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Interictal electrocardiographic alternations in patients with drug-resistant epilepsy

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ABSTRACT

Purpose: Previous studies suggested the possible role of autonomic dysfunction in sudden unexpected death in epilepsy (SUDEP). The aim of this study is to assess the interictal ECG alternations especially heart rate variability (HRV), as a marker of autonomic dysfunction, in patients with drug-resistant epilepsy and determine the effect of epilepsy type and duration, seizure frequency and anti-epileptic drugs (AEDs) on ECG findings.
Methods: In this comparative cross-sectional study, the interictal ECG parameters of 64 consecutive patients with drug-resistant epilepsy and the same number of age and sex-matched controls were analyzed. Epilepsy type and duration, seizure frequency, MRI findings and patients' anti-convulsive medications were determined.
Results: Our study showed significant longer mean PR interval, shorter mean QRS duration, shorter mean QTc interval and longer corrected QT interval dispersion (QTcd) in patients with epilepsy compared to healthy subjects. The analysis of RR intervals revealed reduced RR standard deviation (SDNN), which is a marker of reduced HRV. A positive linear correlation was found between QRS duration and epilepsy duration. No significant correlation was found between taking a certain kind of AED, and ECG alternations, except for mild QTcd prolongation in patients taking valproate.
Conclusion: Our study showed clinically important alternations in interictal ECG parameters in patients with drug-resistant epilepsy which could result in sudden cardiac death.

1. Introduction

Sudden unexpected death in epilepsy (SUDEP) is the major cause of death in patients with epilepsy. It is defined as non-accidental, non-suicidal death in the absence of documented status epilepticus or any other identifiable causes [1]. The annual incidence rate of SUDEP is varied among different literatures according to the population of the study and reported between 0.35–9.3 per 1000 persons [2,3]. This incidence rate increases significantly in patients with drug-resistant epilepsy [4]. SUDEP can affect individuals of any age, but most commonly affect younger adults [5].

The underlying pathophysiological mechanisms of SUDEP remain unknown. Cardiorespiratory dysfunction in parallel with arousal deficits, are proposed mechanisms of SUDEP [6]. It has been believed that SUDEP is due to cardiac abnormalities during the postictal period. However, recent studies have demonstrated that respiratory depression is common following seizure, and can be severe enough to cause a substantial decrease in oxygen saturation [6].

Cardiac arrhythmia is one of the proposed mechanisms of SUDEP. It was suggested by clinical evidences and experimental models that repeated seizures may induce autonomic dysregulations and cardiac arrhythmia [7]. A recent community-based study found that people with epilepsy, irrespective of the cardiac risk factors, had two to threefold increase risk of ECG-confirmed sudden cardiac arrest [8]. In a prospective long-term study, it was shown that about a quarter of patients with epilepsy had clinically significant cardiac arrhythmia, despite the absence of cardiac risk factors [9,10].

Focal and generalized seizures may result in autonomic dysfunction during ictal, postictal or interictal periods [4,11]. Heart rate variability (HRV), defined as the alternations of RR intervals between the heartbeats [12], considered as an index of autonomic nervous system function [13–15].

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High variability of heart rates indicate favorable autonomic adaptability and control [2,12], while decreased HRV signifies impaired autonomic control and could be a predictor of increased SUDEP risk [13–18].

Previous studies based on short or long-term (24 h) ECG recordings revealed decreased HRV in patients with chronic epilepsies, mainly in peri-ictal period [14,19–23].

The results of previous studies in terms of the effect of epilepsy on QT intervals are contradictory. Some studies reported mild QT prolongation, while others showed no significant changes or even QT shortening [8].

Previous studies were mainly focused on ECG alternations in peri-ictal period. We conducted this study to evaluate the interictal electrocardiographic (ECG) changes in patients with drug-resistant epilepsy. We aimed to assess the correlation between ECG alternations with epilepsy type and duration, seizure frequency and different anti-epileptic drugs (AEDs).

2. Methods

In this comparative cross-sectional study, 64 consecutive patients with drug-resistant epilepsy and the same number of age and sex matched healthy volunteers were included. Cases were selected from patients with history of recurrent seizures, admitted to epilepsy monitoring unit (EMU) of Loghman-Hakim Hospital, Tehran, for further evaluation. All the recruiting subjects were between 18 to 55 year-old. Epilepsy duration, seizure types and frequency, epilepsy risk factors and the history of medications were determined.

Patients with pre-existing cardiopulmonary diseases, vascular risk factors (hypertension, diabetes, smoking or alcohol use, body mass index over 25), renal failure, cerebrovascular events or any other chronic medical conditions were excluded from the study. The informed consent form was signed by all the patients and healthy controls before recruiting in the study.

A 5-minutes lead II ECG was recorded from all the patients and control subjects in supine position. All QRS complexes were reviewed for ectopic beats and those with ectopic beats were excluded from the study. The P-wave duration (the time between the upward deflection of the P-wave until its return to the baseline), PR interval (the time between the beginning of the P-wave until the beginning of the QRS complex), QRS duration (the time between the beginning of the Q-wave until the end of S-wave), RR interval (the time between two sequential R-waves) and QT interval (the time between the beginning of QRS complex to the end of T-wave) were measured manually with the digital caliper. In this study, QT duration was corrected according to the heart rate, using Bazett's formula (QT/√RR). QT prolongation was defined according to the European Society of Cardiology Guidelines: > 450 ms in men and > 470 ms in women [6,18]. QT corrected dispersion was determined based on the differences between the longest and shortest calculated QT in 5-min ECG recording. The mean durations of RR intervals in the 5 min-ECG recording was also calculated. The standard deviation for normal ECG intervals (resulting from sinus node depolarizations) (SDNN) was measured and averaged in each group. The analysis of HRV were performed using SDNN, according to the standards of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology task forces [19].

All the patients underwent minimum 48–72 h of scalp video-EEG monitoring. The epilepsy type was determined by an epileptologist according to the ictal and interictal EEG findings and the seizures semiology. A 1.5 T Brain MRI with epilepsy protocol was performed on all the patients and interpreted by an expert radiologist.

2.1. Statistical analysis

Our data were analyzed using SPSS version 22.0 software. Two sample T-tests were used for evaluation of continuous variables. Moreover, Pearson's correlation coefficient was used to measure the linear correlation between two variables (eg, epilepsy duration and ECG findings, or seizure frequency and ECG findings). P-value under 0.05 was considered as significant.

3. Results

Sixty-four patients (35 males and 29 females) with drug-resistant epilepsy and 64 age and sex matched healthy controls (32 males and 32 females) were recruited in the study. The mean age of patients and healthy control subjects were 32.71 ± 10.20 and 32.01 ± 10.03 years, respectively. Forty-five patients (70.31%) had temporal lobe epilepsy, 15 (23.43%) had generalized epilepsy (idiopathic or symptomatic), three (4.68%) had frontal lobe epilepsy and one patient had progressive myoclonus epilepsy. The mean epilepsy duration was 18.78 ± 11.85 years (minimum: one year, maximum: 53 years). The mean seizure frequency was 13.48 ± 19.06 attacks per month.

In terms of anti-epileptic drugs (AEDs), all the patients were on polytherapy. Forty-two patients (65.62%) were on carbamazepine, 33 (51.56%) on levetiracetam, 29 (43.31%) on lamotrigine, 28 (43.75%) on valproate, 18 (28.12%) on phenobarbital, 7 (10.93%) on phenytoin, 7 (10.93%) on topiramate, 7 (10.93%) benzodiazepine, five (7.81%) on oxcarbazepine, one patient on acetazolamide and one on primidone.

Based on brain MRI findings, 24 patients (12.7%) had normal imaging, 16 (8.5%) had mesial temporal sclerosis (MTS), 8 (4.2%) had focal cortical dysplasia (FCD), 8 (4.2%) had diffuse brain atrophy, 3 (1.6%) had focal gliosis, 3 (1.6%) had both MTS and focal gliosis and two patients (1.1%) had polymicrogyria (Tables 1–4).

There was no correlation between the seizures frequency and ECG alternations using Pearson's correlation test. Moreover, there was no significant correlation between the epilepsy duration and ECG alternations, except for QRS duration (P-value: 0.03, R: 0.27). Furthermore, there were no significant differences in ECG variables of patients taking a certain kind of AED, except for a slight increase in QTcd (46.51 ± 11.16 ms vs. 40.16 ± 10.51 ms, P-value: 0.02) in those taking valproate.

3.1. P-wave duration and PR interval

There were no significant differences in the mean P-wave duration between the patients and control group. The patients had longer mean PR interval compared to controls (165.43 ± 36.25 ms vs. 154.3 ± 24.3 ms, P-value: 0.01). There were no significant differences in PR interval based on epilepsy subtypes compared to healthy subjects.

3.2. QRS duration, corrected QT interval (QTc), corrected QT interval dispersion (QTcd)

The mean QRS duration was shorter in patients with epilepsy compared to controls (73.71 ± 17.62 ms vs. 95.3 ± 16.6 ms, $P < 0.0001$), (QRS duration in generalized epilepsy: 68.57 ± 18.11 ms, $P < 0.0001$, TLE: 75.37 ± 17.08 ms, $P < 0.0001$, FLE: 63.06 ± 6.92 ms, P-value: 0.01). The mean QTc was in normal ranges for all the patients and normal subjects but there was

Table 1
The ECG parameters in patients with epilepsy and healthy controls.

Variable (ms)	Patients	Controls	P-value
P wave	75.40 ± 15.46	75.80 ± 10.5	0.83
PR interval	165.43 ± 36.25	154.3 ± 24.3	**0.01**
QRS duration	73.71 ± 17.62	95.3 ± 16.6	< **0.0001**
QTc interval	384.68 ± 24.87	421 ± 27.9	< **0.0001**
QTc dispersion	42.94 ± 11.18	26 ± 11.26	< **0.0001**
RR interval	726.37 ± 131.45	854 ± 112.2	< **0.0001**
SDNN	31.35 ± 9.53	49.11 ± 12.23	< **0.0001**

Table 2
The ECG parameters in patients with generalized epilepsy and healthy subjects.

Variable (ms)	Patients with generalized epilepsy	Controls	P-value
P wave	72.23 ± 14.41	75.80 ± 10.5	0.35
PR interval	172.61 ± 37.27	154.3 ± 24.3	0.07
QRS duration	68.57 ± 18.11	95.3 ± 16.6	< **0.0001**
QTc interval	386.06 ± 27.50	421 ± 27.9	< **0.0001**
QTc dispersion	44.66 ± 12.64	26 ± 11.26	< **0.0001**
RR interval	758.66 ± 194.62	854 ± 112.2	< **0.0001**
SDNN	28.88 ± 6.78	49.11 ± 12.23	< **0.0001**

Table 3
The ECG parameters in patients with temporal lobe epilepsy and controls.

Variable (ms)	Patients with TLE	Controls	P-value
P wave	75.62 ± 15.11	75.80 ± 10.5	0.93
PR interval	163.34 ± 32.87	154.3 ± 24.3	0.07
QRS duration	75.37 ± 17.08	95.3 ± 16.6	< **0.0001**
QTc interval	385.12 ± 25.01	421 ± 27.9	< **0.0001**
QTc dispersion	42.87 ± 10.65	26 ± 11.26	< **0.0001**
RR interval	720.55 ± 108.93	854 ± 112.2	< **0.0001**
SDNN	32.60 ± 9.07	49.11 ± 12.23	< **0.0001**

Table 4
The ECG alternations in patients with frontal lobe epilepsy and controls.

Variable (ms)	Patients with FLE	Controls	P-value
P wave	89.73 ± 25.61	75.80 ± 10.5	0.44
PR interval	175.26 ± 79.67	154.3 ± 24.30	0.69
QRS duration	63.06 ± 6.92	95.3 ± 16.6	**0.01**
QTc interval	370.76 ± 10.75	421 ± 27.9	**0.01**
QTc dispersion	37.90 ± 15.25	26 ± 11.26	0.30
RR interval	676.83 ± 55.91	854 ± 112.2	**0.03**
SDNN	30.46 ± 22.63	49.11 ± 12.23	0.29

significant shorter mean QTc in patients compared to controls (384.68 ± 24.87 ms vs. 421 ± 27.9 ms, P < 0.0001) (generalized epilepsy: 386.06 ± 27.50 ms, P < 0.0001, TLE: 385.12 ± 25.01 ms, P < 0.0001, FLE: 370.76 ms, P value: 0.01). The mean QTcd was longer in patients with epilepsy than healthy subjects (42.94 ± 11.18 ms vs. 26 ± 11.26 ms, P < 0.0001) (generalized epilepsy: 44.66 ± 12.64 ms, P < 0.0001, TLE: 42.87 ± 10.65 ms, P < 0.0001). The patients with FLE did not have significant longer QTcd than healthy controls.

3.3. RR interval, RR standard deviation (SDNN)

The RR interval was significantly shorter in patients than controls. (726.37 ± 131.45 ms vs. 854 ± 112.2 ms, P-value < 0.0001). Similarly, the mean SDNN was statistically shorter in patients than healthy subjects (31.35 ± 9.53 ms vs. 49.11 ± 12.23 ms, P-value < 0.0001). This finding was true in patients with generalized epilepsy (28.88 ± 6.78 ms vs. 49.11 ms ± 12.23, P-value < 0.0001) and TLE (32.60 ± 9.07 vs. 49.11 ms ± 12.23, P-value < 0.0001). However, in patients with FLE the mean SDNN was not significantly different compared to control group.

4. Discussion

SUDEP is an "electrical event" which has been proposed to result in fatal cardiac arrhythmias [24]. The etiology of SUDEP remains elusive and may be multifactorial [25]. The lethal trigger might be a life threatening cardiac arrhythmia initiated ictally or in interictal period [26]. Another proposed mechanism of SUDEP may be ictal-induced prolonged hypoxemia and hypercapnia which could result in acidosis, bradycardias or asystole in vulnerable individuals [26]. Different contributing factors, which could result in pathologic cardiac de- or repolarization, may explain sudden death in patients with epilepsy.

In the present study, we found that patients with epilepsy had longer PR intervals without significant increase in P-wave duration compared to controls. This finding suggests the susceptibility of these patients to cardiac conduction block due to disrupted depolarization. Our finding was consistent with previous studies, which reported the atrioventricular conduction block as one of the seven patterns of ictal/postictal cardiac arrhythmias [27], particularly during generalized convulsive seizures [28–30].

Another interesting result was interictal shorter QRS and QTc intervals in patients with epilepsy, which could be due to disrupted cardiac repolarization. Some previous studies reported the same result [25,31,32], while others reported no changes in QTc duration or even mild QTc prolongation in patients with epilepsy compared to normal subjects [8,33]. These contradictory results could be due to diversity of the study populations in terms of age, risk factors, epilepsy types and durations.

We found a positive linear correlation between the epilepsy duration and QRS duration, suggesting that patients with longer epilepsy durations have the higher odds of having longer QRS durations. Shortening of QRS duration and QTc interval reflect accelerated repolarization, which can result from increased or decreased depolarizing currants [34]. As a result, abnormal QTc shortening reduces refractory period of the ventricular muscle and increases the QTcd and the risk of reentrant tachycardia [32]. This could be the possible explanation of increased QTcd in patients with epilepsy [25,32]. It was shown that, QTcd > 58 ms was associated with 3.4-fold increased risk of cardiovascular death [35]. The occurrence of the pathologic prolongation of QTcd and shortening of QTc may favor life-threatening ventricular tachycardia and fibrillation [2,32]. The pathophysiological mechanism of this finding could be ion channelopathy or enhanced intracellular communication and/or the altered distribution of the His-Purkinje network [31,32,34,36–38]. Some studies reported both prolongation and shortening of QTc in ictal/postictal states in patients with epilepsy [10]. Notably, in our study group, we had patients with QTc prolongation as long as 460 ms, and conversely a patient with QTc < 340 ms. It seems that patients with epilepsy need to be actively screened for QTc prolongation or shortening, due to its association with increased risk of sudden cardiac death [10,25,32,35].

The effect of AEDs on autonomic function, particularly carbamazepine, is controversial [39]. According to one study, among AEDs, phenytoin and felbemate were associated with QT prolongation, while carbamazepine, oxcarbazepine, phenytoin and lamotrigine were reported to have depolarization blocking effects [8,40]. In our study, there were no significant differences in ECG variables among patients taking a certain kind of AED compared to those who were not on that specific drug. The only exception was a slight QTcd prolongation in patients on valproate. Our finding supported the overall non-significant impact of AED on increased risk of SUDEP [41]. Although there are some reports regarding the indirect effect of valproate on QTc prolongation [32], no clinically significant effect on QTcd was described by AEDs [32].

HRV is an acceptable index of autonomic function [14]. Reduced HRV is a significant predictor of poor prognosis in patients with heart diseases and even among healthy subjects [13,14,16]. In our study, the mean SDNN was decreased in patients with drug-resistant epilepsy compared to controls, which is an indicator of reduced HRV. This is compatible with previous studies [2,22,23,41,42]. The absence of reduced HRV in patients with FLE could be due to the small sample size. Reduced HRV in interictal period could be related to chronic structural changes in autonomic centers, which are continuously stimulated or inhibited by repetitive seizures [16].

In our study, no correlation was found between seizure frequency and specific alternations in ECG findings. This is consistent with

previous results [41].

4.1. Limitations

The accuracy of our findings would undoubtedly increase with larger number of patients, especially those with frontal lobe epilepsy, given some of the contradictory results in our study.

5. Conclusion

In the present study, the interictal autonomic function was assessed in patients with drug-resistant epilepsy using sensitive measurements, such as HRV. We found that patients with drug-resistant epilepsy had significant alternations in interictal ECG parameters, which could contribute to sudden cardiac death. Our study showed the non-significant impact of AEDs on increased risk of SUDEP.

Conflict of interest

None to declare.

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