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Medicine

Interictal Electrocardiographic and Echocardiographic Changes in Seizure Patients without Cardiac Symptoms

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Abstract	Original Research Article

A seizure is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain and can cause characteristic changes in electroencephalogram (EEG), likewise it can cause changes in cardiac microstructure and can cause changes in ECG and ECHO. We have taken 120 non-diabetic seizure patients (case) and 62 non-diabetic patients without seizure (control) for this study randomly and standard 12 lead Electrocardiograms and a Echocardiographic (2D and M-MODE) examination performed in all of them in interictal period. Case (85 males and 35 females) and control (44 males and 18 females) had a mean age of 39.06±1.86 and 36.74±2.15 years; respectively. These two populations were also matched with respect to these following parameters (Height (m), Weight (kg), BMI (kg/m^2), and resting systolic and diastolic pressure (mm of Hg)). In univariate analysis, seizure patients (compared to controls) had significantly lower means or PR interval (146.0±1.49 vs 151.2±1.94 msec; p=0.0415), QT interval (361.2±2.51 vs 372.9±1.76 msec; p=0.0019), QTc interval (422.5±3.14 vs 439.2±2.35 msec; p=0.0005), Ejection fraction (EF) (63.51±0.62 vs 65.59±0.58%; p=0.0306),Fractional Shortening (FS) (34.65±0.43 vs 24±0.42%; p=0.0168).Only 18 cases and 2 controls presented with sinus tachycardia and 4 cases presented with sinus bradycardia when ECG and ECHO was done and none of the cases and controls showed any other tachy or bradyarrhythmias. Among 94 patients of GTCS 5(5.31%) died while death was significantly higher in Status Epilepticus 2(66.67%) out of 3 patients. Patients with epilepsy may be predisposed to disturbances of autonomic functions with subsequent cardiac arrhythmias due to effects of recurrent seizures on cardiac microstructure. So, in all seizure patients ECG and ECHO to be done. Further work is needed to stratify the risk of sudden unexpected death in epilepsy (SUDEP) on the basis of interictal autonomic parameters to improve prognosis. The authors declare that there is no conflict of interest.
Keywords: Seizure, QT interval, Autonomic, SUDEP.

INTRODUCTION

Anatomic and functional connections between the heart and brain in both health and disease have long been established [1]. In recent days, the interaction of the heart and brain in patients with epilepsy has been the subject of vigorous scrutiny [2]. Cardiac arrhythmias also may play an important role in the pathogenesis of SUDEP. Erickson in 1939 studied ictal ECG changes for the first time systematically and reported tachycardia, cardiac arrhythmia and T-wave straightening secondary to a right temporal lobe seizure. Initial bradycardia followed by tachycardia was documented in as many as 64% of Focal seizure and 100% of generalized tonic clonic seizure attacks [3]. Nei *et al*. [4] documenting simultaneous EEG and ECG, reported tachycardia in 74-92% of complex partial seizures supporting study by Gilchrist [5]. Persistent bradycardia is less common and is reported in 3-7% of complex partial seizures only[6]. Ictal cardiac rhythm and conduction abnormalities have been documented in 5-42% of patients with partial seizures [7]. However only a few studies have evaluated interictal cardiac functions in patients with epilepsy and the pattern of interictal autonomic disturbance in patients with epilepsy is still debated. Therefore, we designed and conducted the current study to investigate the possible interictal ECG abnormalities in non-diabetic seizure patients, together with evaluating the presence and extent of any structural heart changes by Echocardiography in these patients in comparison with non-diabetic patients without seizure and any cardiac symptoms, taken randomly.

MATERIALS AND METHODS

From April 2017 to March 2018, we studied 120 patients (85 male and 35 female) aged 39.06 ± 1.86

years who were ethnically Central Indian and clinically diagnosed with seizures and the data of these patients were compared to the findings of 62 patients admitted in the Hospital attached to S.S. Medical College and SGMH, REWA due to diagnoses other than seizure (control) (44 male and 18 female) of age 36.74 ± 2.15 years. Both the groups were non-diabetic and didn't have any cardiac symptoms.

All participants underwent thorough history taking and complete general, cardiac and neurological examinations (which were generally unremarkable). Resting Systolic and Diastolic arterial Blood Pressure were recorded by a mercury sphygmomanometer as the average of the last 2 of 3 readings, each 5 minutes apart with the patient sitting.

In order to achieve the best homogeneity of these two population (case and control) and minimize the confounding factors, they were also matched with respect to these parameters (Height(m), Weight(kg), BMI(kg/m^2), resting systolic and diastolic pressure(mm of Hg)) and also we adopted the following inclusion and

Inclusion criteria
We included non-diabetic subjects diagnosed with seizure and ≥ 15 yrs of age.

Exclusion criteria
We excluded any participant with seizure like episodes (Hyperventilation, Narcolepsy, Movement disorder like choreoathetosis, tic disorders and Psychogenic seizures).We also excluded any participant

with clinical signs of autonomic dysfunction or disease affecting autonomic function (such as Diabetes Mellitus).

Statistical analysis
Comparisons of means of continous data across a factor with 2 levels were performed using Students' unpaired t-test. Proportions were compared using the χ2 test. A 2-sided significance level of 0.05 was used for all analysis, which was conducted using the computer programme Statistical Package for Social Sciences (SPSS 11.0), GraphPad Prism 6 and Systat 8.0. Microsoft word and Excel have been used to generate graphs tables etc.

Descriptive analysis was used to compute percentage, to calculate Mean and Standard deviation. The study protocol was reviewed and accepted by the Institute ethics committee (Human Studies) SSMC, Rewa and written informed consent was obtained from each participant. The authors declare the presence of no conflict of interest.

OBSERVATIONS AND RESULTS
The present study was carried out in between 120 x non-diabetic patients of seizure and 62 non-diabetic patients without seizures(control), admitted in medical wards, Department of medicine, S.S. medical college and Associated SGM Hospital, Rewa (M.P.).The baseline characteristics and comparisons between patients with seizure and patients without seizure (control) are shown in following tables—

Table-1: Demographics & Anthropometric measurements

	Variables		Cases (n = 120)	Controls (n = 62)	*P* value
Demographics	1. Age (Years)		39.06 ± 1.86	36.74 ± 2.15	0.443
	2. Gender	M	85 (70.83 %)	44 (70.96 %)	
		F	35 (29.17 %)	18 (29.04 %)	0.980
Anthropometric measurements	1. Height (in mts)		1.66 ± 0.008	1.67 ± 0.012	0.3064
	2. Mass (in kg)		58.27 ± 1.05	61.18 ± 1.07	0.0786
	3. BMI (in kg/m^2)		21.41 ± 0.43	22.12 ± 0.51	0.3184
	4. SBP (in mm Hg)		123.8 ± 2.36	128.1 ± 1.97	0.2297
	5. DBP (in mm Hg)		80.73 ± 1.10	83.10 ± 0.93	0.1595

Values are represented as the mean ± SD, or number of subjects (%). SBP and DBP indicates Systolic and Diastolic blood pressure respectively; BMI, body mass index. *P < 0.05.
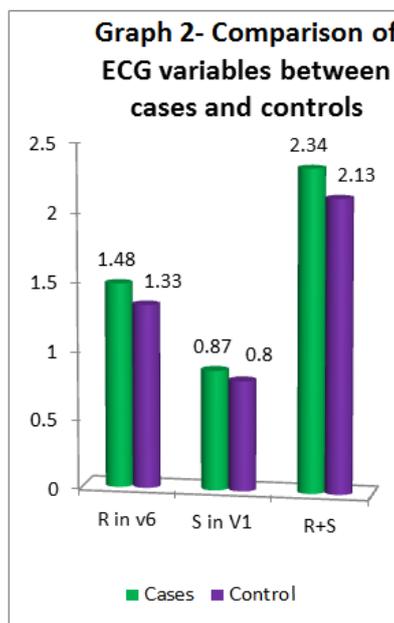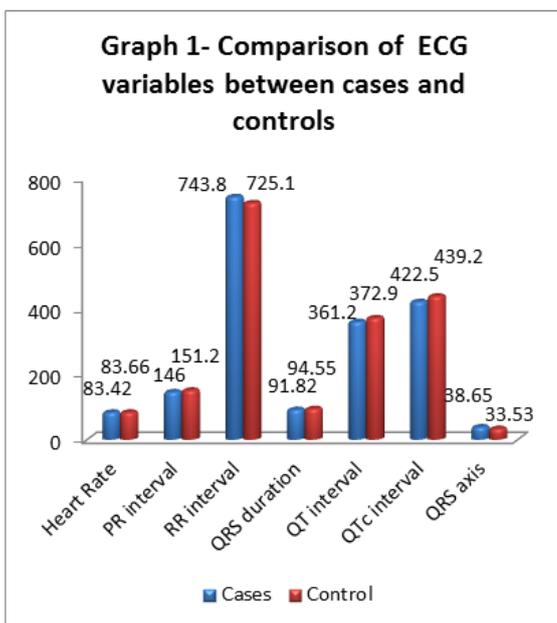
These two populations (cases and controls) were matched with respect to these parameters (Height (m), Weight (kg), BMI(kg/m^2), resting systolic and diastolic pressure(mm of Hg)) (p > 0.05).

Univariate analysis showed that seizure patients (compared to controls) had significantly lower

means of PR interval (146.0 ± 1.49 vs 151.2 ± 1.94 msec; p=0.0415), QT interval (361 ± 2.15 vs 372.9 ± 1.76 msec; p=0.0019), QTc interval (422.5 ± 3.14 vs 439.2 ± 2.35 msec; p=0.0005), FS (%) (34.65 ± 0.43 Vs 36.24 ± 0.42;P =0.0168) and EF(%) (63.51 ± 0.62 Vs 65.59 ± 0.58; p=0.0306). It should be noted that the shorter PR, QT, QTc intervals, Fractional Shortening (FS) and Ejection Fraction (EF) lie within the normal range for these variables (i.e, there is neither short PR,QT or QTc nor low FS and EF by definition). Shown in table 2.

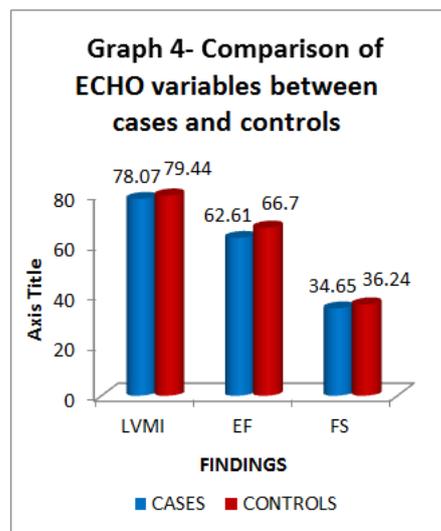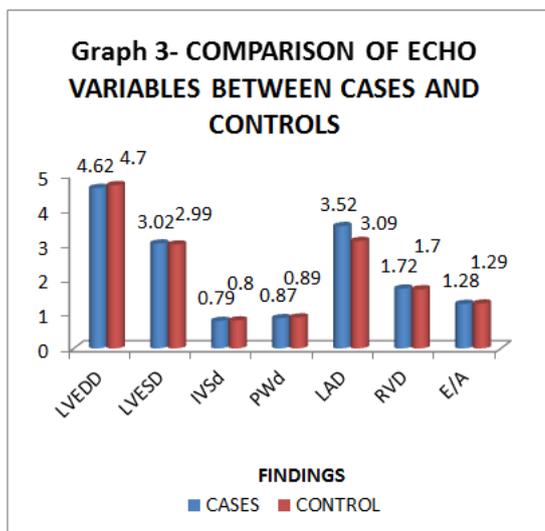**Table-2: Electrocardiographic and Echocardiographic findings**

	Electrocardiographic Findings			
	Parameters	Cases (n=120)	Controls (n=62)	P VALUE
1.	Heart rate (bpm)	83.42 ± 1.45	83.66 ± 1.13	0.9106
2.	PR interval (msec)	146.00 ± 1.49	151.22 ± 1.94	0.0415
3.	RR interval (msec)	743.80 ± 12.27	725.10 ± 9.70	0.3121
4.	QRS duration (msec)	91.82 ± 1.62	94.55 ± 1.35	0.2664
5.	QT interval (msec)	361.20 ± 2.51	372.90 ± 1.76	0.0019
6.	QTc interval (msec)	422.50 ± 3.14	439.20 ± 2.35	0.0005
7.	QRS axis (°)	38.65 ± 2.52	33.53 ± 1.82	0.1742
8.	R in V_6 (mv)	1.48 ± 0.054	1.33 ± 0.042	0.0605
9.	S in V_1 (mv)	0.87 ± 0.04	0.80 ± 0.03	0.2152
10.	R+S (mv)	2.34 ± 0.08	2.13 ± 0.53	0.0775
	Echocardiographic Findings			
1.	LVEDD (cm)	4.62 ± 0.03	4.70 ± 0.03	0.0821
2.	LVESD (cm)	3.02 ± 0.03	2.99 ± 0.02	0.4910
3.	IVSd (cm)	0.79 ± 0.01	0.80 ± 0.01	0.6087
4.	PWD (cm)	0.87 ± 0.01	0.89 ± 0.01	0.0644
5.	LAD (cm)	3.28 ± 0.02	3.26 ± 0.02	0.5710
6.	RVD (cm)	1.72 ± 0.02	1.70 ± 0.01	0.5093
7.	E/A ratio	1.286 ± 0.12	1.289 ± 0.11	0.8645
8.	LVMI (gm/m^2)	78.07 ± 1.57	79.44 ± 1.81	0.5905
9.	EF (%)	63.51 ± 0.62	65.59 ± 0.58	0.0306
10.	FS (%)	34.65 ± 0.43	36.24 ± 0.42	0.0168

Graph 1- Comparison of ECG variables between cases and controls

Graph 2- Comparison of ECG variables between cases and controls

DISCUSSION

Seizures cause challenging physical and mental stress that can cause peri-ictal metabolic and cardiorespiratory abnormalities [8]. In fact, partial and generalised seizures often affect the autonomic functions during the ictal as well as interictal and postictal periods by activation or inhibition of the areas in the central autonomic network that can cause cardiovascular, gastrointestinal, cutaneous, papillary, urinary and genital manifestations [9].

Graph 3- COMPARISON OF ECHO VARIABLES BETWEEN CASES AND CONTROLS

Graph 4- Comparison of ECHO variables between cases and controls

Cardiac Repolarization: Basic Mechanism

The QT interval, which reflects the global sum of intra-cellular action potential durations, is dependent on cycle-length. At faster heart rates the QT interval shortens. To adjust for rate effects a number of formulas have been proposed, relating QT interval to inter beat interval in order to normalize to the QT interval at a heart rate of 60 bpm, termed QT corrected (QTc).This "correction" is complex. Even under steady state, the relation between QT interval and inter beat intervals is not linear. When cycle length varies, QT interval is influenced by changes in the preceding cycle length (electrical restitution) and by preceding inter beat intervals (cardiac memory)[10]. So most correction formulas tend to over- or under-estimate QTc[11]. Bazett's formula ($QTc=QT/RR^{1/2}$) with RR being the interval between two consecutive R waves is commonly used but Fridericia's formula ($QTc=QT/RR^{1/3}$) probably has the least correction error [11, 12].

Linking to cardiac electrophysiology

Cardiac arrhythmias are caused by derangements in cellular cardiac electrophysiology, namely malfunctioning of the cardiac ion channels that control cardiac excitability. Disrupted depolarization (reflected by PR and QRS intervals on ECG) can facilitate tachyarrhythmias caused by re-entrant excitation and bradyarrhythmias resulting from heart block. By contrast, disrupted repolarisation (reflected by prolongation of the QT interval on ECG) can lead to triggered activity and may culminate into torsade de pointes, while very rapid repolarization (shortening of the QT interval) can facilitate reentrant excitation.

Indeed, ion channel dysfunction, resulting from mutations in genes encoding ion channel subunits, has been proposed to underlie both epilepsy and increase in the risk of cardiac arrhythmias [13-15].The cardiac effects of epilepsy are widespread and range from subtle changes in heart rate variability (HRV) to ictal sinus arrest; and from QT interval shortening to

atrial fibrillation [16]. Petkar *et al.* [17] conducted a preliminary study of 128 patients with severe refractory epilepsy and learning disability, and revealed interictal ECG abnormalities in approximately 60% of patients, including first degree atrio-ventricular block and poor r wave progression. However, Nei [18] in another study, suggest that serious cardiac arrhythmias are rare in ambulatory ECG recordings of epileptic patients. Similarly, long term data from patients with refractory epilepsy also suggest that serious cardiac arrhythmias during the interictal period are rare, but these studies documented that early morning bradycardia and asystole may occur [19, 20]. Transient abnormal QT shortening was found to frequently occur with GTCS seizures. The clinical importance of abnormal ictal QT shortening is currently unclear, but such a reduction in QT interval might be involved in pathophysiology of sudden death in epileptics (SUDEP) in the context of GTCS seizures [21-23]. Dogan *et al.* [24], Neufeld *et al.* [25] and Teh *et al.* [26] showed that epilepsy is associated with a shortened QTc interval. The PR interval is a measure of atrioventricular conduction speed. In accordance with our study a longer PR interval in epilepsy could be the result of extrinsic or intrinsic cardiac changes [27, 28] Keilson *et al.* [29] reported 20-24 hour ambulatory ECG-EEG findings in 338 consecutive patients with epilepsy and found that potentially serious cardiac arrhythmias were identified in 5.3% of patients and did not exceed the numbers seen in the general population.

In the present study, the interictal conduction was found to be disturbed (in the form of longer PR and shorter QT and QTc intervals); although these variables were frequently normal in some studies [29-31]. or showed only minor non-significant changes in others[32]. In line with our results transient abnormal QT shortening was found to frequently occur with GTCS seizures [33-35]. Shortening of the QT interval can be induced by raised catecholamine levels, hyperkalemia and acidosis [36-38] all of which are

conditions that occur during or shortly after GTCS seizures [39-41]. Antiepileptic drug-induced QT shortening might also occur with the use of carbamazepine, rufinamide or primidone [42-44].

Linking to Heart Rate Variability (HRV)

HRV is measured by the variation in the beat-to-beat interval and it can be an indicator of the effect of sympathetic and parasympathetic input to the heart [45-47] thus giving information about the ANS. Lower HRV is said to make patients more vulnerable to tachycardia and fibrillation and sudden cardiac death (SCD) [48,49].

Seizure onset within the neocortical and/or limbic cortices that are part of the complex network of the ANS may affect the autonomic output which can become apparent in multiple autonomic functions of the body [48, 50]. An important study performed by Oppenheimer *et al.* [51] in 1992 showed that stimulation of the left insular cortex (IC) provokes a HR decrease and depressor response and stimulation of the right IC provokes a HR increase and pressor responses. Evidence regarding it only been reproduced in electrically induced seizure not in studies "in real life" allowing discussion. The lateralization theory can be used to explain pressor responses seen in seizures originating from the temporal lobe (TLE) contrary to the depressor responses seen in extratemporal seizures (XTLE)[49,16,52]. Pressor responses in TLE could be the result of discharges in the right IC and depressor responses in XTLE could be the result of discharges in the left IC and amygdala. This theory would explain why Britton *et al.* [53] found bradyarrhythmia (a depressor response) to be stronger in association with bilateral hemispheric seizure discharges. However, cases of right hemispheric seizures associated with asystole (also a depressor response) exist, and this questions the lateralisation theory [54]. In a study of HRV in GTCS patients, Evrengul *et al.* [55] reported a reduction of the markers of parasympathetic activity and a reciprocal increase of the measure of sympathetic activity; concluding an increase in the sympathetic control of the heart rate in GTCS patients, which could play a key role in the development of ventricular tachyarrhythmias in patients with epilepsy that may be related to the higher incidence of SUDEP in this disorders as compared to controls. In a study conducted on 70 epileptic patients, Teh *et al.*[26] found that QTc was shorter in these patients (400 msec) than in the control group (420 msec), and half of the patients had a mean QTc shorter than 400 msec. Again, it is possible that the disparity between these studies may be, at least partly, due to the antiepileptic medication used [55].

In current study although mean heart rate (/min) among the cases (83.42 ± 1.45) compared to the controls (83.66 ± 1.13) is insignificant (p value = 0.9106); none of the cases and controls showed any tachy and bradyarrhythmia in interictal phase when ECG and ECHO was done, except for 18 cases and 2 controls presented with sinus tachycardia and 4 cases presented with sinus bradycardia.

Changes in cardiac structure

High levels of sympathetic activity can cause transient dilatation of LV walls that can lead to Takotsubo or stress-induced cardiomyopathy which was reported to occur with GTCS seizures, and could further compromise cardiac output leading to an insufficient peri-ictal supply of oxygen [56, 57]. Lemke *et al.* [58] reported that Takotsubo cardiomyopathy was associated with GTCS seizuresor consecutive to convulsive status epilepticus as per Legriel *et al.* [59] also. According to the cited authors, this cardiomyopathy form resulted from a sympathetic surge during seizures. The same mechanism could be quoted as a reasonable explanation of the decreased Ejection Fraction and Fractional Shortening in seizure patients compared to controls in our study; owing to long duration and frequent attacks of seizures to certain degree of altering the LV geometry [56, 57].

SUDEP and its relation to QTc Shortening:-

Sudden unexpected death in epilepsy (SUDEP) is defined as a sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death in a patient with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause for death[60]. Sinus tachycardia and mild central hypoventilation occur with seizures [30,61]. Central apnea, neurogenic pulmonary edema, bradycardia, and cardiac asystole can also occur [62-64]. That neurologic disease can result in cardiac arrhythmias is supported by observations that cortical networks regulate cardiovascular function and that brain injuries lead, by disrupting autonomic networks, to cardiovascular dysfunction [65]. The clinical relevance of drug-induced or otherwise acquired QTc shortening is unclear though [38, 66].

CONCLUSION

Patients with seizure (compared to controls) had significantly lower means of PR interval, QT and Qtc intervals which can precipitate cardiac arrhythmias and can increase SUDEP probability. The seizure patients had significantly lower Fractional shortening (FS) and Ejection fraction (EF) in ECHO emphasizing probable injury to the cardiac microstructure. Thus interictal ECG and ECHO should be done in all seizure patients and this can play a role in predicting cardiac arrhythmias and SUDEP. Further work is needed to stratify the probability of sudden unexplained cardiac death (SUDEP) on the basis of interictal autonomic parameters to improve prognosis.

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