ($P=0.001$, r -value =0.394).

Discussion

Valproic acid is used to treat various types of seizure disorders, manic episodes related to bipolar disorder, and to prevent migraine headaches.

Side effects of valproic acid include congenital anomalies, infection, flu-like symptoms, gaseroenterstrial (abdominal pain, Jaundice, ascites, vomiting, anorexia, diarrhea, nausea, pancreatitis, elevated liver enzymes), alopecia, hematology (bone marrow suppression, thrombocytopenia, coagulation disorders), neurology (dizziness, tremor, coma, asthenia, drowsiness), hypoglycemia, and Hyperammonemic encephalopathy (13).

Thomas Daniels *et al.*, showed that VPA selectively interferes with the metabolism of both fatty acids (FAs)

and carbohydrates in heart tissue ex vivo. Their results are consistent with the hypothesis that VPA selectively interferes with myocardial fuel oxidation (14).

Alberto Verratti *et al.*, showed that after one year of VPA therapy, oxidative stress occurs in overweight children. This increase in the levels of oxidant markers, probably caused by obesity, might contribute to the development of endothelial dysfunction and atherosclerosis later in life (8).

These findings discover that VPA may be harmful in obese children, especially that we found subclinical cardiac function in children. Of course, in our patient, MBI and weight did not assess.

Ebru Arhan *et al.*, demonstrated that epilepsy does not seem to cause an increase of lipid peroxidation but provides evidence that Nitric oxide (NO) related oxidative damage might be involved in epilepsy. Their results also indicate decreased lipid peroxidation with an antiepileptic drug (10).

Our study brings up that it seems the VPA interferes with oxidative metabolism in the cardiac function, the same showed in liver function. Many cardiovascular complications have been documented in VPA and other antiepileptic drugs, including congestive heart failure,

peripheral vascular diseases, myocardial infarction, LV hypertrophies, hypercholesterolemia, and hypotension in both adult and pediatric patients. Cardiac complications such as cardiac conduction disturbances or LV dysfunction have been frequently reported in adults. The lipid metabolism disorder is induced by increased serum levels of lipoprotein A (15). It may also elevate the serum level of neuropeptide Y, cortisol, and leptin (16).

In obese patients, the chance of sodium valproate-induced metabolic syndrome is higher than other AEDs (8). It is also associated with several mechanical complications, such as pharmacodynamics tolerance, disturbed sympathetic tone, myocardial fibers, and idiosyncratic responses to drugs (4). As a result, the diagnosis of myocardial function, the clinical follow-up, and the determination of drug intoxication are important in healthy epileptic children during the subclinical stage. There are limited reports on the direct effects of VPA immunotherapy in children.

In our study, all subjects had normal weight; BMI and systolic and diastolic blood pressure were within the normal range. These parameters were not significant differences between the two groups. The standard echocardiography is the first-line method for evaluating cardiac function. Also, the standard echocardiography was useful for the evaluation of LV geometry disorders and RV longitudinal motion. The parameters functional such as [EF (%), FS (%)] assessed between two groups. The parameters geometry calculated such as (LA/AO ratio, LVESD (mm), LVEDD (mm), LVESV (mL), LVEDV (mL), PWT (mm), SWT (mm) LVM (g), LV mass/BSA (g/m²). The parameters longitudinal motion evaluated between groups such as TAPSE (cm), MAPSE (cm), also. The epileptic children had not significantly of subjects in the control group. It seems that the use of VPA was safe in cardiac function and geometry, and no made disorder in cardiac. These findings were different from other papers.

Bilgi *et al.*, exhibited LV subclinical myocardial dysfunction and significant differences in the LVEDD and LVEDV of epileptic pediatrics using adult assessment techniques (12). Our study demonstrated there are no significant differences in LV structural parameters (LVEDV, LA/AO Ratio) between the control and epileptic subjects. We documented that there is not any increase in the left ventricular volume of LV enlargement.

The TAPSE and MAPSE were not also different between the two groups. The findings indicated diminished longitudinal RV systolic function in epileptic patients based on the standard echocardiography. The

VPA did not down the longitudinal motion of the right and left ventricle and not induced RV systolic function. The MAPSE was similar between epilepsy and control groups.

According to finding PWD parameters, the epileptic subjects revealed no significant differences in systolic and diastolic cardiac function in both right and left ventricular. By using the TDI method, our study indicated both systolic and diastolic subclinical dysfunction in the right and left ventricular. Subclinical diastolic dysfunction was detected in RV and LV; however, these findings were not identified in systolic RV evaluations, though our study presented significant LV subclinical systolic and diastolic dysfunction.

Right ventricular free wall tricuspid annulus was evaluated by the TDI method. The E', A', E'/A' ratio, and RVMPI were significant differences between the two groups and revealed diastolic dysfunction. RVMPI shows global cardiac function (systolic and diastolic to gather). This index was a disorder in the epileptic group.

The systolic myocardial velocities of the mitral lateral wall (S') declined in the epileptic group. The epileptic and the control groups differed in terms of regional myocardial deformation properties (IVRT, E', MPI) on the mitral lateral wall, but the E/E' ratio was identical in both groups (Table 4). This is inconsistent with other research (*e.g.*, Bilgi *et al.*) who reported a higher mitral E/E' ratio in the intervention control (11).

Ayse Esin Kibar *et al.*, showed that the use of AEDs was associated with LV end-diastolic and end-systolic diameters and LVMI. Also, they observed an increase in the MPI and mitral E/E' ratio in epileptic patients. The IVRT, E', and MPI parameters were not associated with the duration of AED treatment, but there were correlated with increased LVM and LVMI in the epileptic children. Also, they demonstrated that DI (indicating LV systolic function) and MPI of the basal and mid-segments of the LV lateral wall and septum were negatively correlated (17).

As shown by TDI, on the free wall RV, the systolic myocardial velocity of the right ventricle (S') was similar in both groups. Diastolic dysfunction and regional myocardial deformation were detected in RV (Table 4). We used TDI for a detailed analysis of the diastolic function. Subclinical systolic and diastolic dysfunction was detected on the valve of lateral wall mitral, and tricuspid free wall. Interventricular septum showed further subclinical diastolic dysfunction with an increase in the MPI of tricuspid free wall and interventricular septum in epileptic patients.

We found that the dose and duration of VPA were not

correlated with the LV and RV systolic and diastolic dysfunction, except for RVMPI and LVMPI. It seems that the duration of VPA treatment indicates higher diastolic rather than systolic phase disorder. Overall, our findings suggested that subclinical ventricular dysfunction was associated with VPA.

We propose that the more studies perform in obese children that undergo treatment VPA due to seizure and also evaluation insulin, glucose, vitamin E, and Malondialdehyde (MDA) at blood serum level.

A major limitation of this study is that we did not measure levels of VPA concentration in patients. Another limitation was the small number of subjects. Also, we did not have sufficient information on echocardiographic or ECG findings before VPA administration in participants. Moreover, we did not evaluate the RV and LV function in patients with partial and general seizures. Besides, we did not measure hemoglobin (HB), a factor that may influence cardiac function in both groups. In the end, we did not measure any oxidative metabolic, FAs, carbohydrates in blood serum.

Our study revealed that VPA therapy was occasioned subclinical right and left ventricular systolic and diastolic dysfunction and myocardial deformation in patients. It appears that follow-up and analysis of cardiac function are vital in the epileptic pediatrics to detect subclinical myocardial dysfunction. It seems that the duration of use of VPA is more important than the dose of use. We suggest the application of TDI to determine the cardiac effects of VPA during treatment.

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Sodium valproate and cardiac function in epileptic children

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