J Surg Med. 2021;5(5):412-416.
DOI: 10.28982/josam.843042

Research article

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effects of treatment with hydroxychloroquine and azithromycin on the index of cardiac electrophysiological balance in patients with COVID-19: A retrospective cohort study

Songül Araç [1], Zülküf Karahan [2], Mehmet Özel [1], Ramazan Yiğit [3], Hasan Akkoç [4], Eşref Araç [5]

[1] Department of Emergency Medicine, University of Health Sciences, Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey
[2] Department of Cardiology, Diyarbakır Gazi Yasargil Training and Research Hospital, University of Health Sciences, Diyarbakır, Turkey
[3] Department of Emergency Medicine, Diyarbakır Ergani State Hospital, Diyarbakır, Turkey
[4] Department of Pharmacology, Faculty of Medicine, Dicle University, Diyarbakır, Turkey
[5] Department of Internal Medicine, Diyarbakır Gazi Yasargil Training and Research Hospital, University of Health Sciences, Diyarbakır, Turkey

ORCID ID of the author(s)

SA: 0000-0001-6830-3639
ZK: 0000-0001-8145-9574
MÖ: 0000-0002-4797-7017
RY: 0000-0002-0420-6837
HA: 000-0003-2836-2452
EA: 0000-0001-6041-3817

Corresponding Author
Songül Araç
Department of Emergency Medicine, University of Health Sciences, Diyarbakır Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey
E-mail: drsongularac@gmail.com

Ethics Committee Approval
This study was approved by the ethics committee of Gazi Yaşargil Education and Research Hospital with the decision numbered 452 and dated April 28, 2020.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 May 3

Copyright © 2021 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Background/Aim: The common cardiac toxicities of hydroxychloroquine (HCQ) and azithromycin (AZ) are not well defined in COVID-19 patients. Index of cardiac electrophysiological balance (iCEB) is used as a novel risk marker for drug-induced arrhythmias. The purpose of this study was to evaluate ventricular repolarization using iCEB and other conventional ECG parameters such as the end of electrocardiographic T wave (Tp-e) interval, Tp-e/QT ratio, and Tp-e/ heart rate-corrected QT (QTc) ratio in COVID-19 patients treated with HCQ and AZ.

Methods: This retrospective study enrolled 164 patients diagnosed with COVID-19 pneumonia in the Emergency Department (ED) and then transferred to the ward or the intensive care unit in April 2020.

Results: A total of 164 patients with a mean age of 47 (18) years (range: 18-97 years) included 83 (50.6%) females. There were 38 and 126 patients in Groups HTQ and HTQ+AZ, respectively. On the 5th day of hospitalization, all patients' heart rates were significantly lower (P<0.001), while QTc, QT max (V5-V6), QTmin, Tp-e (V5-V6), and iCEB values were significantly higher (P=0.01 and P<0.001 for the rest, respectively) compared to the basal values measured in the ED (P<0.001). iCEB values of the HTZ+AZ group were significantly higher than those of the HTQ group (P=0.03). iCEBc strongly positively correlated with Tp-e/QT (V5), and strongly negatively correlated with Tp-e (V5).

Conclusion: The iCEB values were increased after HTQ and AZ treatment among COVID-19 patients, and strongly correlated with Tp-e and Tp-e/QT. iCEB is a simple, non-invasive method that can be a useful marker to evaluate ventricular repolarization in COVID-19 patients.

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

How to cite: Araç S, Karahan Z, Özel M, Yiğit R, Akkoç H, Araç E. Effects of treatment with hydroxychloroquine and azithromycin on the index of cardiac electrophysiological balance in patients with COVID-19: A retrospective cohort study. J Surg Med. 2021;5(5):412-416.

Introduction

In December 2019, cases of pneumonia, caused by a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), occurred in Wuhan, China [1]. The World Health Organization has announced the official name of this disease as coronavirus disease 2019 (COVID-19) [2]. Repositioning of old drugs for use as a possible therapeutic agent to treat COVID-19 can be an attractive approach because knowledge on clinical safety, efficacy profile, side effects, and drug interactions are well defined [3].

In the previous severe acute respiratory syndrome (SARS) outbreak, hydroxychloroquine (HCQ) was confirmed to have antiviral activity in vitro [4]. This suggests that HCQ may be a possible therapeutic agent for patients with COVID-19. Based on available evidence, an authorization was published by the United States Food and Drug Administration to permit the use of HCQ and chloroquine treatment in COVID-19 patients [5]. Also, in a previous study, HCQ treatment in combination with azithromycin (AZ) was related to 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. Few studies have evaluated adverse events potentially linked to the use of HCQ or chloroquine and AZ in COVID-19 patients, including electrophysiological cardiac conditions of prolonged QT and arrhythmia [8–10].

Fatal arrhythmias can be caused by electrophysiological changes during ventricular repolarization [11]. In a previous clinical study, 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 ratio were novel electrocardiogram (ECG) parameters to assess ventricular repolarization and associated with malignant ventricular arrhythmias [13–15]. A novel marker index of cardio-electrophysiological balance (iCEB), measured as QT interval divided by QRS duration, is an ECG-based derivative of cardiac wavelength λ (λ = conduction velocity x effective refractory period or QT/QRS). Cardiac wavelength λ is related to arrhythmogenesis: Drugs that decrease the wavelength are may raise the risk for non-TdP VT or VF while drugs that increase wavelength may raise the risk for TdP [16, 17]. ICEB projects the balance between cardiac repolarization and depolarization of the action potential, similar to cardiac wavelength λ [18].

The purpose of this study was to evaluate ventricular repolarization using iCEB and other conventional ECG parameters such as the end of electrocardiographic T wave (Tp-e) interval, Tp-e/QT ratio, and Tp-e/QTc ratio in COVID-19 patients treated with HCQ and AZ.

Materials and methods

This is a retrospective cohort study. The institutional ethics board of the Gazi Yasargil Training and Research Hospital, an affiliate of the University of Health Sciences, reviewed and approved this retrospective study (decision date: 28 April 2020, no: 452).

Patients

This study enrolled 164 patients who were diagnosed with COVID-19 in the emergency department and then transferred to the ward or the intensive care unit of a tertiary hospital in Diyarbakır, Turkey, in April 2020. The diagnoses 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 in the emergency department, C) Being 18 years of age or older. All hospitalized patients diagnosed with COVID -19 pneumonia were treated with hydroxychloroquine 400 mg twice a day followed by 200 mg twice a day for 4 days, in combination with azithromycin 500 mg orally a day for 5 days [7]. Patients who stayed in the hospital for less than five days, treated for acute electrolyte imbalance and/or were on antiarrhythmic drugs were excluded from this study, in addition to those who used any drugs (antibiotics, antifungals, antipsychotics) associated with QTc prolongation in addition to standard treatment in the first five days. Patients were divided into two groups, as those treated with only hydroxychloroquine (Group HCQ) and those treated with a combination of hydroxychloroquine and azithromycin (Group HCQ + AZ).

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

Electrocardiogram (ECG) analysis

Initial ECGs were obtained in the emergency department and after the completion of treatment (on the 5th day of hospitalization). ECGs were obtained at a rate of 25 mm/s, while patients were in resting position (Nihon Kohden, Tokyo, Japan,). All ECGs were recorded to a computer to reduce error measurements. A software (Adobe Photoshop**, Adobe Systems**, CC 2015, San Jose, CA, USA) was used for 400% magnification. All ECGs were evaluated for 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 QT interval was measured from the onset of the QRS complex until the end of the T wave. The longest QT intervals in V_5 and V_6 leads were considered QT maximum and the shortest QT interval in any lead was considered 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 leads V5 and V6. Tp-Te/QT ratio was calculated separately on V5 and V6. ICEB was calculated by dividing QT interval by QRS interval and iCEBc was calculated by dividing QT_c interval by QRS interval in the leads V5-V6.

Statistical analysis

SPSS version 22.0 (IBM SPSS Statistics for Windows, Armonk, United States of America) was used for statistical analysis. Descriptive statistics were presented as frequency and percentage for categorical variables and mean and standard deviation for numerical variables. When conditions for normal distribution were not met, comparisons for two independent

groups were performed using the Mann-Whitney test. To analyze the interaction between measures and treatments, repeated-measures analysis of variance (ANOVA) was used. Spearman correlation test was utilized 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

Demographic and clinical characteristics of study patients

The demographic features, vitals, laboratory parameters, and outcomes of the study population are summarized in Table 1. A total of 164 patients with a mean of 47 (18) years (range, 18-97 years) included 83 (50.6%) females. Thirty-eight patients were treated with hydroxychloroquine only (HCQ group), and 126 patients received a combination of hydroxychloroquine and azithromycin (HCQ + AZ group). The demographic data, vital parameters, and comorbidities of the two groups were similar (Table 1). There was no significant difference between the HCQ group and HCQ + AZ group in terms of admission to the ward or the intensive care unit and length of hospital stay (Table 1). Of 164 patients, the positive reverse transcription-polymerase chain reaction (RT-PCR) tests of 71 (43.3%) were positive, among which 18 patients belonged to the HCQ group (47.4%). The RT-PCR positivity rates were similar between the two groups (P=0.69). The mortality rate in the study population was 5.5% (n=9). HCQ group had 2 (5.3%) in-hospital patient deaths, while the HCQ+AZ group had 7 (5.6%) (P=1). Among all, 17.7% had hypertension, 8.5% had cardiovascular diseases, and 15.9% had diabetes. Nineteen cases with comorbidities (11.6%) were admitted to the intensive care unit (Table 1).

Table 1: Demographics and comorbidities of patients by survival or non-survival during hospitalization

	Total (n=164)	Group HCQ (n=38)	Group HCQ + AZ (n=126)	*P*-value
Age (years/old)	47.7 (18.9)	44.8 (19.7)	48.6 (18.7)	0.27
Sex (n,%)				0.64
Female	83 (50.6)	21 (55.3)	62 (49.2)	
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,%)				0.24
Non-ICU	145 (88.4)	36 (94.7)	109 (86.5)	
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, SPO2: oxygen saturation, ICU: intensive care unit

Clinical laboratory data

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

Table 2: Laboratory parameters

	Total (n=164) n (%)	Group HCQ (n=38) n (%)	Group HCQ + AZ (n=126) n (%)	*P*-value **
WBC (4.000-10.000/mm^3)				0.652
in ED	7.85 (6)	6.70 (3)	8.19 (6.3)	
5th day	7.07 (5)	6.16 (2)	7.35 (5.2)	
P-value *	0.044			
Neutrophil (2.000-7.000/mm^3)				0.695
in ED	5.4 (4)	4.65 (3)	5.62 (4.1)	
5th day	4.32 (2)	3.77 (2)	4.5 (2.4)	
P-value *	0.002			
Lymphocyte (800-4000/mm^3)				0.659
in ED	1.58 (0.7)	1.48 (0.7)	1.61 (0.7)	
5th day	2.07 (3.5)	1.77 (0.7)	2.17 (4)	
P-value *	0.164			
Platelet (150.000-450.000/mm^3)				0.776
in ED	233.8 (8)	219.02 (65.8)	238.32 (87.2)	
5th day	266.2 (8)	254.23 (72)	269.81 (83.1)	
P-value *	<0.001			
Hemoglobin (11-16 gr/dl)				0.051
in ED	13.5 (2)	13.29 (2.4)	13.6 (1.8)	
5th day	13.1 (1.9)	13.1 (2.3)	13.02 (1.8)	
P-value *	<0.001			
Hematocrit (37-54 %)				0.046
in ED	41.8 (5.3)	40.9 (6.8)	42.1 (4.8)	
5th day	40.4 (5.2)	40.4 (6.5)	40.3 (4.8)	
P-value *	<0.001			
C-reactive protein (0-5 mg/L)				0.675
in ED	43.1 (62.4)	40.9 (72)	43.6 (60)	
5th day	35.9 (59.6)	30.8 (61)	37.5 (59.3)	
P-value *	0.083			
Calcium (8,8-10,6 mg/dl)				0.443
in ED	8.7 (0.5)	8.7 (0.5)	8.7 (0.5)	
5th day	8.4 (0.5)	8.4 (0.6)	8.4 (0.5)	
P-value *	<0.001			
Chlorine (98-107 mmol/l)				0.897
in ED	103.8 (3.2)	103.7 (3.7)	103.8 (3.1)	
5th day	104.7 (3.4)	104.6 (4.2)	104.8 (3.1)	
P-value *	0.007			
LDH (135-225 U/l)				0.33
in ED	254.4 (104.6)	241.2 (122.4)	258.4 (99)	
5th day	268.5 (150.2)	238.2 (123.4)	277.7 (156.7)	
P-value *	0.479			
Potassium (3.5-5.2 mEq/L)				0.38
in ED	4.03 (4.3)	4.0 (0.4)	4.0 (0.4)	
5th day	4.3 (0.5)	4.2 (0.5)	4.3 (0.5)	
P-value *	<0.001			
Sodium (134-146 mEq/L)				0.821
in ED	137.2 (2.9)	137.1 (2.7)	137.7 (3)	
5th day	138.4 (2.5)	138.4 (2)	138.4 (2.7)	
P-value *	<0.001			

HCQ: hydroxychloroquine, AZ: azithromycin, WBC: white blood cell, ED: emergency department, LDH: lactate dehydrogenase, *within subjects, **between subjects

Electrocardiogram data

All patients' ECGs were obtained in the emergency department and after the treatment was completed (on the 5th day of hospitalization) (Table 3). On the 5th day of hospitalization, heart rates (HR) were significantly lower compared to those obtained in the emergency department (P<0.001), while QTc, QT maximum (V5-V6), QT minimum, Tp-e (V5-V6) and ICEB values were significantly higher (P=0.01 and P<0.001 for the rest, respectively). The changes in QT max (V5-V6), QT minimum, Tp-e (V5-V6), and QTc values were similar between the groups. The iCEB values of the HCQ+AZ group were significantly higher than those of the HCQ group (P=0.03).

The iCEBc values had changed insignificantly in all patients from admission until the 5th day of hospitalization; they were increased in the HCQ+AZ group and decreased in the HCQ group.

iCEBc was strongly correlated with Tp-e/QT (V5), strongly negatively correlated with Tp-e (V5), and weakly correlated with QTc and QT (Table 4).

Table 3: Electrocardiogram parameters

	Total (n=164) n (%)	Group HCQ (n=38) n (%)	Group HCQ + AZ (n=126) n (%)	*P*-value **
Heart rate (bpm)				0.856
in ED	89.9 (16.6)	90.9 (19.02)	89.7 (16)	
5th day	79.6 (14.3)	80.2 (16.52)	79.5 (13.7)	
P-value *	0			
V_5 QT max (ms)				0,128
in ED	350.2 (51.3)	356.4 (52.6)	348.38 (5)	
5th day	390.9 (70.5)	381.7 (53.1)	393.66 (7)	
P-value *	0			
V_6 QT max (ms)				0.155
in ED	349.9 (52.1)	356.0 (54.1)	348.06 (51.6)	
5th day	390.6 (69.8)	381.7 (53.1)	393.33 (74)	
P-value *	0			
QT min (ms)				0.166
in ED	327.0 (5)	329.6 (46.6)	326.3 (48.8)	
5th day	363.6 (7)	350.4 (60.3)	367.6 (69.4)	
P-value *	0			
DII QRS (ms)				0.432
in ED	98.51 (24.7)	100.4 (30.9)	97.9 (22.6)	
5th day	101.9 (60)	96.9 (17.9)	103.4 (67.8)	
P-value *	0.869			
V_5 QRS (ms)				0.423
in ED	100 (22.6)	99.1 (22)	101.5 (16.9)	
5th day	99.4 (21)	101.5 (17)	98.8 (22.1)	
P-value *	0,836			
V_6 QRS (ms)				0.471
in ED	98.8 (23.7)	97.9 (23.1)	99.1 (24)	
5th day	98.9 (20.6)	100.8 (18.0)	98.4 (21.4)	
P-value *	0.668			
V_5 Tp-e (ms)				0.387
in ED	81.3 (21.7)	82.1 (25.2)	81 (20.6)	
5th day	91.8 (25.5)	89.2 (26.9)	92.6 (25.1)	
P-value *	0			
V_6 Tp-e(ms)				0.45
in 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-value *	0			
QTc (ms)				0.06
in ED	423.7 (49.4)	432.2 (48.4)	421.1 (49.6)	
5th day	444.2 (60.1)	436.1 (53.1)	446.7 (62.1)	
P-value *	0.012			
iCEB (QT/QRS)				0.03
in ED	3.6 (0.7)	3.7 (0.8)	3.59 (0.7)	
5th day	4.0 (0.7)	3.8 (0.7)	4.06 (0.7)	
P-value *	0			
iCEBc (QTc/QRS)				0.03
in ED	4.4 (0.8)	4.5 (0.9)	4.3 (0.8)	
5th day	4.6 (0.8)	4.4 (0.9)	4.6 (0.7)	
P-value *	0.354			
V_5 Tp-e/QT				0.96
in ED	0.2 (0.04)	0.23 (0.05)	0.23 (0.04)	
5th day	0.2 (0.05)	0.23 (0.05)	0.23 (0.05)	
P-value *	0.469			
V_5 Tp-e/QTc				0.93
in ED	0.19 (0.1)	0.18 (0.05)	0.19 (0.04)	
5th day	0.20 (0.1)	0.20 (0.04)	0.20 (0.04)	
P-value *	0.003			
V_6 Tp-e/QT				0.88
in ED	0.23 (0.05)	0.22 (0.1)	0.23 (0.1)	
5th day	0.23 (0.05)	0.23 (0.1)	0.23 (0.1)	
P-value *	0.37			

Data are represented as mean values (standard deviation); *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-value	R	*P*-value	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

Discussion

This is the first human study to demonstrate the clinical usability of iCEB 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 increases ventricular repolarization heterogeneity and ventricular arrhythmias. iCEB may a more sensitive marker than QT prolongation in predicting the risk of multi-drug arrhythmia.

In this study, the most prevalent comorbidities were hypertension (17.7%), diabetes (15.9%), and cardiovascular disease (8.5%). The literature offers few studies about the incidence of comorbidities among COVID-19 patients. Yang et al. assessed the prevalence of comorbidities in COVID-19 patients in a meta-analysis and found various underlying diseases, including hypertension (21.1%), cardiovascular (8.4%,) and respiratory system diseases (1.5%) [19]. Another meta-analysis by Li et al. examined comorbidity incidence among COVID-19 cases and reported the most prevalent as hypertension (17.1%), diabetes (9.7%) cardio-cerebrovascular diseases (16.4%) [20].

Few studies have evaluated adverse events potentially linked to the use of HCQ and AZ in patients with COVID-19, including electrophysiological cardiac conditions of prolonged QT and arrhythmia [8–10]. Arrhythmic events frequently encountered in COVID-19 patients and drugs used in treatment also have a pro-arrhythmic effect. COVID-19 causes direct and indirect damage to the cardiovascular system at varying levels [20]. In COVID-19 patients, HCQ, used as a possible therapeutic agent, can lead to QT interval prolongation and Torsades de Pointes (TdP). Erythromycin, azithromycin, clarithromycin, telithromycin, and roxithromycin are listed either as drugs that are definitely or possibly linked to TdP [21]. Possible therapeutic agents (HCQ, AZ, lopinavir/ritonavir, remdesivir, and others) for treatment of COVID-19 carry a risk of inducing 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 effects of QT interval prolongation. This side effect could be a mechanism that predisposes to ventricular arrhythmias [23,24]. However, it is known that 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 to 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]. Alsancak et al. reported that patients with two or three-vessel coronary artery ectasia had a higher Tp-e and Tpe/QT ratio than those with one vessel coronary artery ectasia [27]. A new non-invasive marker, ICEB, projects the balance between cardiac depolarization and repolarization, similar to cardiac wavelength λ, which is related to arrhythmogenesis [16,17,28]. Our study is the first report evaluating iCEB, which was 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 QRS duration) and repolarization (changes QT interval) of the cardiac action potential. Also, they suggested that iCEB predicts potency of drug-related arrhythmia risk beyond long QT and TdP [29].

Robyns et al. reported that iCEB was more useful than the other ECG parameters in predicting ventricular arrhythmia

risk, 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. The others are its single-center design and the limited number of patients. Additional long-term and large-scale studies are required to confirm and clarify our data.

Conclusion

Based on our results, the iCEB values increased after HCQ and AZ treatment in COVID-19 patients. Also, iCEBc values strongly correlated with Tp-e and Tp-e/QT. We think that iCEB is a simple, non-invasive method that can be a beneficial marker to evaluate ventricular repolarization in COVID-19 patients.

References

1. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 2020;63(3):457-60. PMID: 32009228; doi: 10.1007/s11427-020-1637-5.
2. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it. Accessed in 2020 (Sep 11).
3. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020;55(4):105932. PMID: 32145363; doi: 10.1016/j.ijantimicag.2020.105932.
4. Biot C, Daher W, Chavain N, Fandeur T, Khalife J, Dive D, et al. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. J Med Chem. 2006;49(9):2845-9. PMID: 16640347; doi: 10.1021/jm0601856.
5. Food and Drug Administration (FDA). Emergency Use Authorization. Available from: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization. Accessed in 2020 (Sep 11).
6. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949. PMID: 32205204; doi: 10.1016/j.ijantimicag.2020.105949.
7. Bilim Kurulu Çalışması. COVID-19 (SARS-CoV-2 Enfeksiyonu) Rehberi. Available from https://covid19bilgi.saglik.gov.tr/tr/covid-19-rehberi.html. Accessed in 2020 (Sep 11).
8. Chorin E, Dai M, Shulman E, Wadhwani L, Bar-Cohen R, Barbhaiya C, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med. 2020;26(6):808-9. PMID: 32488217; doi: 10.1038/s41591-020-0888-2.
9. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA Netw Open. 2020;3(4):e208857. PMID: 32339248; doi: 10.1001/jamanetworkopen.2020.8857.
10. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of Treatment with Hydroxychloroquine or Azithromycin with In-Hospital Mortality in Patients with COVID-19 in New York State. JAMA. 2020;323(24):2493-502. PMID: 32392282; doi: 10.1001/jama.2020.8630.
11. Monitillo F, Leone M, Rizzo C, Passantino A, Iacoviello M. Ventricular repolarization measures for arrhythmic risk stratification. World J Cardiol. 2016;8(1):57-73. PMID: 26839657; doi: 10.4330/wjc.v8.i1.57.
12. Chugh SS, Reinier K, Singh T, Uy-Evanado A, Socoteanu C, Peters D, et al. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: The Oregon sudden unexpected death study. Circulation. 2009;119(5):663-70. PMID: 19171855; doi: 10.1161/CIRCULATIONAHA.108.797035.
13. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, et al. Prolonged T peak-to-T end Interval on the Resting ECG Is Associated With Increased Risk of Sudden Cardiac Death. Circ Arrhythm Electrophysiol. 2011;4(4):441-7. PMID: 21593198; doi: 10.1161/CIRCEP.110.960658.
14. Castro-Torres Y, Carmona-Puerta R, Katholi RE. Ventricular repolarization markers for predicting malignant arrhythmias in clinical practice. World J Clin Cases. 2015;3(8):705-20. PMID: 26301231; doi: 10.12998/wjcc.v3.i8.705.
15. Antzelevitch C, Oliva A. Amplification of spatial dispersion of repolarization underlies sudden cardiac death associated with catecholaminergic polymorphic VT, long QT, short QT and Brugada syndromes. J Intern Med. 2006;259(1):48-58. PMID: 16336513; doi: 10.1111/j.1365-2796.2005.01587.x.
16. Aidonidis I, Poyatzi A, Stamatiou G, Lymberi M, Stamatoyannis N, Molyvdas PA, et al. Dose-Related Shortening of Ventricular Tachycardia Cycle Length After Administration of the KATP Channel Opener Bimakalim in a 4-Day-Old Chronic Infarct Anesthetized Pig Model. J Cardiovasc Pharmacol Ther. 2009;14(3):222-30. PMID: 19587223; doi: 10.1177/1074248409338929.
17. Lu HR, Hermans AN, Gallacher DJ. Does terfenadine-induced ventricular tachycardia/fibrillation directly relate to its QT prolongation and Torsades de Pointes?. Br J Pharmacol. 2012;166(4):1490-502. PMID: 22300168; doi: 10.1111/j.1476-5381.2012.01880.x.
18. Robyns T, Lu HR, Gallacher DJ, Garweg C, Ector J, Willems R, et al. Evaluation of Index of Cardio-Electrophysiological Balance (iCEB) as a New Biomarker for the Identification of Patients at Increased Arrhythmic Risk. Ann Noninvasive Electrocardiol. 2016;21(3):294-304. PMID: 26305685; doi: 10.1111/anec.12309.
19. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-5. PMID: 32173574; doi: 10.1016/j.ijid.2020.03.017.
20. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109(5):531-8. PMID: 32161990; doi: 10.1007/s00392-020-01626-9.
21. Cubeddu LX. Drug-induced Inhibition and Trafficking Disruption of ion Channels: Pathogenesis of QT Abnormalities and Drug-induced Fatal Arrhythmias. Curr Cardiol Rev. 2016;12(2):141-54. PMID: 26926294; doi: 10.2174/1573403x12666160301120217.
22. Kapoor A, Pandurangi U, Arora V, Gupta A, Jaswal A, Nabar A, et al. Cardiovascular risks of hydroxychloroquine in treatment and prophylaxis of COVID-19 patients: A scientific statement from the Indian Heart Rhythm Society. Indian Pacing Electrophysiol J. 2020;20(3):117-20. PMID: 32278018; doi: 10.1016/j.ipej.2020.04.003.
23. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent Guidance for Navigating and Circumventing the QTc-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for Coronavirus Disease 19 (COVID-19). Mayo Clin Proc. 2020;95(6):1213-21. PMID: 32359771; doi: 10.1016/j.mayocp.2020.03.024.
24. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the Risk of Cardiovascular Death. N Engl J Med. 2012;366(20):1881-90. PMID: 22591294; doi: 10.1056/NEJMoa1003833.
25. Yayla Ç, Bilgin M, Akboğa MK, Gayretli Yayla K, Canpolat U, Dinç Asarcikli L, et al. Evaluation of Tp-E Interval and Tp-E/QT Ratio in Patients with Aortic Stenosis. Ann Noninvasive Electrocardiol. 2016;21(3):287-93. PMID: 26246339; doi: 10.1111/anec.12298.
26. Yontar OC, Karaagac K, Tenekecioglu E, Tutuncu A, Demir M, Melek M. Assessment of ventricular repolarization inhomogeneity in patients with mitral valve prolapse: Value of T wave peak to end interval. Int J Clin Exp Med. 2014;7(8):2173-8. PMID: 25232403.
27. Y. Alsancak, Gürbüz AS, Saklı B, A. İçli, Evaluation of index of cardio-electrophysiological balance and Tp-e/QT ratio in patients with coronary artery ectasia, J. Surg. Med. 2019;3(3) 223–226. https://doi.org/10.28982/josam.485247.
28. King JH, Huang CL, Fraser JA. Determinants of myocardial conduction velocity: Implications for arrhythmogenesis. Front Physiol. 2013;4:154. PMID: 23825462; doi: 10.3389/fphys.2013.00154.
29. Lu HR, Yan GX, Gallacher DJ. A new biomarker − index of Cardiac Electrophysiological Balance (iCEB) − plays an important role in drug-induced cardiac arrhythmias: Beyond QT-prolongation and Torsades de Pointes (TdPs). J Pharmacol Toxicol Methods. 2013;68(2):250-9. PMID: 23337247; doi: 10.1016/j.vascn.2013.01.003.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.