Original Research Article

Cardiac Troponin (cTnI) Level and Myocardial Functions in Children with Idiopathic Convulsive Status Epilepticus

Abstract

Background:A Seizure represents the clinical expression of abnormal, excessive, synchronous discharges of neurons residing primarily in the cerebral cortex.The aim of this study is to evaluate the myocardial functions and serum cardiac troponin (cTn-I) in children with convulsive status epilepticus without evidence of previous cerebrovascular diseases.

Methods: This study was a case control study which was carried out in the duration of 1 year from December 2021 to December 2022in Tanta University Hospital, Pediatric Department, Intensive care unit (ICU) and the emergency room. The diagnosis of status epilepticus had been made in accordance with the criteria of the International League against Epilepsy clinically as a generalized seizure (epileptic seizure with duration more than 5 minutes or recurrent again without regaining consciousness in between seizures). Another thirty (30) healthy children (16 males, 14 female) with age range from (3-15) years, with the mean age was (6.367±3.449) years, with no history of epilepsy or family history of neurological diseases, were enrolled in this study and were served as control group. Inclusion criteria were no sex predilection, Patients with age of (3-15) years, and children with convulsive status epilepticus. Convulsion type with duration more than 5 minutes or recurrent again without regaining consciousness in between seizures.

Results: There was significant increase in serum level of cardiac troponin cTn-I among children with idiopathic convulsive status epilepticus than healthy Control children, (P <0.001*).All patients with elevated serum levels cTn-I had documented ECG changes. The

test result had a high positive predictive value which indicates high specificity of the of mean serum level of cardiac troponin test and that, Children have high probability of having myocardial ischemia and injury following attacks of idiopathic convulsive status epilepticus.**Conclusions:**Convulsive status epilepticus triggers severe physical activities, while skeletal muscle contraction increases the cardiac afterload in the tonic stage, leading to a transient imbalance in the cardiac tissue demand, which is associated with myocardial cell damage. Neural-hormonal factors contribute to myocardial cell damage (e.g., prolonged seizure activity that occurs in status epilepticus).

Keywords: Cardiac Troponin (cTnI), Myocardial,Children , Idiopathic Convulsive Status, Epilepticus

Introduction:

A Seizure represents the clinical expression of abnormal, excessive, synchronous discharges of neurons residing primarily in the cerebral cortex.[1]This abnormal paroxysmal activity is intermittent and usually self-limited, lasting seconds to a few minutes.[2]The clinical diagnosis of Epilepsy usually requires the occurrence of at least one unprovoked epileptic seizure with either a second such seizure or enough EEG and clinical information to convincingly demonstrate an enduring predisposition to develop recurrences.[3]Epilepsy is considered to be present when 2 or more unprovoked seizures occur in a time frame of longer than 24 hours.[4]Status epilepticus (SE) is the most common pediatric neurological emergency, previously; [5]status epilepticus was defined as a seizure with duration equal to or greater than 30 minutes, or a series of seizures in which the patient does not regain normal mental status between seizures.[6]The Neurocritical Care Society guidelines revised the definition to a seizure with at least 5 minutes of continuous clinical and/or electrographic seizure activity, or recurrent seizure activity without recovery between seizures.[7]This new definition has been favored and generally accepted to emphasize the risks involved with the longer durations of seizures as it become more difficult in treatment, can progress to refractory statutsepilepticus (RSE) and lead to significant morbidity or mortality.[8]

Pediatric status epilepticus has several causes, identification of these causes is important to the overall therapeutic approach to the child's illness and the formulation of prognosis,on the basis of the etiology, children with SE can be divided into the following groups: Febrile SE, symptomatic SEand idiopathic SE.[9]

Febrile status epilepticus (FSE) is the most common cause of SE in pediatric group, and it occurs in up to 5% of all cases of febrile seizures.[10]Children with FSE are at high risk for development of acute brain insult as hippocampal injury and subsequent temporal lobe epilepsy (TLE). [11]Symptomatic causes of SE include many factors such as Acute head

trauma, intracranial hemorrhage, ischemic (arterial or venous) stroke, brain tumors, brain malformations, hypoxic ischemic injury (e.g., after cardiac arrest).[12]CNS Infections such as meningitis, encephalitis, meningoencephalitis, and acute disseminated encephalomyelitis (ADEM) also play a role in development of SE.[13]About 9% of causes of status epilepticus are caused by drug or poison such as: tricyclic anti-depressant toxicity (TCA), or other psychotropic medications toxicity.These findings potentially change the method of monitoring and managing children with CSE.

Cardiac troponin I (cTnI) is a myofibrilliar structural protein in myocardial cells used as a highly specific and sensitive serum biomarker for diagnosis of acute myocardial infarction.[14, 15]however,it has been shown that other conditions including cardiac amyloidosis,pheochromocytoma, carcinoid syndrome,and massive pulmonary emboli can be presented with elevated serum level of cTnI.

Although there are several controversial studies about serum level of cTnI after CSE.[16]Some studies have reported elevated serum level of cTnI after uncomplicated CSE. [17]meanwhile, several investigations reported contradictory results with respect to the value of monitoring cTnI in epileptic seizures.[18] Additionally, an association between serum level of cTnI and number of previous seizures in children with uncomplicated CSE has been shown. [17]In another study, an increasing serum level of cTnI was demonstrated in complicated (generalized convulsive SE) as well.[19]

The aim of this study is to evaluate the myocardial functions and serum cardiac troponin (cTn-I) in children with convulsive status epilepticus without evidence of previous cerebrovascular diseases.

Patients and Methods:

This study was a case control study which was carried out in the duration of 1 year from December 2021 to December 2022.This study was carried out in Tanta University Hospital,

Pediatric Department, Intensive care unit (ICU) and the emergency room. This study was done after informed consent from the parents.

In this study, thirty (30) children with idiopathic convulsive status epilepticus with the age ranging from (3-15) years, with the mean age was (7.780±3.661) years, (17 male, 13 female), were selected from those admitting the intensive care unit (ICU) and the emergency room of pediatric department, Tanta university.

The diagnosis of status epilepticus had been made in accordance with the criteria of the International League against Epilepsy clinically as a generalized seizure (epileptic seizure with duration more than 5 minutes or recurrent again without regaining consciousness in between seizures).None of these cases had history ofprevious cerebral disease either metabolic, demyelinating brain disease or with family history of early heart diseases or history of cardiac disease due to congenital or acquired cause.

Another thirty (30) healthy children (16 males, 14 female) with age range from (3-15) years, with the mean age was (6.367±3.449) years, with no history of epilepsy or family history of neurological diseases, were enrolled in this study and were served as control group.

Inclusion criteria were no sex predilection, Patients with age of (3-15) years, and children with convulsive status epilepticus.Convulsion type with duration more than 5 minutes or recurrent again without regaining consciousness in between seizures.

Exclusion criteria were patients with non-convulsive status epilepticus, patients with pseudo-seizure, Patient with previous cerebral disease either metabolic or demyelinating brain disease, Patients with history of cardiac disease due to congenital or acquired cause.Family history of early heart diseases, Obese children, and children with diabetes mellitus.

All children were subjected to the following:Full history taking: Careful history taking as name, age, sex and the careful neurological history regarding convulsion’s time of onset, course, frequency, severity and duration, Past and family history of epilepsy, Antiepileptic

drug intake regarding dose, duration and frequency, Control of seizures by medication, Type of seizures. Clinical examinationtthorough: General, respiratory, cardiac and abdominal examination.Local examination with special emphasis on full neurological examination with stress on mental status, cranial nerve affection, muscle tone, muscle power and reflexes.

Routine neuroimaging& electro-physiological study for children with Status epilepticus after control of status epilepticus:

Magnetic resonance imaging (MRI):MRI was done for children with status epilepticus for exclusion of underlying structural cause such as tumors, abscess, old stroke or mesial temporal sclerosis.Electroencephalogram (EEG):EEG was done for children with status epilepticus for assurance whether the seizure is epileptic or another paroxysmal event, focal or generalized, and if it belongs to specific syndrome.ECGs were done using 3 channels a 1000 apparatus and were initially classified by defining specific parameters of conduction abnormalities, ischemic changes, rhythm abnormalities, and their frequency of occurrence.

Echocardiography: was done using M mode, 2 D, Doppler and tissue Doppler to determine cardiac function using vivid 7 ultrasound machine (GE Healthcare, Horten, Norway, with 3.5 and 4S multi-frequency transducers).

Blood samples were obtained from all cases and control groups for the following:

Measurement of **serum cardiac troponin (cTn-I)** for all children.Measurement of Liver function tests (LFT), kidney function tests (KFT), serum sodium, potassium, magnesium, phosphorus, arterial blood gases (ABG) and random blood sugar (RBS).

Quantitativedetermination of cardiac troponin-I in human serum by chemiluminescent immunoassay (CLIA) processed by iFlash immunoassay analyzer:

Intended use:The iFlash-Troponin-I assay is a paramagnetic particle chemiluminescent immunoassay (CLIA) for the quantitative determination of Troponin-I in human serum and plasma using the iFlash Immunoassay Analyzer.

Assay principle: The iFlash-Troponin-I assay is a sandwich immunoassay.

Incubation: Troponin-I in the sample, anti-Troponin-I coated paramagnetic microparticles and antiTroponin-I acridinium-ester-labeled conjugate react to form a sandwich complex.

Wash: The unbound materials are washed away from the solid phase in a magnetic field.

Trigger of signal: The Pre-Trigger and Trigger Solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs).

A direct relationship exists between the amount of Troponin-I in the sample and the RLUs detected by the iFlash optical system.

Results are determined via a calibration curve, which is instrument-specifically generated by 3-point calibration and a master curve provided via the reagent QR code.

Quantitative determination of phosphorus in human serum:

Supplied by Biotecnica Instruments SpA Company.

Principle of the method:

In sulfuric acid solution phosphate react with ammonium molybdate to form a yellow phosphorus molybdate complex. maximum complex absorption is at 340 nm. It is proportional to the concentration of inorganic phosphate in the sample.

Quantitative determination of Magnesium in human serum:

Method: Phosphonazo l, Colorimetric Endpoint.

Assay Principle:

Magnesium ions form a colored chelate complex when reacting with PhosphonazolI, the intensity of the color is proportional to the magnesium concentration. Calcium ions are masked by EGTA (ethylene glycol-bis (β-aminoethyl ether)- tetraacetic acid).

Quantitative determination of random blood sugar, liver function test and renal function test: Is done by BT1500 automated system analyzer.

Determination of sodium, potassium and arterial blood gase in human serum:

Is done by Siemens RAPIDLAB 348 automated system analyzer.

Results:

There was no significant difference between children with idiopathic convulsive status epilepticus and the healthy control children as regard to the age.There was no significant difference between Children with idiopathic convulsive status epilepticus and the healthy Control children as regard to the Sex, **(P > 0.05.).Table (1)**

Table (1): Comparison between children with idiopathic convulsive status epilepticus and healthy control children as regard age and sex.

Age (Years)	**Group**						**T-Test**	
	Case			**Control**			**t**	**P-value**
Range	5	-	14	5	-	15	-1.949	0.056
Mean ±SD	7.733	±	3.172	9.233	±	2.775		

Sex	**Group**						**Chi-Square**	
	Case		**Control**		**Total**			
	N	**%**	**N**	**%**	**N**	**%**	**X^2**	**P-value**
Male	17	56.67	16	53.33	33	55.00	0.067	0.795
Female	13	43.33	14	46.67	27	45.00		
Total	30	100.00	30	100.00	60	100.00		

Electrocardiographic findings among children with idiopathic convulsive status epilepticus**:**

ECG changes were present in **56.67**% (17 out of 30) of children with idiopathic convulsive status epilepticus in the first 6h. The most frequently observed ECG abnormalities were: **Conduction abnormalities, Ischemic change, and Arrhythmias** respectively.

Arrhythmias were observed in **5** patients in the form of sinus bradycardia in **2** patients, atrial fibrillation/flutter in **2** patient, and premature atrial contractions (PACs) in **l** patient**.**

Ischemic changes were detected in **6** patients. The most common ischemic changes were: T wave inversion changes detected in **3** patients, followed by ST segment depression in **2** patients, and ST elevation in **1** patient.**All of these patients with ischemic changes had elevated serum levels of cTnI.Conduction abnormalities** were detected in **6** patients including **2** patients with shortened QTc interval due to high catecholamines,

1 patient with prolonged PR interval, **1** patient with left bundle branch block (LBBB), **1** patient with right bundle branch block (RBBB), and **1** patient with AV block (AVB).**Table (2)**

Table (2): Electrocardiographic findings among children with idiopathic convulsive status epilepticus.

ECG Affected		
Case	**N**	**%**
Arrhythmias	5	29.41
Conduction abnormalities	6	35.29
Ischemic changes	6	35.29
Total	17	100.00

Echocardiographic findings among children with idiopathic convulsive status epilepticus revealed that: Echocardiographic changes were present in 60% (18 out of 30) of children with idiopathic convulsive status epilepticus. Ejection Fraction (EF) and Fraction Shortening (FS) were significantly lower in children with idiopathic convulsive status.

There was significant increase in Left ventricular end diastolic diameter (LVEDD) and Left ventricular end systolic diameter (LVESD) in children with idiopathic convulsive status epilepticus. There was slight increase right ventricular diameter (RVD) in children with idiopathic convulsive status epilepticus.As regard to conventional E/A ratio (E wave/ A wave), which reflect function of the left ventricle of the heart, abnormality was noted among children with idiopathic convulsive status epilepticus. Tissue Doppler examination revealed early decrease in LV systolic function and in RV diastolic function in children with idiopathic convulsive status epilepticus.**Table (3)**

Table (3): Echocardiographic findings among children with idiopathic convulsive status epilepticus.

ECHO Affected		
Case	**N**	**%**
Low EF, FS	9	50.00
High LVESD, LVEDD	5	27.77
Abnormal E/A ratio	1	5.55
Increase in RVD	1	5.55

Decrease in LVSF, RVDF	2	11.11
Total	18	100.00

There was **significant increase** in serum level of cardiac troponin cTn-I among children with idiopathic convulsive status epilepticus than healthy Control children, **(P <0.001*).**

All patients with elevated serum levels cTn-I had documented ECG changes.**Table (4)**

Table (4): Comparison between serum level of cardiac troponin (ng/dl) in children with idiopathic convulsive status epilepticus and the healthy control children.

cTn (ng/ml)	**Group**						**T-Test**	
	Case			**Control**			**T**	**P-value**
Range	0.01	-	0.6	0.01	-	0.05	5.559	<0.001*
Mean ±SD	0.173	±	0.152	0.018	±	0.013		

* Statistically significant at p <0.05

Table (5) show percentage of Sensitivity, Specificity, Accuracy, positive predictive value and negative predictive value of mean serum level of cardiac troponin test result. The test result had a high positive predictive value which indicates high specificity of the of mean serum level of cardiac troponin test and that, Children have high probability of having myocardial ischemia and injury following attacks of idiopathic convulsive status epilepticus.**Table (5),Figure (1)**

Table (5): Show Sensitivity, specificity, Accuracy, positive predictive value and negative predictive value of cardiac troponin test result.

ROC curve between Case and Control						
	Cutoff	**Sens.**	**Spec.**	**PPV**	**NPV**	**Accuracy**
cTn (ng/ml)	>0.03	86.67	90.00	89.7	87.1	90.4%

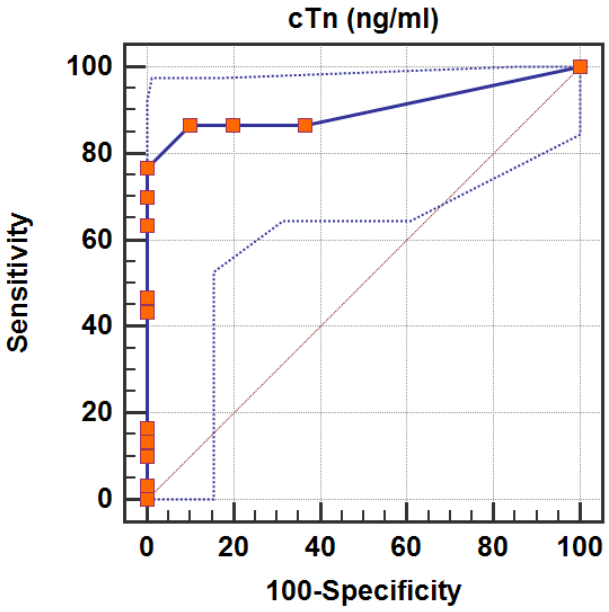

Figure (1): Show Sensitivity, specificity, Accuracy, positive predictive value and negative predictive value of cardiac troponin test result.

Discussion:

This study was carried out to evaluate cardiac Troponin (cTn-I) and myocardial functions in children with idiopathic convulsive status epilepticus.

Status epilepticus is defined clinically as a seizure or series of recurring seizures lasting for more than 30 min although there is a consensus now, that single seizure exceeding 5–10 min should be treated as SE.[20]

The results of this study showed that; **ECG changes** were present in **56.67 %** of children with CSE in the form of conduction abnormalities, ischemic changes, and arrhythmias respectively, all of these patients with ischemic changes had elevated serum levels of cTn-I.

Arrythmia were in the form of sinus bradycardia, atrial fibrillation/flutter and premature atrial contractions (PACs), Ischemic changes were in the form of T wave inversion changes, followed by ST segment depression, and ST elevation, Conduction abnormalities were in the form of shortened QTc interval due to high catecholamines, prolonged PR interval, left bundle branch block (LBBB), right bundle branch block (RBBB), and AV block (AVB).

Echocardiographic abnormalities were present in **60%** of children with CSE and revealed; a significant increase in left ventricular end-diastolic dimension (**LVEDD**) and left ventricular end systolic dimension (**LVESD**) in children with CSE.

Moreover, a significant decrease in LV systolic function and RV diastolic function were detected by tissue Doppler in children with convulsive status epilepticus, Ejection Fraction (**EF**) and Fraction Shortening (**FS**) were significantly lower in children with convulsive status epilepticusn , there was slight increase right ventricular diameter **(RVD)**, And as regard to **conventional E/A ratio** (E wave/ A wave), which reflect function of the left ventricle of the heart, abnormality was noted among children with convulsive status epilepticus.

The mean plasma concentrations of cTn-I were significantly higher in children with convulsive status epilepticus 'CSE' than the control group, all patients with elevated plasma cTn-I levels had documented ECG changes.

This study agree with the result of the study obtained by **Ibrahim, A, et al.,**[21], who had studied serum level of cardiac troponin (cTn-I) and myocardial functions in the form of electrocardiography (ECG) and echocardiography changes in children with convulsive status epilepticus.

This prospective observational study included (74) children with CSE, Cardiac injury was evaluated and defined using combination of; cardiac troponin, electrocardiography (ECG) and echocardiography. Thirty-six (48.6%) children demonstrated markers of cardiac injury; ECG changes occurred in (45.9%) and echocardiographic signs of left ventricular systolic and diastolic dysfunction reported in (5.4%) and (8.1%), respectively, mean serum level of cardiac troponin was significantly higher in children with convulsive status epilepticus than healthy control group.

So, the results of the present study agree with this study as regard to; cardiac injury among children with convulsive status epileptics is common, in the form of; elevated serum level of cardiac troponin, electrocardiography (ECG) abnormalities and Echocardiographic affection.

The result of this study agree with the result of the study obtained by **Castle, Met al.,**[22]who had studied cardiac involvement in children with acute neurologic disease as "convulsive status epilepticus",by use of cTn-I level, ECG and echocardiography to determine the incidence of cardiac injury in children with acute neurologic illness and then to define its clinical correlates. This study included total number of eighty nine (89) children with CSE,all children underwent 12-lead ECG and 2-dimensional echocardiography, and blood samples were obtained for measurement of cTn-I serum level. This study had shown that; (50%) n: 45 children with CSE had elevations of cTnI levels(≥0.4 µg/L), and Overall, 23 patients (35%) in the entire cohort study had ECGs suggestive of cardiac injury. Echocardiographic abnormalities in the form of global right or left ventricular dysfunction or regional wall-motion abnormalities were seen in 20 (23%) of 89 children who underwent echocardiography on hospital admission, Ten patients had global ventricular dysfunction and 10 had regional wall-motion abnormalities, Two patients had a combination of global dysfunction with more pronounced regional changes.

So, this study agrees with the result of the present study as regard to There is a substantial prevalence of myocardial injury in the form of elevated cardiac troponin level cTn-I, ECG abnormality and affection of echocardiography in children with acute neurologic illness such 'CSE' which seems to adversely affect prognosis of status epilepticus.

The results of this study are contradictory to the results obtained by **John M. Schreiber, et al.,** [23]who had studied myocardial dysfunction in children with convulsive status epilepticus (CSE).

Two children were enrolled in this study after being admitted in the hospital for convulsive status epilepticus (CSE) and were re-evaluated 4–8 weeks after discharge in the outpatient cardiology clinic, Children underwent a focused echocardiography protocol on a standard ultrasound machine (Philips Healthcare iE33). Apical four-chamber and parasternal short-axis images were acquired for evaluation, and conventional echocardiographic measures including EF, fraction shortening (FS), mitral inflow E wave velocity, and lateral tissue Doppler E' velocity were recorded, Also ECG were done for children following attack of CSE.

Convulsive status epilepticus can cause physical and mental stress that can trigger metabolic and cardiorespiratory changes. In fact, CSE often activates the autonomic nervous system, increasing the sympathetic discharge causing massive catecholamine release and subsequent neurogenic myocardial stunning, resulting in the formation of cardiac contraction bands that lead to subtle structural and functional myocardial damage with a cardiac contractile dysfunction and high incidence of arrhythmia, stress-related cardiomyopathy, and heart failure, (348) Moreover, cardiac injury in CSE may be iatrogenic due to intravenous fluid overload and cardio-depressive effects of anti-seizure medications (ASMs), and that's all may represent the cause of death in CSE.[24]The results of the present study support the hypothesis of a **"reversible ischemia model"**[25] due to a temporarily reduced coronary blood flow; this hypothesis proposes an autonomic involvement resulting from alterations of the central nervous system, predominantly causing a sympathetic over activity that lead to tachycardiac ischemia effect. [26]

In the present study, Serum cTn-I level exceeded the normal level in children with idiopathic convulsive status epilepticus with no evidence of myocardial infarction or history of cardiac duisease; therefore, cardiac monitoring of patients with convulsive status epilepticus may be helpful in the ictal and postictal phases for evaluating cardiac injury.

Some researchers explain that;[27] an increase in troponin level after a convulsive status epilepticus arises from the release of unbound cytosolic troponins due to the increased permeability of myocardial cell membranes and damage to myocytes, while others believe that an increase in the troponin content suggests a transient myocardial injury,[28] In this regard, another study suggested that the increased level of CTnI could be a risk factor for convulsive status epilepticus in children.[29]

Echocardiographic evaluation in this present study revealed significant increase in LVESD and LVEDD in children with CSE and significant decrease in LV systolic function and RV diastolic function, slight increase in RVD, Ejection Fraction (EF) and Fraction Shortening (FS) were significantly lower in children with convulsive status epilepticusn, And as regard to conventional E/A ratio (E wave/ A wave), abnormality was noted among children with convulsive status epilepticus. **This can be explained by** the effect of high levels of sympathetic activity, catecholaminergic toxicity, microvascular ischemia, and anesthetic drugs are believed to be potential causes, leading to structural and functional myocardial alterations, a heart failure-like phenotype and cause dilatation of the left ventricle with subsequent increase in LVESD, LVEDD and can lead to stress induced cardiomyopathy (Takotsubo cardiomyopathy) or atypical form of it which was reported after CSE and could decrease cardiac output affecting the tissue oxygen supply and predispose to arrhythmias and cardiac ischemia.[30]

ECG changes in this study were present in **56.67 %** of children with CSE in the form of conduction abnormalities, ischemic changes, and arrhythmias respectively; Arrhythmia varies from bradyarrhythmia in some cases and tachyarrhythmia in other cases

This variation could be explained by difference of seizure onset. If a seizure onset started at left hemisphere, bradycardia would occur and if seizure onset started at right hemisphere,

tachycardia would occur. Moreover, convulsive seizures stimulate sympathetic activity and catecholamine release leading to tachyarrhythmias.[31]

Several recent studies[32, 33]have attempted to investigate the brain–heart relationship in the setting of status epilepticus,Some investigators;[32]explained increased risk of cardiac arrhythmias with status epilepticus by malfunctioning of the cardiac ion channels that control and regulate cardiac excitability, resulting from mutations in genes encoding ion channel subunits, This cardiac ion channel dysfunction has been proposed to underlie both status epilepticus and increased risk of cardiac arrhythmias Also , arrhythmiainpediatric CSE could be explained by severe tachycardia following the activation of the sympathetic nervous system that lead to myocardial ischemia, resulting in arrhythmogenic alteration in cardiac electrical activity.

The main limitation of the present study is that; this was a cross-sectional study, and baseline ECG and Echocardiography could not be obtained in most CSE children, so we couldn't exclude that ECG and echocardiographic changes were already existing in the patients before the CSE, but being reversible in the second ECG examination raise the suspicious that these cardiac changes were due to CSE itself. Another limitation in this study is that; there was no long term follow up for these patients to detect further adverse outcomes.

Conclusions: Convulsive status epilepticus triggers severe physical activities, while skeletal muscle contraction increases the cardiac afterload in the tonic stage, leading to a transient imbalance in the cardiac tissue demand, which is associated with myocardial cell damage.Neural-hormonal factors contribute to myocardial cell damage (e.g., prolonged seizure activity that occurs in status epilepticus). The imbalance of autonomic nervous system increases in the sympathetic nervous system, and significant release of catecholamine in blood during seizure can damage cardiac tissues, The increased myocardial wall tension, besides neural-hormonal stress, leads to troponin release associated with cardiac cell wall

damage, In the present study, this mechanism had greater effects on myocardial tissue damage due to hypoxia in seizures.

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