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Subtle Right Ventricular Myocardial Dysfunction in Children with Refractory Epilepsy using 2-D speckle tracking echocardiography

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Abstract

Objective: Recent echocardiographic modalities can detect subclinical structural and functional myocardial changes allow early prediction of those at high risk for adverse cardiac events. This study aimed to evaluate right ventricle (RV) function in children with refractory epilepsy and its relation to clinical characteristics of epilepsy.

Methods: Forty children with refractory epilepsy and 40 age and sex matched healthy children were enrolled. Clinical, electroencephalographic characteristics and seizure severity score were determined. RV function was assessed using conventional echocardiography, tissue Doppler and speckle tracking modalities.

Results: Despite preserved ejection fraction, children with refractory epilepsy have significant higher RV end systolic dimension. RV tissue Doppler imaging and speckle tracking parameters revealed statistically significant higher RV myocardial performance index and significant lower RV global strain in children with refractory epilepsy than healthy control. The younger age of onset, the longer duration of epilepsy and the higher scores of epilepsy severity were significantly associated with worse right ventricular performance.

In conclusion, children with refractory epilepsy had subtle RV systolic and diastolic dysfunction that correlated to the duration and severity of epilepsy. Speckle tracking modality of echocardiography provides simple efficient tool for early detection of subclinical RV dysfunction in children with epilepsy.

Keywords: Refractory epilepsy, right ventricle, echocardiography, Children.

1. INTRODUCTION

Despite advances in epilepsy management, about 25-30% of subjects with epilepsy continue to have long term uncontrolled seizures. Refractory seizures lead to increase the morbidity and mortality burden of epilepsy (Janson and Bainbridge, 2021).

The relation between epilepsy and sudden cardiac death is complex and multifactorial. Prolonged duration of exposure to abnormal neuronal electrical discharges may interrupt the central autonomic cardiac regulation causing chronic sympathetic overactivity that presented as decreased heart rate variability and arrhythmia. Furthermore, Antiepileptic drugs especially sodium channel blockers can induce cardiac arrhythmia (Bleakley et al., 2020).

Uncontrolled seizures, generalized tonic clonic seizures, and antiepileptic medication polytherapy are clinical predictors of sudden unexplained death in epilepsy (SUDE) (Ryvlin et al., 2019). Reduced heart rate variability and echocardiographic indications of cardiac fibrosis are two cardiac predictors (May & Israel, 2019)

Echocardiography is an important bedside noninvasive tool for evaluation of cardiac structure and function in high risk populations. Evidences showed that patients with chronic epilepsy especially those with uncontrolled seizures have 24 fold higher incidence of sudden unexplained death than their healthy peers. There is emerging interest in identification of echocardiographic markers of cardiac mortalities in children with epilepsy (Manolis et al.2019).

Echocardiography has been emerged as a widely available diagnostic and prognostic tool for assessment of cardiac fibrosis. The right ventricle has received much less attention in cardiac research than the left, particularly in those involving children. Lack of data regarding right ventricle function evaluation may be attributed to difficulties in obtaining global view of right ventricle using conventional echocardiography in addition to previous concept that left ventricle is more important than right ventricle function assessment. However with advances in echocardiographic techniques, several evidences showed the important prognostic value of the right ventricle assessment (Wu and Takeuchi, 2018).

Despite that conventional Doppler and two - dimension echocardiography may miss early myocardial structural changes; studies showed that advanced modalities including speckle tracking for assessment of fibrosis. Using advanced echocardiographic modalities allow early detection of myocardial dysfunction even in asymptomatic subjects. Speckle tracking is an advanced modality in echocardiography that allows better assessment of myocardial deformation for early identification of both systolic and diastolic myocardial dysfunction (Cameli et al., 2019)

Assessment of cardiac function in subjects with epilepsy has gain great interest over the last decades with most researches identify left ventricular dysfunction that was linked to increased mortality in animal models of epilepsy. However there is limited data regarding the right ventricular function alteration in subjects with epilepsy. As children with intractable seizures represent a vulnerable population with high risk for mortality so our study aimed to assess right ventricular function in children with refractory epilepsy and its relation to clinical characteristics of epilepsy.

2. Methods

2.1. Study design & data collection

This comparative study included 40 children with documented refractory epilepsy. Another 40 healthy children of matched age, sex and body surface area were involved as a control group. Children were selected consecutively from outpatient pediatric and neurology clinic at Al-Zahraa Hospital, Cairo Egypt. We get a written informed consent from caregivers of studied children in accordance with principles of ethics committee at faculty of medicine, Al-Azhar University and the Declaration of Helsinki.

Inclusion criteria were male and female children aged 12–17 years who had documented diagnosis of refractory idiopathic epilepsy. Diagnosis of idiopathic epilepsy was based on history, normal neurological examination and normal neuroimaging. Epilepsy was considered refractory if seizures are uncontrolled despite using at least 2 or more antiepileptic drugs in proper maximum doses that is optimal of the type of epilepsy for at least 1 year. The International League Against Epilepsy (ILAE) categorizes epilepsy as focal, generalized, focal to bilateral tonic clonic, or undetermined onset (Scheffer et al., 2017). Serum levels of sodium valproate and carbamazepine were within the therapeutic range.

Exclusion criteria were children with structural cardiac abnormalities either congenital or acquired, children with systemic illness (e.g., obesity, respiratory, hepatic, renal, endocrinal, or hematological disorders) or those who received cardiotoxic drugs (e.g. chemotherapy), children with musculoskeletal or metabolic disorders based on previous investigation.

Control group were healthy children of matched age, sex, and body surface area to epilepsy group who are neurologically free. They did not have cardiac, neurologic or systemic diseases or history of previous brain insult (e.g. hypoxia, trauma, or infection).

Medical history including demographic data, perinatal, developmental history, and epilepsy details (age of onset, seizures type, frequency, and level of control). Data regarding antiepileptic drugs type, dose, duration and response. Systemic and neurological examinations were carried out with the aid of a body surface area assessment. The bodily surface area was calculated by blotting the weight and length on a surface area chart and dividing the weight in kilograms by the square of the height in meters (Briars & Bailey, 1994). Clinical and electroencephalographic data were obtained. The severity of the seizures was determined using the Chalfont severity scale (Duncan & Sander, 1991).

Cardiac examination was performed for all involved children by the same cardiologist who was blind to children clinical data to avoid inter-observer errors. Electrocardiography was done to all children to detect any rhythm abnormalities. Assessment was done during interictal status at least 48 hours after the last seizures.

2.2. Echo-Doppler evaluation for RV function

Vivid-E9 GE ultrasound equipment from Horten Norway was used by the cardiology department at Al Zahra University Hospital to investigate the right ventricular function. STE capabilities were also used. In order to capture standard views from all of the windows, a multi-frequency (1.5-4.6 MHz) matrix probe M5S was employed. An echoPAC workstation version 201 was used to digitize the pictures and cine-loops for further offline processing.

RV function was assessed using the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines (Lang et al., 2015) as follows:

1. In 2D-guided M-mode at the level of the aorta left atrium, we may infer the RV end diastolic and end systolic dimensions from images of the parasternal short axis that were acquired.

2. The basal RV dimension (basal RVD) is measured using a 2D apical four-chamber picture at the tricuspid annulus.

3. The mid cavity RV linear dimension refers to the transverse RV diameter in the middle third of RV inflow, about halfway between maximal basal diameter and peak at end diastole at papillary muscle level (Mid RVD).

4. RVD is a measure of the distance from the right ventricular apex to the base of the RV at the level of the tricuspid annulus.

5. The right ventricular ejection fraction is determined by the RV diastolic and systolic volumes.

6. By dividing RV end-diastolic (RVED) by RV end-systolic (RVES) area, the RV

fractional area change is determined (RVED area).

7. For the purpose of this study, TAPSE (tricuspid annular plane systolic excursion) was assessed utilizing 2D-guided, apical four-chamber views. The lateral tricuspid annulus traveled following the path of the M-mode cursor. By measuring the distance between the diastole's final contraction peak and the largest peaks of the contraction, the total systemic displacement was computed.

8. To measure the E/A ratio, we measured the transtricuspid Doppler flow velocity's early and late diastolic peak speeds, respectively.

9. The sum of isovolumic contraction time, isovolumic relaxation time, and ejection time is calculated by measuring the time gap between the end of one tricuspid Doppler flow signal and the start of the next (Tei index) Myocardial performance index in the RV (am interval). The pulmonary Doppler flow signal was used to calculate the ejection time (bm).

RV tei index= am-bm/bm

2.3. Tissue Doppler imaging (TDI) parameters :

The TDI function was activated at the apical four-chamber for data gathering at speeds more than 100 frames per second, and the color Doppler velocity range was adjusted to avoid aliasing in the image. The digitally recorded loops were analyzed using trace profiling and positioning the sample volume at the RV free wall at the level of the tricuspid annulus in an apical four-chamber perspective. Ea was Computed by pulsed-Doppler echocardiography, whereas Sa, Ea, and Aa were derived from the trace profile. The ratio of E/Ea was then calculated from these three values: the peak systolic annular velocity measurements. Using the average of the free wall segments from the RV's basal, mid, and apical regions, a Tissue Doppler-derived RV genotype was generated.

2.4. Speckle tracking echocardiography derived RV global strain (STE-RVGST)

To measure global RVSTE, STE-RVGST was collected from the apical view using a software package (Echo-pac, USA). At a frame rate of 70-90 frames per second, standard gray scale 2D images were produced. An end-of-systole frame was used to manually trace the RV endocardial boundary. The program then determined the epicardial boundary, and the area of interest was manually altered to encompass the full RV myocardial wall. To achieve optimum tracking, the quality of the tracking was checked, and the area of interest was updated and rectified as needed.

2.5. Statistical analysis

For data analysis, we utilized the Statistical Package for Social Sciences (SPSS version 22, USA). For quantitative data, mean SD was used, while for qualitative data, number and percentage were used. For comparisons between the groups, independent student t tests and chi square tests were performed. To analyze the relationships between variables, the Pearson correlation coefficient was utilized. P-values of less than 0.05 were deemed significant.

3. Results

This case control study included 40 children with refractory epilepsy they were 25 male and 15 females; their mean age was 15.19±1.576 years. The age of onset of epilepsy ranged between 2.5-6 years old with mean value of 4.2±1.1 years and the duration of epilepsy ranged between 6-14.5 years with mean value of11.1±2.5 years. Epilepsy severity score ranged between 80 to 128. Electroencephalography showed focal epileptic discharge in 23 child and focal with secondary generalization discharge in 10 children and generalized epileptic discharge in 7 children. Epilepsy was categorized into focal onset in 10 children, generalized onset in 15 children, focal to bilateral tonic clonic in 8 children, and unknown onset in 7 children. In addition 40 healthy children were included as control group. They were 24 male and 16 females. Their mean age was14.7±1.6 years. No significant difference in age or sex was

detected between both groups (p-value 0.170 and 0.818 respectively).

Evaluation of conventional RV 2D and M-mode echocardiographic parameters demonstrated significant higher RVESD and lower long-RVD in children with refractory epilepsy than healthy control. However, no significant difference was detected between both groups as regard RVEDD, Basal-RVD, Mid-RVD, RVEF, TAPSE, RV-FAC as shown in table 1

When the Tissue Doppler (TDI) echocardiographic examination was used to compare children with refractory epilepsy to healthy controls, there were statistically significant variations in TV E/A between the epilepsy group and the control group. The difference in TV-E vel between the two groups was not noticeable, as shown in Table 2.

Free Ea, Free Sa, and TD-derived RV strain were lower in the refractory epilepsy group than in the control group, but there was no statistically significant difference between E/Ea and E/Ea in the refractory epilepsy group compared to the control group.

Seizure onset age is significantly correlated positively with RV strain, STE-RVGST, and negatively with RV Tei index, with the former being significantly significant. However, epilepsy duration has a strong negative connection with RV EF %, Tissue Doppler–derived RV strain, STE-RVGST and significant positive correlation with RV Tei index. Epilepsy severity score has significant negative correlation with TAPSE, Tissue Doppler–derived RV strain, STE-RVGST and significant positive correlation with RV Tei index as shown in table 4.

4. Discussion

Myocardial hypoxic stress together with excessive sympathetic over-activation during active seizures can induce cardiomyocytes injury that increases the vulnerability to sudden death in patients with epilepsy. There is a great interest in early identification of subclinical cardiac changes to guide selection of antiepileptic medications and allow optimization of management strategy to decrease cardiac mortality in patients with epilepsy. Non-invasive echocardiographic modalities may provide diagnostic and prognostic markers for early detection of cardiac injury allow early identification of those at higher risk for cardiac adverse events later in life (Hayabuchi et al., 2019).

The current study showed significant subtle myocardial dysfunction in children with refractory epilepsy that was significantly correlated to the severity and duration of epilepsy suggesting that frequent seizures are associated with greater risk for cardiomyocyte injury with subsequent cardiac remolding that alter the cardiac structure and function. Tigaran el al (2003) demonstrated myocardial ischemic changes in the form of depressed S-T segment during ictal and the postictal period in 40% of patients with refractory epilepsy suggesting cardiac ischemia occurred during seizure activity. Auzmendi et al (2018) found that prolonged seizure activities cause hypoxic myocardial insult with increase the expression of P-Glycoprotein causing altered depolarization of the cardiomyocyte membranes inducing prolonged QT interval and arrhythmia that in experimental animal models was associated with sudden death. Ryvlin et al (2011) meta-analysis provided evidence that frequent active seizures contributes to the development of myocardial dysfunction and the risk for sudden death may be reduced through optimization of antiepileptic medications to eliminate seizures. Autopsy studies of the heart in epileptic subjects with sudden unexplained death demonstrated subtle cardiac morphological changes in the form of fibrosis, apoptosis, atrophy, cardiomyocytes vacuolization and deposition of extracellular matrix (Bu et al., 2017).

Among our studied children there was significant association between epilepsy severity score and worse right ventricular performance. In accordance with our findings, frequent active seizures induce hypoxia, promote free radical formation and increase oxidation stress causing direct myocardial

injury. Furthermore, seizures induced sympathetic overactivity lead to altered calcium handling by cardiomyocytes causing ventricular stiffness and impaired function (Fialho et al., 2019). Postictal catecholamine surge may contribute to neurogenic stunned myocardium causing stress cardiomyopathy (Nass et al., 2019), (Oduah & Iwanowski, 2020). Alehan et al (2009) reported increased serum level of brain natriuretic peptides and a cardiac-specific creatine kinase in subjects with epilepsy suggesting subtle seizure induced myocardial injury in such patients. Repeated injury leads to remodeling of myocardium that later on predispose to cardiac dysfunction and contribute to increased cardiac mortality among patients with epilepsy. Read et al (2014) found that medications to decrease the sympathetic overactivity in animal models of status epilepticus provide a promising therapeutic modality to decrease seizure-induced cardiac injury. Histological examination of animal model of epilepsy showed that the main cardiac findings in subjects with SUDEP were cardiac hypertrophy and fibrosis. Post ictal histological changes include myocardial inflammatory cells infiltration, edema, and hemorrhage (Damasceno et al., 2013). Experimental models of induced recurrent seizures revealed accumulated cardiac damage that adversely interfere with cardiac conductive system and impair myocardial performance predispose those subjects to SUDEP (Akyuz et al., 2020). P-Codrea Tigaran (2005) postpartum cardiac histological examination found that 40% of SUDEP subjects had myocardium fibrotic changes in comparison to 6.6% of non-epileptic subjects with sudden death.

Çelik et al (2018) found that despite normal ejection fraction detected by conventional echocardiography, myocardial strain analyses showed abnormal myocardial deformation index in children with epilepsy. However, there was no significant correlation between two-dimensional Speckle Tracking echocardiography parameters and seizure types. Schreiber et al (2020) demonstrated systolic ventricular dysfunction in children with drug resistant epilepsy that was not related to epilepsy characteristics. Prolonged exposure to sympathetic overactivity contribute to cardiac ischemia, induce remodeling and fibrosis, leading to decreased ventricular performance (Verrier et al., 2020).

In contradictory to previous study, we could not detect any rhythm abnormalities among our studied children. This could be explained by using conventional electrocardiographic recording rather than holter recording which is less sensitive to detect rhythm changes. Also we evaluate children in between seizures attacks; most rhythm abnormalities develop mainly during seizure activities.

The present research had some limitations, including a limited number of participants and a cross-sectional design that prevented us from establishing a cause-and-effect link, and lacking of follow up of those children to evaluate whether myocardial dysfunction is temporary or cumulative. Longitudinal large scale multicenter studies are required. It's possible that the absence of variations or relationships in cardiac measurements across epilepsy subgroups is due to the fact that this research only included kids with refractory epilepsy, who are more susceptible to SUDEP risk factors than the general juvenile epilepsy population. To thoroughly explore the relevance of cardiac strain across the different patient groupings, more individuals spanning the range of epilepsy and SUDEP risk, as well as repeated assessments on patients, are required.

5. Conclusion

Children with epilepsy are liable for impaired systolic and diastolic function especially those with drug resistant epilepsy. Speckle tracking modality of echocardiography allows early detection of subclinical cardiac impairment in children with epilepsy. Assessment of cardiac function using advanced modalities of echocardiography may improve identification of those at higher risk for cardiac adverse events allowing early implementation of supportive care.

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Table-1: Comparison of conventional echocardiographic Doppler right ventricular parameters (M-mode& 2Dimension echocardiography) between children with refractory epilepsy and healthy controls

Parameter	Epilepsy group n=40	Control group n=40	T test	P value
RVEDD (mm)	26.97±4.05	24.93±3.91	1.977	0.053
RVESD (mm)	16.30±2.56	14.88±2.79	2.059	0.044*
RVEF%	66.00±2.90	68.17±6.25	-1.723	0.090
Basal-RVD(mm)	30.13±2.72	29.30±2.49	1.236	0.222
Mid-RVD (mm)	22.16±2.31	21.93±1.59	0.456	0.650
Long-RVD (mm)	67.63±3.64	71.30±4.36	-2.602	0.032*****
TAPSE (mm)	2.25±0.29	2.16±0.19	1.392	0.169
RV-FAC %	44.40±3.02	44.36±2.93	0.043	0.966

* significant (p-value <0.05)

Table-2: Comparison of conventional right ventricular Doppler flow parameters between children with refractory epilepsy and healthy controls

Parameter	Epilepsy group n=40	Control group n=40	T test	P value
TV-E vel (m/s)	0.75±0.32	0.71±0.20	0.495	0.623
TV-A vel(m/s)	0.71±0.26	0.53±0.17	3.221	0.002*
TV-E/A ratio	1.09±0.38	1.39±0.31	-3.282	0.002*
TR vel (m/s)	2.62±0.33	2.17±0.25	5.908	0.000*
TV-SPG (mmHg)	12.83±3.75	13.50±3.42	-0.686	0.495
RV Tei index	0.44±0.13	0.36±0.06	2.859	0.006*

* Significant; ** highly significant.

Table-3: comparison of right ventricular parameters as measured by tissue Doppler imaging and spiked tracking echocardiography between the studied groups

Parameter	Epilepsy group n=40	Control group n=40	T test	*P value*
Free-Sa (cm/sec)	12.67±0.71	13.24±0.29	-4.032	<0.0001*
Free-Ea (cm/sec)	9.55±2.55	11.04±1.16	-2.916	0.005*
Free-Aa (cm/sec)	10.38±1.76	10.06±1.19	0.836	0.407
E/Ea	8.01±2.99	6.52±1.92	2.297	0.025*
TD-derived RV strain %	25.32±3.72	32.87±2.89	-8.783	<0.0001*
STE-RVGST	21.98±2.48	28.10±2.12	-10.280	<0.0001*

* Significant

Table 4: Correlation of age of onset and duration of epilepsy and echocardiographic findings of children with epilepsy

	Onset		**duration**		**score**	
	r	p-value	r	p-value	r	p-value
RVEDD (mm)	0.052	0.748	-0.101	0.537	-0.112	0.49
RVESD (mm)	0.151	0.353	-0.234	0.147	-0.215	0.183
RVEF%	0.266	0.098	-.345*	0.029	-0.125	0.442
TAPSE (mm)	0.179	0.269	-0.160	0.326	-.322*	0.043
PAT (ms)	-0.016	0.921	-0.014	0.933	0.019	0.905
TR vel (m/s)	0.008	0.959	0.025	0.877	-0.046	0.780
PASP (mmHg)	0.006	0.972	0.016	0.921	0.09	0.581
TV-E vel (m/s)	-0.179	0.270	0.184	0.257	0.170	0.294
TV-A vel(m/s)	-0.012	0.940	-0.093	0.570	-0.005	0.976
TV-E/A ratio	-0.089	0.587	0.251	0.118	0.243	0.130
RV Tei index	-0.508	0.001*	0.541	<0.0001*	0.466	0.002*
free-Sa (cm/sec)	-0.009	0.955	-0.014	0.931	-0.148	0.362
free-Ea (cm/sec)	-0.256	0.110	0.282	0.078	0.229	0.155
free-Aa (cm/sec)	0.214	0.185	-0.163	0.315	-0.199	0.219
E/Ea	-0.055	0.735	0.041	0.802	0.042	0.798
TD-RV strain %	0.690	<0.0001*	-0.780	<0.0001*	-0.708	<0.0001*
STE-RVGST	0.772	<0.0001*	-0.898	<0.0001*	-0.769	<0.0001*
Basal-RVD(mm)	0.129	0.429	-0.163	0.315	-0.101	0.534
Mid-RVD (mm)	-0.081	0.621	-0.010	0.951	-0.049	0.762
Long-RVD (mm)	-0.197	0.223	0.255	0.113	0.039	0.809
RV-FAC %	0.166	0.307	-0.287	0.072	-0.241	0.134

* Significant (p-value <0.05)