Title: The Assessments of Electrocardiographic Parameters in the Patients with Drug-Resistant Temporal Lobe Epilepsy; A Case-Control Study

Running Title: ECG Parameters in Drug-Resistant TLE

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Abstract:

Introduction: Sudden unexpected death in epilepsy (SUDEP) is the substantial cause of death in patients with epilepsy (PWE). Electroconductive disorders leading to life-threatening arrhythmia are mostly hypothesized to play a crucial role; however, there is paucity of knowledge in variable among the patients with drug-resistant temporal lobe epilepsy (TLE) compared to the healthy controls.

Methods: The current case-control study has been conducted on 50 drug-resistant TLE patients as the cases and 50 age- and gender-matched healthy subjects selected from their first-degree family members. ECGs were taken when admitted at the hospital (base line), immediately after a seizure incidence and within an hour after the end of the seizure from the cases compared with a random ECG of the controls considering parameters including PR-, RR-, and corrected QT interval (QTc), P wave duration and heart rate (HR) variability.

Results: Shorter corrected QTc interval was notified among the drug-resistant TLE patients compared to the controls (P-value=0.017) in the base line taken ECGs, while the assessments immediately after the seizure revealed significant differences in terms of RR-interval (P-value=0.005) and heart rate (P-value=0.005). Post-ictal ECGs did not differ between the groups (P-value>0.05).

Conclusion: According to the findings of this study, shortened QTc interval at base line ECGs, shortened RR interval and increased HR during the seizure were the ECG elements affected in drug-resistant TLE patients; however, to generalize the outcomes, further studies are required.

Keywords: Sudden Unexpected Death in Epilepsy, Temporal lobe epilepsy, Cardiac arrhythmia, Electrocardiography

Introduction:

Sudden unexpected death in epilepsy (SUDEP) is the substantial cause of death in patients with epilepsy (PWE). SUDEP is defined as non-accidental, nonsuicidal death in the absence of documented status epilepticus or any other identifiable causes(1). This can occur at any ages, but mostly affect younger adults. The annual incidence rate of SUDEP differs according to the studied population, but it ranges from 0.35-to-9.3 per 1000 persons(2, 3). The risk of SUDEP increases considerably among drug-resistant PWE(4).

Epileptic seizures are accompanied by autonomic function alterations that can affect respiratory, cardiovascular, gastrointestinal, urinary and genital systems during the phase of epilepsy or early in the ictal phase(5, 6).The Cardiovascular system is the most noted system of the body due to its most crucial potential role in SUDEP. However, recent studies have focused on respiratory depression following seizure as a common cause of improper oxygenation(7).

Since long time ago, scientists were searching for an ambulatory, non-invasive, applicable means to early detect or forecast seizure incidence(8). Valuable outcomes have been achieved by electrocardiographic (ECG) studies. Significant increase in heart rate immediately before seizure initiation have been noted in 64-100% of the patients and ignited a theory in terms of vagal stimulation to prevent or shorten the seizure duration(9, 10).

Cardiac arrhythmia is another factor that maybe contributed to SUDEP. Studies in the literature have represented that patients with recurrent seizures are at two-to-three folds increased risk of arrhythmia development. A prospective long-term study represented that one-fourth of the PWE had clinically significant cardiac arrhythmia; even if no cardiac risk factor was detected(11, 12).

The underlying reason for cardiac variabilities in pre-seizure, seizure and postictal phases are attributed to catecholamine release primarily and then, due to the stimulated site of the brain(13, 14).

Cortical-stimulation studies notified that the left insular cortex was responsible for cardiovascular depressor response and bradycardia. Surprisingly, the opposite site acted as a stimulatory part. This characteristic was reinforced when ictal tachycardia was found by the occurrence of right hemispheric seizures in temporal lobe epilepsy (TLE) patients. However, further confirmatory investigations are required. The other part of the brain hypothesized to play a key role in neural regulation of the heart rate and rhythm is amygdala; however, further human studies revealed that the amygdala role to affect cardiac function was not to the expected extent. Nevertheless, widespread involvement of the unilateral limbic system is required to remarkably modulate the cardiac function(10).

Most of the previous studies have focused on ECG alternations in periictal period. We conducted this study to evaluate the ECG changes in patients with drug-resistant TLE immediately by the end of the seizure and then within an hour after the postictal phase.

Methods:

This is a case-control study conducted on 50 drug-resistant TLE patients admitted at Kashani Hospital, a referral center of neurologic disorders affiliated at Isfahan University of Medical Sciences, from January 2018 to December 2019.

The study proposal that met Helsinki ethics declaration criteria was approved by the Ethics Committee of Isfahan University of Medical Sciences. The study protocol was explained to the patients and their legal guardians and the control group. They were reassured about the confidentiality and signed written consent for participation in the study.

The case group with documented drug–resistant TLE by an expert epileptologist was included. The diagnosis was made according to magnetic resonance imaging (MRI), video electroencephalography (EEG) monitoring and medical history.

The controls were selected from the age- and gender-matched first-degree family members of the patients who did not have any history of seizure or epilepsy. Less than 18 years of age, flawed medical records, any history of cardiovascular diseases, hypertension, diabetes mellitus, dyslipidemia and cardiac anomalies were determined as the exclusion criteria.

The studied patients were recruited by convenience sampling and the control group who met the study criteria were selected until achieving the desired number of the studied population.

The demographic information of the study population including age, gender, epilepsy age of onset, and marital status was recorded in the study checklist. Furthermore, the epileptic characteristics including the duration of the seizure, age of onset, seizure frequency (daily, weekly, monthly, annually or others), seizure semiology (dialeptic, automotor, focal and secondary generalized), positive family history, involved part of the brain based on MRI (hippocampal sclerosis (HS), temporal atrophy, temporal gliosis, temporal glioma, temporal heterotopia) and medications (sodium valproate, carbamazepine, levetiracetam, phenytoin, phenobarbital, lamotrigine, and topiramate) were entered into the checklist.

Standard 12-lead electrocardiography (ECG) was taken from the cases at baseline (when admitted at the hospital), immediately by the end of the seizure and within an hour after the post-ictal phase. Similarly, standard electrocardiography was taken from the controls, as well.

The ECGs were interpreted by a cardiologist. The normal ranges of the assessed parameters were determined as RR interval of 0.6-1.2 s, PR interval of 0.12-0.2 s, QTc of 0.35 to 0.44 s for men and from 0.36 to 0.46 s for women that is calculated from Bazett formula QTc = QT /

√RR, ST segment depression and elevation for more than 0.2 mV from the isoelectric line and P wave duration of less than 0.12 s and 1-1.4 mV height.

The ECGs were assessed regarding arrhythmia including atrial fibrillation, sinus tachy- or bradycardia, premature atrial depolarization, premature ventricular depolarization, branch blocks and supraventricular arrhythmias.

The obtained data were entered into the Statistical Package for Social Sciences (SPSS; version 15.0, SPSS Inc., Chicago, IL, USA). The descriptive data were presented in mean, standard deviation, absolute numbers and percentages. To compare the frequencies between groups chi-square test was utilized. The continuous variables were compared using t-test. P-value of less than 0.05 was defined as the level of significance.

Results:

The current study has been conducted on 50 drug-resistant temporal lobe epileptic patients and 50 other normal patients as the control group. The case group was predominantly consisted of males (52%), half of them (50%) were married and had the mean age of 32.88±1.91 years old (range: 18-73 years old). The comparison of demographic characteristics of the cases and controls is demonstrated in Table 1. Given that, the two groups were similar regarding their age (P-value=0.058) and gender distribution (P-value=0.84), but their marital status was different (P-value<0.001).

Table 1. Demographic characteristics of the studied groups

Variables	Case group (n=50)	Control group (n=50)	P-value
Age, years (mean±standard deviation)	32.88±1.91	36.66±7.19	0.058*
Gender, n (%)			
Female	24 (48)	25 (50)	0.84**
Male	26 (52)	25 (50)	
Marital status, n (%)			
Single	25 (50)	5 (10)	<0.001**
Married	25 (50)	45 (90)	

* t-test
** Chi-square test

Table 2 represents the epilepsy-related characteristics in the case group.

Table 2. Epilepsy-related characteristics

Variable	Measurements	Variable	Measurements
Age of onset	14.35±13.76	**Type of lesion in MRI**	
Epilepsy duration	18.57±11.67	**Mesial temporal sclerosis**	25 (50%)
Positive family history of epilepsy	12 (24%)	**Temporal atrophy**	1 (2%)
Epilepsy semiology		**Encephalomalacia**	1 (2%)
Dialeptic	16 (32%)	**Temporal tumor**	4 (8%)
Automotor	29 (58%)	**Temporal gliosis**	1 (2%)
Focal	27 (54%)	**Temporal heterotopia**	1 (2%)
Secondary generalized	8 (16%)	**Seizure frequency**	
Medications		**Daily**	6 (12%)
Sodium valproate	32 (64%)	**Weekly**	12 (24%)
Carbamazepine	29 (58%)	**Monthly**	20 (40%)
Levetiracetam	34 (68%)	**Annually**	2 (4%)
Phenytoin	3 (6%)	**Variable**	8 (15%)
Phenobarbital	10 (20%)		
Lamotrigine	5 (10%)		
Topiramate	10 (20%)		

Based on the ECG assessments of the patients, shorter corrected QTc interval was notified among drug-resistant TLE patients compared to the controls (P-value=0.017) in base line assessments. The evaluations done immediately after the seizure revealed significant differences in terms of RR-interval (P-value=0.005) and heart rate (P-value=0.005). The ECG assessment within an hour after the end of the seizure did not differ between the groups.

ST-segment alterations, including elevation or depression was noted in 3 (6%) cases (1 depression and 2 elevations) immediately after the seizure and 2 (4%) cases after an hour. None

of the controls represented ST-segment changes in any of the assessments. The comparison of the groups revealed insignificant differences immediately after the seizure (P-value=0.24) and within an hour (P-value=0.49). all the ST-segment alterations were early depolarization, but not ischemic changes.

Furthermore, the assessment of electrocardiograms to find arrhythmia revealed nothing compatible with arrhythmogenic manifestations in any of the cases or controls.

Table 3. The comparison of electrocardiographic findings between the studied groups

Group	Baseline			Immediately after the seizure			Within an hour after the seizure		
	Case	Control	P-value*	Case	Control	P-value*	Case	Control	P-value*
PR interval	120 (120, 160)	120 (120, 160)	0.225	120 (120, 160)	120 (120, 160)	0.496	120 (120, 160)	120 (120, 160)	0.678
RR interval	780 (710, 840)	800 (735.5, 852)	0.524	700 (600, 840)	800 (735, 852.5)	0.005	760 (640, 850)	800 (735, 852.5)	0.074
QTc interval	320 (320, 360)	360 (320, 360)	0.017	360 (320, 360)	360 (320, 360)	0.125	360 (320, 360)	360 (320, 360)	0.278
Heart rate	76.50 (71, 84.25)	75 (70, 81.5)	0.558	85.50 (71, 100)	75 (70, 81.5)	0.005	79 (70.75, 93)	75 (70, 81.5)	0.083
P-wave duration	80 (80, 80)	80 (80, 80)	0.708	80 (80, 80)	80 (80, 80)	0.258	80 (80, 80)	80 (80, 80)	0.755

*Mann-Whitney U test

The patients' age was not associated with any of the changes in electrocardiographic abnormalities (Table 4).

Table 4. Assessment of age role in electrocardiographic abnormality

Variables		Immediately after the seizure			Within an hour after the seizure		
		Normal	Abnormal	P-value	Normal	Abnormal	P-value
Age	**RR interval**	34.09±12.85	30.53±9.77	0.322	33.66±11.96	29.33±11.70	0.329
	QTc interval	32.63±11.90	45±0.0	0.309			
	ST segment	32.87±12.08	33±10.81	0.896	32.63±12.08	39±4.24	0.464

Discussion:

Our investigation revealed that the cases, the patients with drug-resistant TLE, and the controls, their first-degree healthy family members, significantly differed regarding their QTc interval when they had no seizure; while by the end of the seizures, the cases heart rate was remarkably higher and RR-interval was significantly lower than the controls. Nevertheless, the ECGs taken within an hour after the seizure revealed insignificant differences.

SUDEP seems to occur due to an electrical event following a fatal cardiac arrhythmia; nevertheless, the exact etiology of SUDEP remained unknown and may be multifactorial(15). The lethal cardiac arrhythmia may be initiated ictally or just in the interictal period(16). Another hypothesis regarding the mechanism by which SUDEP occurs refers to prolonged hypoxemia or hypercapnia in the ictal phase that leads to a persistent acidosis, bradycardia and eventually, asystole(17). Various contributing factors which interferes with the normal de- or repolarizatory activity of the myocardium may be attributed to this sudden death in PWE(7).

P wave and PR interval were in the normal range in both cases and controls of our study, which is consistent with the study by Asadollahi et al. (7); however, an insignificant increase in PR interval was found in their investigation among the PWE both interictally and in the post-ictal phase. The elongated PR interval has been noted in other previous studies, particularly among those with generalized epilepsy, as well(18). One of the strong theories about the localization of arrhythmia in PWE targets atrioventricular conduction block due to disrupted depolarization(19).

QT interval is one of the popular elements of ECG accused of the incidence of arrhythmia in PWE. Shortness of QT interval occurs because of disrupted cardiac repolarization. QTc interval was remarkably lower in PWE cases than the controls in ECGs taken at the base line; a finding that is consistent with most of the studies in the literature representing shortened QT

interval(21, 22), while some investigations presented no or mild alterations in QT interval(11, 20). These controversial outcomes can be attributed to age, study population, risk factors and epilepsy types.

Shortness of QT interval reflects the acceleration of repolarization that is an outcome of either increased or decreased depolarizing currents(23). The irregular shortness of QT interval is accompanied by a reduced ventricular muscle refractory period and therefore, an increased risk of reentrant tachycardia development(21). Ion channelopathies, alteration in His-Purkinje network distribution and changes in intracellular communication are the probable mechanisms by which a shortened QT interval can lead to a life-threatening arrhythmia(23, 24).

Shortened RR interval during the seizure was notified between the case and control groups. De Sousa and colleagues presented an insignificant difference in their case-control study(3), while the latter study by Asadollahi et al. in line with our study presented a significantly shorter RR interval in PWE than the control group. This finding was noted in all types of epilepsies including generalized, TLE, and frontal lobe epilepsy(7).

Catecholamine release by seizure affects heart rate variability which is associated with RR interval variabilities. The significance of RR interval is due to its role in heart rate variability which is affected by shortened RR interval. On the other hand, shortened RR interval is representative of autonomic nervous system function(13, 25). Therefore, a significant deviation in RR interval shows autonomic dysfunction during the seizure presented in both focal and generalized seizures(14, 26). The shortened RR interval immediately by the end of the seizure reflects tachycardia during the seizure and in the early ictal phase which is confirmed in numerous studies representing increased heart rate in up to 100% of the PWE(27, 28).

We observed that the age of the patients was not associated with ECG abnormalities; however, Leutmezer presented an increased risk of life-threatening ECG abnormalities in younger adults(10).

Limitations:

The small number of the studied population and observational design of our study is the most remarkable limitations of this study. Further studies by consideration of the probable confounders are strongly recommended.

Conclusion:

According to the findings of this study, shortened QTc interval at the base line ECG, shortened RR interval and increased HR during the seizure were the ECG elements affected in drug-resistant TLE patients; however, to generalize the outcomes, further studies are required.

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