EVALUATION OF INDEX OF CARDIO-ELECTROPHYSIOLOGICAL BALANCE AND TP-E/QT RATIO IN COVID-19 PATIENTS TREATED WITH HYDROXYCHLOROQUINE AND AZITHROMYCIN

Abstract

Aim: The common cardiac toxicities of hydroxychloroquine (HCQ) and azithromycin(AZ) are not well defined in COVID -19 patients . The purpose of this study was to evaluate ventricular repolarization in COVID-19 patients treated with HCQ and AZ using iCEB, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

Methods: This retrospective study enrolled 164 patients diagnosed with COVID-19 pneumonia in the Emergency Department (ED) and then transferred to the medical floor or ICU in April 2020

Result: A total of 164 patients were mean aged 47 ± 18 years (range, 18-97 years) and 83 (50.6%) were women in study population. Group HTQ had 38 patients , Group HTQ + AZ had 126 patients. On the 5th day of hospitalization heart rates (HR) were significantly lower than ED ($p<0,001$). On the 5th day of hospitalization QTc , QT max (V5-V6), QTmin, Tp-e (V5-V6) and iCEB values were significantly higher than ED ($p=0,01$and all the rest $p<0,001$ respectively). On the 5th day of hospitalization iCEB values of HTZ+AZ group were statistically significant higher than iCEB values of HTQ group ($p=0,03$). iCEBc had strong correlation between Tp-e/QT (V5). iCEBc had strong negative correlation between Tp-e (V5).

Conclusion: The iCEB values were significant increased after HTQ and AZ treatment in COVID-19 patients. We think that iCEB is a more sensitive marker than QT prolongation in predicting the risk of multi-drug arrhythmia.

Summary statement

What is already known about this topic?

- In the antecedent severe acute respiratory syndrome (SARS) epidemic, hydroxychloroquine (HCQ) has been confirmed to have an antiviral activity in vitro. This suggests that HCQ may be a probable therapeutic drug for patients diagnosed with COVID-19. Based on available evidence, an authorization was published by the United States Food and Drug Administration to permit of HCQ and chloroquine treatment in COVID-19 patients. Also, in a previous study HCQ treatment in combination with azithromycin (AZ), was related with viral load decrease/dissolution in COVID-19 patients.
- The common cardiac toxicities of HCQ and AZ are not well defined in COVID-19 patients. In previous studies have appraised adverse events likely related to the using of HCQ or chloroquine and AZ in COVID-19 patients, including electro-physiological cardiac situations of prolonged QT and arrhythmia.
- Fatal arrhythmias can be caused by electro-physiological cardiac changes during ventricular repolarization. In a previous clinical study usability the QT interval (QT) and corrected QT interval (QTc) were reported to predict ventricular arrhythmias and sudden death.

What this paper adds?

- This study is the first human study to demonstrate that the clinical usability of ICEB is a priority as a predictor of arrhythmias in COVID-19 patients treated with HCQ and AZ.
- We believe that increased ICEB values are due to HCQ and AZ treatment, which increase ventricular repolarization heterogeneity and ventricular arrhythmias.

We think that ICEB is a more sensitive marker than QT prolongation in predicting the risk of multi-drug arrhythmia.

The implications of this paper:

- In this study, the ICEB values were significant increased after HCQ and AZ treatment in COVID-19 patients. ICEB is a simple, non-invasive method that can be a beneficial marker to evaluate ventricular repolarization in COVID-19 patients.

Keywords

COVID-19, Hydroxychloroquine, Azithromycin, ECG, iCEB,Tp-e interval

Introduction

In early January 2020, the new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was discovered to cause cases of atypical pneumonia in China.[1] A month later, the disease caused by SARS-CoV-2, official name was announced as Coronavirus Disease 2019 (COVID -19) by the World Health Organization.[2] Repositioning of old drugs for use as a possible therapeutic agent to treat COVİD-19 can be an attractive approach because knowledge on clinical safety, efficacy profile, side effects, and drug interactions are well defined.[3]

In the antecedent severe acute respiratory syndrome (SARS) epidemic, hydroxychloroquine (HCQ) has been confirmed to have an antiviral activity in vitro.[4] This suggests that HCQ may be a probable therapeutic drug for patients diagnosed with COVID-19. Based on available evidence, an authorization was published by the United States Food and Drug Administration to permit of HCQ and chloroquine treatment in COVID-19 patients.[5] Also, in a previous study HCQ treatment in combination with azithromycin (AZ), was related with viral load decrease/dissolution in COVID-19

patients.[6] According to the Diagnosis and Treatment of COVID-19 Pneumonia (trial 13 April) recommended by Turkey's National Health Commission, all hospitalized patients diagnosed with COVID-19 pneumonia should be treated with HCQ, in combination with AZ for five days.[7] The common cardiac toxicities of HCQ and AZ are not well defined in COVID-19 patients. In previous studies have appraised adverse events likely related to the using of HCQ or chloroquine and AZ in COVID-19 patients, including electro-physiological cardiac situations of prolonged QT and arrhythmia.[8-10]

Fatal arrhythmias can be caused by electro-physiological cardiac changes during ventricular repolarization.[11] In a previous clinical study usability the QT interval (QT) and corrected QT interval (QTc) were reported to predict ventricular arrhythmias and sudden death.[12] Few studies suggested that Tp-e interval and Tp-e/QT ration were novel electrocardiogram (ECG) parameters to assess ventricular repolarization and were found related with malignant ventricular arrhythmias.[13-15] A novel marker index of cardio-electrophysiological balance (ICEB), measured as QT interval divided by QRS duration, can help to as an ECG-based derivative of cardiac wavelength λ (λ = conduction velocity x effective refractory period or QT/QRS). Cardiac wavelength λ is related with arrhythmogenesis: drugs, decrease the wavelength are predisposed to raise the risk for non-TdP VT or VF while drugs, increase wavelength are predisposed to raise the risk for TdP while agents that decrease the wavelength are predisposed to raise the risk for non-TdP VT or VF.[16,17] ICEB projects the balance between cardiac repolarization and depolarization of the action potential likewise cardiac wavelength λ.[18]

The purpose of this study was to evaluate ventricular repolarization in COVID-19 patients treated with hydroxychloroquine and azithromycin using ICEB, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

Materials and Methods

This is a retrospective study. Ethical approval was reviewed and approved from a local tertiary hospital ethics committee (decision date: 28 April 2020, nº: 452).

Patients

This study enrolled 164 patients who were diagnosed COVID-19 in the emergency department and then transferred to the medical floor or intensive care unit of a tertiary hospital in Diyarbakır, Turkey, in April 2020. The diagnosis were made according to the Diagnosis and Treatment of Novel Coronavirus Pneumonia (trial 13 April) recommended by Turkey's National Health Commission.[7] The inclusion criteria were as follows: A) having an epidemiological history; B) having a non-contrast chest computed tomography (CT) with signs of pneumonia on the emergency department; C) being 18 year or older; D) Five days as standard treatment in all patients hospitalized with the diagnosis of covid-19 pneumonia; HCQ was given 400mg twice a day on the first day, 200mg twice a day in the next four days, and azithromycin 500 mg a day.[7] Patients who stayed in the hospital for less than five days were treated for acute electrolyte imbalance and/or were on antiarrhythmic drugs, were excluded from this study. Also, we excluded the patients who associated any drugs (antibiotics, antifungals, antipsychotics) with QTc prolongation in addition to usual treatment in the first five days. Patients were separated into two groups; treated with only hydroxychloroquine (Group HCQ) and treated with hydroxychloroquine and azithromycin (Group HCQ + AZ).

Hence, sociodemographic information such as age, gender, as well as past medical histories such as hypertension, diabetes mellitus, cardiac disease, dementia, chronic obstructive pulmonary disease, malignancy, chronic kidney disease, vitals, laboratory results, ECG parameters were collected.

Electrocardiograms (ECGs) analysis

Initial ECGs in the emergency department and after the treatment completed (on the 5th day of hospitalization) ECGs were recorded. ECGs were obtained at a rate of 25 mm/s, while patients were at the resting position (Nihon Kohden, Tokyo, Japan,). All ECGs were recorded to decrease the wrong measures. A software (Adobe Photoshop**,** Adobe Systems, 2015, San Jose, United States of America) was used for 400% magnification. All ECGs were measured electrocardiographic repolarization parameters manually. Measurement of ECG parameters and evaluation of heart conduction disorders were examined by a cardiologist blinded to all clinical features of the study population. The longest QT interval in V_5 and V_6 lead was determined as QT maximum and the shortest QT interval in any lead was determined as QT minimum. Corrected QT intervals were calculated according to Bazett's formula ($QTc = QT/\sqrt{\ }RR$). The interval from T peak to T end was defined as Tp-Te which was measured on lead V5 and V6. Tp-Te/QT ratio was calculated separately on V5 and V6. ICEB was calculated as QT interval divided by QRS interval and ICEBc was calculated as QT_c interval divided by QRS interval in the v5-v6 leads.

Statistical analysis

The SPSS version 22.0 (IBM SPSS Statistics for Windows, Armonk, United States of America) was used for statistical analysis. Descriptive statistics are presented as frequency and percentage for categorical variables and as mean and standard deviation for numerical variables. When conditions for normal distribution were not met, comparisons for two independent groups were performed using Mann-Whitney U test. To analyze the interaction between measures and treatments using a repeated measures

analysis of variance (ANOVA). In repeated measures ANOVA, measures as a within subjects and treatments as a between subject factor. Spearman correlation was used to evaluate the relationship between QT, QTc, Tp-e, Tp-e/QTc and ICEB parameters. P-values below 0.05 were considered statistically significant

Results

Clinical and demographic characteristics of the patients

The demographic features, vitals, laboratory parameters and outcomes of the study populace are outlined in **Table 1**. A total of 164 patients were mean aged 47 ± 18 years (range, 18-97 years) and 83 (50.6%) were women in study population. 38 patients were treated with only hydroxychloroquine (HCQ group), 126 patients were treated with hydroxychloroquine and azithromycin (HCQ + AZ group) had. The demographic data, vital parameters and presence of comorbidities of group HCQ and group HCQ + AZ were similar (**Table 1**). There was no factually noteworthy contrast between HCQ group and HCQ + AZ group in terms of admission to the medical floor or intensive care unit and length of hospital stay (**Table 1**). Of 164 patients, 71 had positive reverse transcription polymerase chain reaction (RT-PCR) results with a positive rate of 43.3% (71/164). The HCQ group had 18 patients with positive RT-PCR results, with a positive rate of 47.4% (18/38). There was no factually noteworthy contrast between HCQ group and HCQ + AZ group in terms of positive RT-PCR results (P = 0.69). The mortality rate in all study patients was 5.5% (N = 9). HCQ group had 2 (5.3%) patients' death in hospital, HCQ+AZ group had 7 (5.6%) patients' death in hospital. There was no factually noteworthy contrast between HCQ group and HCQ + AZ group in terms of survival (P = 1). Patients' presence of comorbidities was: hypertension 17.7%, cardiovascular disease 8.5%, and diabetes 15.9%. Patients presented in 19 (11.6%) cases with comorbidities admitted to the intensive care unit (**Table 1**).

Clinical laboratory data

All laboratory tests of all patients performed on admission and on the 5th day of hospitalization, were compared regardless of the treatments groups (**Table 2**). All laboratory tests of all patients were compared with HCQ group and HCQ + AZ group. The effect of HCQ and HCQ + AZ groups were observed similar on the 5th day of hospitalization biochemical parameters ($P > 0.05$) (**Table 2**).

Electrocardiogram data

All of the patients' ECGs, recorded in the emergency department and after the treatment was completed (on the 5th day of hospitalization), were compared (**Table 3**). On the 5th day of hospitalization heart rates (HR) were significantly lower than in the emergency department ($P < 0.001$). On the 5th day of hospitalization, QTc, QT maximum (V5-V6), QT minimum, Tp-e (V5-V6) and ICEB values were significantly higher than in the emergency department ($P = 0.01$ and all the rest $P < 0.001$, respectively). All ECGs of all patients, performed in in the emergency department and the in 5th day of hospitalization, were compared in HCQ group and HCQ + AZ group heart rate, QT maximum (V5-V6), QT minimum, Tp-e (V5-V6) and QTc values were similarly changed in between the groups. On the 5th day of hospitalization, ICEB values of HCQ + AZ group were statistically significant higher than ICEB values of HCQ group ($P = 0.03$).

There was no statistically significant difference compared regarding the treatments groups between the admission and the 5th day of hospitalization in terms of ICEBc values. Also, ICEBc values on ECGs performed on in the emergency department and in the 5th day of hospitalization, were compared in HCQ group and HCQ + AZ

group. On the 5th day of hospitalization, ICEBc values were increased in HCQ + AZ group, but ICEBc values were decreased in HCQ groups.

The affair between ICEBc and Tp-e/QT (V5), Tp-e (V5), QTc, QT was evaluated (**Table 4**). ICEBc had strong correlation between Tp-e/QT (V5). ICEBc had strong negative correlation between Tp-e (V5). Also, ICEBc had weak correlation between QTc. ICEBc had weak negative correlation between QT (**Table 4**).

Discussion

This study is the first human study to demonstrate that the clinical usability of ICEB is a priority as a predictor of arrhythmias in COVID-19 patients treated with HCQ and AZ. We believe that increased ICEB values are due to HCQ and AZ treatment, which increase ventricular repolarization heterogeneity and ventricular arrhythmias. We think that ICEB is a more sensitive marker than QT prolongation in predicting the risk of multi-drug arrhythmia.

In this study, the most commonplace comorbidities were hypertension (17.7%), diabetes (15.9%) and cardiovascular disease (8.5%). The literature offers few studies about COVID-19 incidences of the comorbidities. Yang et al. evaluated the prevalence of comorbidities in COVID-19 patients in a meta-analysis. They found underlying diseases, including hypertension (21.1%), cardiovascular disease (8.4%) and respiratory system disease (1.5%).[19] Another meta-analysis, Li et al. performed COVID-19 incidences of the comorbidities. They reported the prevalent comorbidities in patients with COVID-19, such as hypertension (17.1%), diabetes (9.7%) cardia-cerebrovascular disease (16.4%).[20]

In previous studies have appraised adverse events likely related to the using of HCQ or chloroquine and AZ in COVID-19 patients, including electro-physiological cardiac situations of prolonged QT and arrhythmia.[8-10] Arrhythmic events frequently encountered in COVID-19 patients and drugs used in treatment also have a pro-arrhythmia effect. COVID-19 has caused direct and indirect damage to the cardiovascular system at varied levels.[20] Erythromycin, azithromycin, clarithromycin, telithromycin and roxithromycin are listed either as drugs that are known or that are probably related to torsades de pointes (TdP).[21] Possible therapeutic agents (HCQ, AZ, lopinavir/ritonavir, remdesivir and others) for treatment COVİD-19 have risk of ventricular arrhythmia. This side effect is uncommon, but co-prescription of other drugs like azithromycin could improve that risk.[22] Previous studies reported that treatment with chloroquine (HCQ) combined with AZ in COVID-19 patients had cardiovascular side effect of prolongation of the QT interval. This side effect could be a mechanism that predisposes to ventricular arrhythmias.[23,24] The risk of TdP is not a linear function of basic QTc or drug-related prolongation in the QTc range. In addition, TdP will not develop in all patients with drug-induced QTc prolongation.[22]

Yayla et al. reported that the increase in the distribution of ventricular repolarization was related with lethal arrhythmias.[25] Yontar et al. suggested that Tp-e interval, Tp-e/QT and Tp-e/QTc rations, were better ECG parameters to assess ventricular repolarization than QT parameters.[26] A new non-invasive marker ICEB projects the balance between cardiac depolarization and repolarization likewise cardiac wavelength λ which is related with arrhythmogenesis.[16,17,27] Our study is the first report regarding to evaluate the ICEB which was found to be increased in COVID-19 patients treated with HCQ and AZ. We believe that increased ICEB values due to HCQ and AZ treatment in COVID-19 patients increases ventricular repolarization heterogeneity and

ventricular arrhythmias. Lu et al. reported that ICEB projected the balance between the depolarization (changes in QRS duration) and repolarization (changes in the QT interval) of the cardiac action potential. Also, they suggested that a novel marker ICEB predicts potency risk of drug-related arrhythmias beyond long QT and TdP.[28]

Robyns et al. reported that the novel ECG parameter ICEB was more useful than the other ECG parameters in predicting the potency risk for ventricular arrhythmias, particularly for its potency to differentiate between long-QT belong arrhythmias and TdP.[18]

Limitations

This study had some limitations. First, we measured electrocardiographic repolarization parameters manually. This study was performed at a single center. Also, the number of patients in two groups was small. Additional long-term and large-scale studies are required to confirm and clarify our data.

Conclusion

In this study, the ICEB values were significant increased after HCQ and AZ treatment in COVID-19 patients. We think that ICEB is a more sensitive marker than QT prolongation in predicting the risk of multi-drug arrhythmia. ICEB is a simple, non-invasive method that can be a beneficial marker to evaluate ventricular repolarization in COVID-19 patients.

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Table 1. Demographics and comorbidities of patients by survival or non-survival during hospitalisation

	Total	**Group HCQ**	**Group HCQ + AZ**	**P**
	(n: 164)	**(n: 38)**	**(n: 126)**	

Age (years/old)	47.7 ± 18.9	44.8 ± 19.7	48.6 ± 18.7	0.27
Sex (n,%)				
Female	83 (50.6)	21 (55.3)	62 (49.2)	0.64
Male	81 (49.4)	17 (44.7)	64 (50.8)	
Comorbidities at baseline (n, %)				
Hypertension	29 (17.7)	8 (21.1)	21 (16.7)	0.71
Diabetes	26 (15.9)	4 (10.5)	22 (17.5)	0.44
COPD-asthma	8 (4.9)	1 (2.6)	7 (5.6)	0.68
Cardiovascular disease	14 (8.5)	3 (7.9)	11 (8.7)	1
Cancer story	3 (1.8)	2 (5.3)	1 (0.8)	0.,13
Chronic kidney disease	7 (4.3)	1 (2.6)	6 (4.8)	1
Other comorbidities	9 (5.5)	0 (0.0)	9 (7.21)	0.12
Length of stay (days)	9.8 ± 6.4	8.6 ± 4.47	10.1 ± 6.9	0.82
Systolic BP (mmhg)	118 ± 16	118 ± 13	118.4 ± 17	0.86
Diastolic BP (mmhg)	72.7 ± 9.7	71.7 ± 7	73 ± 10	0.75
Fever (^{0}C)	37.1 ± 0.7	37.0 ± 0.7	37.1 ± 0.7	0.55
Pulse (per minute)	90 ± 17	91 ± 19	90 ± 2	0.77
SPO_2 (%)	96 ± 3	97 ± 3	96 ± 3	0.25
D Dimer (0-243 ng/ml)	328.9 ± 495	270.05 ± 341	346.6 ± 533	0.72
Troponin (0-0.16 ng/ml)	0.1 ± 0.1	0.1 ± 0.01	0.1 ± 0.15	0.91
Hospitalization (n,%)				
Non-ICU	145 (88.4)	36 (94.7)	109 (86.5)	0.24
ICU	19 (11.6)	2 (5.3)	17 (13.5)	

Data are mean (SD) or n (%). HCQ = hydroxychloroquine; AZ = azithromycin; COPD = chronic obstructive pulmonary disease; BP = blood pressure; SPO_2 = oxygen saturation; ICU = intensive care unit.

Table 2. Laboratory parameters

	Total (n: 164) n (%)	**Group HCQ (n: 38)**	**Group HCQ + AZ (n: 126)**	**P ****
		n (%)	**n (%)**	

WBC (4.000-10.000/mm^3)				
on ED	7.85 ± 6	6.70 ± 3	8.19 ± 6.3	0.652
5th day	7.07 ± 5	6.16 ± 2	7.35 ± 5.2	
P*	0.044			
Neutrophil (2.000-7.000/mm^3)				
on ED	5.4 ± 4	4.65 ± 3	5.62 ± 4.1	0.695
5th day	4.32 ± 2	3.77 ± 2	4.5 ± 2.4	
P*	0.002			
Lymphocyte (800-4000/mm^3)				
on ED	1.58 ± 0.7	1.48 ± 0.7	1.61 ± 0.7	0.659
5th day	2.07 ± 3.5	1.77 ± 0.7	2.17 ± 4	
P*	0.164			
Platelet (150.000-450.000/ mm^3)				
on ED	233.8 ± 8	219.02 ± 65.8	238.32 ± 87.2	0.776
5th day	266.2 ± 8	254.23 ± 72	269.81 ± 83.1	
P*	< 0.001			
Hemoglobin (11-16 gr/dl)				
on ED	13.5 ± 2	13.29 ± 2.4	13.6 ± 1.8	0.051
5th day	13.1 ± 1.9	13.1 ± 2.3	13.02 ± 1.8	
P*	< 0.001			
Hematocrit (37-54 %)				
on ED	41.8 ± 5.3	40.9 ± 6.8	42.1 ± 4.8	0.046
5th day	40.4 ± 5.2	40.4 ± 6.5	40.3 ± 4.8	
P*	< 0.001			
C-reactive protein (0-5 mg/ L)				
Admission ED	43.1 ± 62.4	40.9 ± 72	43.6 ± 60	0.675
5th day	35.9 ± 59.6	30.8 ± 61	37.5 ± 59.3	
P*	0.083			
Calcium (8,8-10,6 mg/dl)				
on ED	8.7 ± 0.5	8.7 ± 0.5	8.7 ± 0.5	0.443
5th day	8.4 ± 0.5	8.4 ± 0.6	8.4 ± 0.5	
P*	< 0.001			

Chlorine (98-107 mmol/l)				
on ED	103.8 ± 3.2	103.7 ± 3.7	103.8 ± 3.1	0.897
5th day	104.7 ± 3.4	104.6 ± 4.2	104.8 ± 3.1	
P*	0.007			
LDH (135-225 U/l)				
on ED	254.4 ± 104.6	241.2 ± 122.4	258.4 ± 99	0.33
5th day	268.5 ± 150.2	238.2 ± 123.4	277.7 ± 156.7	
P*	0.479			
Potassium (3.5-5.2 mEq/L)				
on ED	4.03 ± 4.3	4.0 ± 0.4	4.0 ± 0.4	0.38
5th day	4.3 ± 0.5	4.2 ± 0.5	4.3 ± 0.5	
P*	< 0.001			
Sodium (134-146 mEq/L)				
on ED	137.2 ± 2.9	137.1 ± 2.7	137.7 ± 3	0.821
5th day	138.4 ± 2.5	138.4 ± 2	138.4 ± 2.7	
P*	< 0.001			

HCQ = hydroxychloroquine; AZ = azithromycin; WBC = white blood cell; ED = emergcy department; LDH = lactate dehydrogenase; *within subjects; **between subjects .

Table 3. Electrocardiogram parameters

	Total (n: 164) n (%)	Group HCQ (n: 38) n (%)	Group HCQ + AZ (n: 126) n (%)	P**
Heart rate (bpm)				
Admission ED	89.9 ± 16.6	90.9 ± 19.02	89.7 ± 16	0.856
5th day	79.6 ± 14.3	80.2 ± 16.52	79.5 ± 13.7	
P*	0			
V_5 QT max (ms)				
Admission ED	350.2 ± 51.3	356.4 ± 52.6	348.38 ± 5	0,128
5th day	390.9 ± 70.5	381.7 ± 53.1	393.66 ± 7	
P*	0			
V_6 QT max (ms)				
Admission ED	349.9 ± 52.1	356.0 ± 54.1	348.06 ± 51.6	0.155
5th day	390.6 ± 69.8	381.7 ± 53.1	393.33 ± 74	
P*	0			
QT min (ms)				
Admission ED	327.0 ± 5	329.6 ± 46.6	326.3 ± 48.8	0.166
5th day	363.6 ± 7	350.4 ± 60.3	367.6 ± 69.4	
P*	0			
DII QRS (ms)				
Admission ED	98.51 ± 24.7	100.4 ± 30.9	97.9 ± 22.6	0.432
5th day	101.9 ± 60	96.9 ± 17.9	103.4 ± 67.8	
P*	0.869			
V_5 QRS (ms)				
Admission ED	100 ± 22.6	99.1 ± 22	101.5 ± 16.9	0.423
5th day	99.4 ± 21	101.5 ± 17	98.8 ± 22.1	
P*	0,836			
V_6 QRS (ms)				
Admission ED	98.8 ± 23.7	97.9 ± 23.1	99.1 ± 24	0.471
5th day	98.9 ± 20.6	100.8 ± 18.0	98.4 ± 21.4	
P*	0.668			
V_5 Tp-e (ms)				
on ED	81.3 ± 21.7	82.1 ± 25.2	81 ± 20.6	0.387
5th day	91.8 ± 25.5	89.2 ± 26.9	92.6 ± 25.1	
P*	0			
V_6 Tp-e(ms)				0.45

on ED	80.9 ± 21.8	81.4 ± 26.2	80.8 ± 20.3	
5th day	91.8 ± 25.5	89.2 ± 26.9	92.5 ± 25.2	
P*	0			
QTc (ms)				
on ED	423.7 ± 49.4	432.2 ± 48.4	421.1 ± 49.6	0.06
5th day	444.2 ± 60.1	436.1 ± 53.1	446.7 ± 62.1	
P*	0,012			
iCEB (QT/QRS)				
on ED	3.6 ± 0.7	3.7 ± 0.8	3.59 ± 0.7	0.03
5th day	4.0 ± 0.7	3.8 ± 0.7	4.06 ± 0.7	
P*	0			
iCEBc (QTc/QRS)				
on ED	4.4 ± 0.8	4.5 ± 0.9	4.3 ± 0.8	0.03
5th day	4.6 ± 0.8	4.4 ± 0.9	4.6 ± 0.7	
P*	0.354			
V_5 Tp-e/QT				
on ED	0.2 ± 0.04	0.23 ± 0.05	0.23 ± 0.04	0.96
5th day	0.2 ± 0.05	0.23 ± 0.05	0.23 ± 0.05	
P*	0.469			
V_5 Tp-e/QTc				
on ED	0.19 ± 0.1	0.18 ± 0.05	0.19 ± 0.04	0.93
5th day	0.20 ± 0.1	0.20 ± 0.04	0.20 ± 0.04	
P*	0.003			
V_6 Tp-e/QT				
on ED	0.23 ± 0.05	0.22 ± 0.1	0.23 ± 0.1	0.88
5th day	0.23 ± 0.05	0.23 ± 0.1	0.23 ± 0.1	
P*	0.37			

Data are represented as mean values ± standard deviation (SD); *within subjects; **between subjects; ED = emergency department; max = maximum; min = minimum; iCEB = index of cardio-electrophysiological balance.

Table 4. Spearman correlation test for index of cardio-electrophysiological balance (iCEB) and corrected index of cardio-electrophysiological balance ($iCEB_{c)}$

	iCEB		**$iCEB_C$**	
	P	**R**	**P**	**R**
QT	0.15	−0.11	0	−0.32
QTc	0.18	0.1	0	0.326
V_5 Tp-e	0.38	0.69	0	−0.69
V_6 Tp-e	0.007	0.21	0.93	−0.006
V_5 Tp-e/QT	0.046	0.15	0	0.88
V_6 Tp-e/QT	0.57	0.04	0.009	−0.2
Tp-e/QTc	0.51	0.05	0.01	−0.2