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Relationship between index of cardio-electrophysiological balance and hydroxychloroquine in patients with COVID-19

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Abstract

Hydroxychloroquine (HCQ) treatment is frequently prescribed for coronavirus disease 2019 (COVID-19). Electrocardiographic (ECG) monitorization is recommended because HCQ causes QT interval prolongation. The index of cardioelectrophysiological balance (iCEB), calculated as the ratio of QT interval / QRS duration. In recent years, iCEB has been described as an important marker for dysrhthmias. Decreased or increased iCEB is related with lethal ventricular arrhythmias. In our research, we purposed to investigate the relationship between iCEB and HCQ in patients with COVID-19. 200 patients (males, 84; females, 116; 60.4 ± 13.8 years) with PCR positive and chest tomography findings compatible with COVID-19 pneumonia were registered in the research. Demographic, clinical, and laboratory data for all patients were collected. ECG was recorded from all patients on admission to COVID-19 clinic, in oral treatment with HCQ (200 mg, twice daily) for at least 5 days. iCEB (QT/QRS) was calculated from the 12-lead electrocardiogram.The mean age of the patients was 60.4 ± 13.8 years. Compared to admission ECG, ECG on day 5 showed significant increases in heart rate, QT interval, corrected QT (QTc) interval, and iCEB. Our results suggested that iCEB is related with HCQ treatment in patients with COVID-19. Previous studies stated that high iCEB is related with torsade de Pointes (TdP), ventricular tachycardia.

Keywords: electrocardiography, hydroxychloroquine, arrhythmia, COVID-19

1. Introduction

Coronavirus disease-2019 (COVID-19) is the important reason of the pandemic disease. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is cause of COVID-19. COVID-19 is an important cause of disability and fatality. The clinical manifestation of COVID-19 is various, from myalgia to severe acute respiratory distress syndrome (1). To date, there are no efficacious COVID-19 treatment. Patients are treated with several nonspecific drugs. Gautret et al. shows that HCQ is now one of the most used therapies for COVID-19 patients (2). However, HCQ can cause QT prolongation. Drug related QT-interval prolongation is important risk of fatal ventricular dysrhythmias and mortality. Therefore, ECG records of COVID-19 patients treated with HCQ treatment is important to recognize QT prolongation (3).

QT dispersion (QTd) is an indirect ECG measures of the ventricular repolarization (4). There are different results of the prognostic value of QTd in COVID-19 patients. For this reason, its prognostic value in COVID-19 remain contradictory. Recently a new noninvasive marker iCEB among the repolarization and the depolarization of the action potential was developed as an important risk parameter of dysrhythmia. iCEB was measured as the proportion of QT interval / QRS duration, which plays a significant role in dysrhythmia (5).

In this study, we researched the relation between iCEB and HCQ treatment in COVID-19 patients.

2. Materials and Methods

2.1. Study participants and design

A total of 282 patients with PCR positive and chest tomography results appropriate with COVID-19 pneumonia admitted to the COVID-19 clinics were enrolled in this study between 1 April 2020 and 1 September 2020. COVID-19 patients with ECGs that could not be calculated (n = 8), patients with right and left bundle branch block in ECG (n = 12), and those without control ECG (n = 29) were excepted. Furthermore, patients with a hospitalization duration < 5 days (n = 33) were excluded from the study. Therefore, 200 COVID-19 patients (males, 84; females, 116; mean age, 60.4 ± 13.8 years) were included in the research. Clinical characteristics of patients were recorded. The patients were treated with HCQ (400 mg/d for 5 days). Twelve-lead ECGs were analysed in each patient before HCQ treatment, 3 and 5 days after HCQ treatment. The HCQ treatment was not started in patients with contraindications, including hypopotasemia, or when the QTc interval was greater than 500 ms, according to the Bazett formula. The HCQ treatment was stopped if there was a QTc greater than 60 ms compared with a baseline or when the QTc interval was more than 500

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ms. We also paid important attention to possible drug interactions. Particularly, medications that could prolong the QTc interval. Our research was accepted by the Ethics Committee of Health Sciences University of Turkey, Diyarbakir Gazi Yasargil Education and Research Hospital (Reference Number of Ethic Committee: 499, Date:03 / 07 / 2020), and informed assent was obtained. The study was performed with respect to the Helsinki Declaration of ethical guidelines revised in 2013.

Table 1. Demographic features of patients on admission

Baseline characteristics	N (%)
Sex	
Female	116 (58%)
Male	84 (42%)
Age (years)	60.4 ± 13.8
Smoking	46 (23%)
Heart failure	8 (4%)
Hypertension	24 (12%)
Coronary artery disease	14 (7%)
Cerebrovascular disease	6 (3%)
Diabetes mellitus	38 (19%)
Chronic kidney disease	12 (6%)

2.2. Analysis of QT, iCEB

12-lead ECGs were saved at 10 mm/mv gain and 25 mm/s speed with ECG-9132K Nihon Kohden ECG (Nihon Kohden Corporation, Tokyo, Japan). ECG was saved at hospitalization in the COVID-19 clinic for patients with a COVID-19. Thereafter ECG parameters were manually calculated. All ECG parameters were calculated by skilled cardiolog who was oblivious of the clinical parameters. The QT interval was calculated from the onset of the QRS to the termination of the T-wave. The termination of the T-wave was described as the dot of go back to the isoelectric line. In patients where the T-wave was interrupted by a U-wave, the end of the T-wave was described as the lowest point between the T- and U-waves. For example, the T-wave could not be dependable described owing to especially low voltage (< 0.1 mV), calculation of QT interval was not performed. As a result, these leads were excepted from the ECG analysis. So that, except the efficacy of the heart rate (HR), the QT interval was calculated with respect to the Bazett formula (QTc=QT/square root of RR interval). QTd was described as the maximum QT minus minimum QT intervals. T peak to T end (Tpe) was calculated with a scale from the peak of the T-wave to its end. The QRS duration was calculated from the inception of the Q wave, or the R wave if Q wave was not observable, to the J point. iCEB was measured by both the ratio of QT/QRS, calculated from the ECG recordings (6).

2.3. PCR Analyses for COVID-19

Nasopharyngeal swab technique (nose or throat) for specimen collecting for COVID-19 based upon the disease control guidelines for COVID-19 (7). Nasopharyngeal and oropharyngeal specimens were gathered from the cases by synthetic fiber swabs (Citotest Scientific Co, Haimen City, PR China). The swab materials were put into 3 ml sterile viral transport material (Citotest Scientific Co) in the course of the gathering and carried with biohazard sample bag. Thereafter the specimen was received, they were carried to the PCR analyses laboratory and tested about a few hours. Specimens were swirled for 3–5 s previous to testing and a adjusted pipette was utilized to carry the specimen volume defined in producer's directives for utilization. The molecular identification methods include the analysis of nucleic acids present in the sample to detection the virus. The identification of COVID-19 was done by reverse transcription-polymerase chain reaction (RT-PCR) testing utilizing the CFX96 Real-Time System (Bio-Rad, USA) (8). Identification was made with the RT-PCR kits, the Bio-Speddy (Bioeksen R&D Technologies Inc. COVID-19 RT-qPCR Detection Kit v2.0, Istanbul, Turkey). Viral RNA subtraction from specimen were carried to with respect to the producer's directives. In order to automated viral nucleic acid subtraction process CFX96 Real-Time System (Bio-Rad, USA) was utilized. A negative (human specimen control) was contained in each RNA subtraction process, and a non-formwork (water) control was contained in each RT-PCR actuate. An internal control amplification was carried out to observe RNA subtraction and RT-PCR quality.

Table 2. Laboratory findings of patients on admission to hospital

Parameters	Values
Hemoglobin, g/dL	11.7 ± 2.1
Platelet count, ($\times 10^3/\mu L$)	274 ± 156
White blood cell count, ($\times 10^3/\mu L$)	8.6 ±3.5
Neutrophil cell count, ($\times 10^3/\mu L$)	5.7 ± 2.9
Lymphocyte cell count, ($\times 10^3/\mu L$)	1.4 ± 0.8
Serum creatinine, mg/dL	1.13 ± 0.89
Alanine aminotransferase, U/L	36 ± 14
Serum potassium, mEq/L	4.1 ± 0.7
Serum sodium, mEq/L	135.7 ± 2.9
Albumin , g/L	39 ± 11
Calcium , mg/dL	8.56 ± 0.9
C-reactive protein, mg/dL	37.8 ± 24.2
Ferritin, ng/mL	118 (52 - 220)
D-dimer, ng / mL	357 ± 223
Systolic BP, mm Hg	125.7 ± 18.6
Diastolic BP, mm Hg	75 ± 12.3

*BP.Blood pressure

2.4. Statistical analysis

Statistical analysis was execute with the SPSS statistical program (Version 12.0; SPSS Inc., Chicago, IL,USA). All baseline parameters were analyzed. Continuous variables are stated as mean±SD and categorical parameters are defined as percentages. Continuous variables were compared utilizing the paired t-test if the data were normally deployed and Wilcoxon's rank sum test if the data were not normally deployed. p values < 0.05 were contemplated statistically important. Correlation analyses were utilized to identify the relationship between iCEB and clinical parameters.

3. Results

3.1. Patient characteristics

Baseline clinical parameters of the 200 study cases are listed in Table 1. Mean patient age was 60.4 ± 13.8 years, and 116

of the patients (58%) were female. Cardiovascular comorbidities contained arterial hypertension (n = 24 [12%]), systolic heart failure (n = 8 [4%]), coronary artery disease (n = 44 [7%]), and diabetes mellitus (n = 38 [19%]). A total of 12 patients (6%) had renal failure. A whole of 12 patients (6%) had cerebrovascular disease (Table 1). The laboratory parameters of the cases at the time of presentation are demonstrated in Table 2.

3.2. ECG characteristics during HCQ treatment

A 12-lead ECG was saved at admission before starting HCQ therapy and fifth day after HCQ treatment in whole study cases. ECG parameters in the course of HCQ treatment are listed in Table 3. Heart rate, QT interval, QTc interval, iCEB, Tp-e and Tp-e/QT were importantly higher after HCQ therapy than before HCQ treatment. There are no significant changes in QRS duration.

Table 3. Electrocardiographic parameters of the patients

Variables	1. Day	5.day	p Value
Heart rate (beats/min)	83 (76-91)	96 (81-106)	< 0.001
QT interval (ms)	363.6 ± 35	379 ± 30	< 0.001
QTc interval (ms)	418 ± 36.5	455.6 ± 29.4	0.005
QRS (ms)	84.8 ± 6.8	89.3 ± 11.8	0.899
Tp-e interval (ms)	58.2±5.4	66.4±7.1	<0.001
Tp-e / QT ratio	0.15±0.04	0.17±0.06	0.02
iCEB	4.57 ± 0.27	5.11 ± 0.51	< 0.001

* iCEB: İndex of cardioelectrophysiological balance

Correlation analysis performed to research the association between iCEB and clinical parameters showed a positive correlation between the iCEB and HCQ and age and negative correlation between iCEB and potassium level (Table 4).

Table 4. Correlation between 5. day iCEB score and clinical parameters in patients with COVID-19

Parameters	Correlation coefficient (r value)	p Value
Age	0.571	0.032
Coronary artery disease	0.314	0.567
Hypertension	0.213	0.574
Diabetes mellitus	0.287	0.615
Cr Cl level at initiation	0.419	0.714
Potassium level at initiation	-0.374	0.040
Calcium level at initiation	0.325	0.591
HCQ treatment	0.618	0.032
CRP	0.028	0.756

*CrCl: Creatinin Clirence, † iCEB: İndex of cardioelectrophysiological balance, ‡ HCQ: Hydroxychloroquine

4. Discussion

Previous clinical studies show that prolonged QT interval is associated with arrhythmia risk (6,9). Drug-related QT interval prolongation is a significant cause for TdP. Also, it is significant to contemplate that already attentive monitoring of the QT interval may solely reduce the risk of TdP. Lethal arrhythmias frequently become in the setting of unexpected episodic alteration in the R-R interval, such as when APCs, VPCs, or pauses consist. In these patients, TdP can occur although the QTc interval in merely slightly extended at baseline (10).

HCQ activates calcium and sodium channel blockades. These channels have got membrane-stabilizing effects. Calcium and sodium channel blockades might conclusion in conduction disturbances with a QRS interval widening, QT prolongation, and atrioventricular block (11). This side effect might be also increased in the COVID-19 disease. Other causes of arrythmias are drug-to-drug interplay (clarithromycin, azithromycin, antivirals, etc) and acute infection related fever, dehydration and electrolyte abnormalities (12). COVID-19 is especially responsible for an acute respiratory disease. In addition, COVID-19 can cause acute coronary syndrome and myocarditis (13,14).

Previous study stated that, addition of azithromycin to chloroquine can cause prolongation of about 15 ms in the QTc interval (15,16). Nevertheless, drug related lethal arrythmia risk is significantly higher in hospitalized patients. Lethal arrythmia risk is significantly higher in cases who have another risk factors for arrythmia. Arrythmia risk factors are genetic factors (17), advanced age, existence of underlying cardiovascular disease, electrolyte disturbances, and combination thearpy with other QT-prolonging drugs (18-20). In the present study, we found that heart rate, Tp-e, Tp-e/QT, QT, QTc were importantly higher after HCQ treatment in COVID-19 patients.

Nevertheless, there is some drawbacks the usage of QT prolongation as the unique risk sign for dysrhythmias. The normal QT interval is no guarantee for absence of proarrhythmia. For this reason, an investigation is in progress for better evaluation of arrhythmia risk markers. In recent years, iCEB was recommended as a novel and noninvasive biomarker to estimate the risk for both TdP and non-TdP VT/VF. It was proposed that an optimum equilibrium between repolarization (QT interval), and depolarization (QRS duration) are very important to protect the electrical steadiness of the ventricles: diverging too much from this sensitive equilibrium may actually be proarrhythmic (21).

iCEB (QT/QRS) is an easy but efficacious ECG substitute of the cardiac wavelength. Robyns et al. found that the correlation between the effective refracter period calculated during electrophysiologic study and the uncorrected QT interval, so ancillary the notion of this novel parameter as an ECG substitute for cardiac wavelength (6). Only limited data are present on cardiac wavelength as a risk determinative, primarily owing to the invasive character to calculate it. They found that iCEB is a readily measurable local estimate of the cardiac wavelength. iCEB is increased in circumstances that make susceptible predispose to TdP. iCEB calculated from the ECG, could serve as a significant, novel and non-invasive parameter for potential risks of cardiac dysrhythmias beyond long QTs and TdP. Causes of prolonged QT-interval (inherited long QTs) are significantly increasing iCEB. Increasing iCEB is associated with TdPs (6). For this reason, iCEB might use as a noninvasive and easily quantifiable marker to determine increased arrhythmic risk (6). Nevertheless, to our knowledge, no studies in the literature have researched the association between the iCEB and HCQ treatment in COVID-19 patients.

In this research, we found that iCEB score was importantly higher after HCQ treatment in COVID-19 patients. For this reason, we propose that individual risk/benefit evaluating should be carried out before treatment with HCQ. We suggested that daily ECG monitoring, with reappraisel of treatment if high-risk parameters seem (iCEB, QTc interval).

Conflict of interest

The authors report no conflicts of interest.

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