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Evaluation of electrocardiographic ventricular repolarization variables in patients with newly diagnosed COVID-19

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) is a newly recognized infectious disease that has spread rapidly. COVID-19 has been associated with a number of cardiovascular complications, including arrhythmias. The mechanism of ventricular arrhythmias in patients with COVID-19 is uncertain. The aim of the present study was to evaluate the ventricular repolarization by using the Tp-e interval, QT dispersion, Tp-e/QT ratio, and Tp-e/QTc ratio as candidate markers of ventricular arrhythmias in patients with newly diagnosed COVID-19. In addition, the relationship between the repolarization parameters and the CRP (C-reactive protein) was investigated.

Methods: 75 newly diagnosed COVID-19 patients, 75 age and sex matched healthy subjects were included in the study between 20th March 2020 and 10th April 2020. The risk of ventricular arrhythmias was evaluated by calculating the electrocardiographic Tp-e and QT interval, Tp-e dispersion, corrected QT (QTc), QT dispersion (QTd), corrected QTd, Tp-e/QT and Tp-e/QTc ratios. CRP values were also measured in patients with newly diagnosed COVID-19.

Results: Tp-e interval (80.7 ± 4.6 vs. 70.9 ± 4.8 ; $p < .001$), Tp-e / QT ratio (0.21 ± 0.01 vs. 0.19 ± 0.01 ; $p < .001$) and Tp-e/QTc ratio (0.19 ± 0.01 vs. 0.17 ± 0.01 ; $p < .001$) were significantly higher in patients with newly diagnosed COVID-19 than the control group. There was a significant positive correlation between Tp-e interval, Tp-e/QTc ratio and CRP in patients with newly diagnosed COVID-19 ($r_s = 0.332$, $p = .005$, $r_s = 0.397$, $p < .001$ consecutively). During their treatment with hydroxychloroquine (HCQ), azithromycin and favipiravir, ventricular tachycardia episodes were observed in in two COVID-19 patients during their hospitalization in the intensive care unit.

Conclusion: Our study showed for the first time in literature that the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio, which are evaluated electrocardiographically in patients with newly diagnosed COVID-19, were prolonged compared with normal healthy individuals. A positive correlation was determined between repolarization parameters and CRP. We believe that pre-treatment evaluation of repolarization parameters in newly diagnosed COVID-19 would be beneficial for predicting ventricular arrhythmia risk.

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Introduction

In December 2019, the world started to face a new pandemic situation. This new virus (SARS-CoV-2) belongs to the same severe acute respiratory syndrome-coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV) family. After this virus appeared in Wuhan-China, coronavirus disease 2019 (COVID-19)

began to spread rapidly to the world. Although most of the clinical findings of the disease belong to the respiratory system in COVID-19, complications of the cardiovascular system such as myocardial damage, hypoxia, hypotension, increased inflammatory response and proarrhythmic changes have also started to be reported. Studies evaluating COVID-19 patients presenting with increased cardiac involvement show that it is associated with poorer outcomes, and arrhythmic events are not uncommon [1]. In a single-centre study, cardiac involvement was observed in 19% of hospitalized COVID-19 patients and the risk of in-hospital mortality in these patients was higher [2]. Therefore, the risk of cardiac arrhythmia may be higher in COVID-19 patients.

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Ventricular repolarization parameters can be measured in the electrocardiogram (ECG) by the QT interval, QT dispersion and T wave measurements [3]. Increased dispersion of ventricular repolarization showing heterogeneity of repolarization is an important marker of ventricular arrhythmias. Recent studies have shown that the Tp-e interval (i.e., the interval between the peak and the end of the T wave) is a novel index of transmural dispersion of repolarization. Thus, Tp-e interval and Tp-e/QT ratio has been proposed to be a better marker of ventricular repolarisation [4]. The incidence of ventricular arrhythmias has been shown to be more frequent in patients with inflammatory and infectious diseases than in the normal population [5–6]. To our knowledge, no previous studies have investigated the Tp-e interval and Tp-e/QTc ratio as markers of ventricular arrhythmogenesis in SARS-CoV-2 infected patients. The aim of the study is to research the assessment of Tp-e interval and Tp-e/QT ratio in patients with newly diagnosed COVID-19.

Methods

Diagnosis of COVID-19

According to the World Health Organization [7] and the Republic of Turkey Ministry of Health according to the COVID-19 Treatment Guidelines [8–9], patients who were matching the definition of probable SARS-CoV-2 infection case underwent testing with molecular methods to scan for viruses. Throat and nasopharynx swab samples were collected from all patients in our study to extract SARS-CoV-2 RNA. Real-time reverse transcription polymerase chain reaction assay (RT-PCR) molecular method was applied for RNA analysis of SARS-CoV-2 virus. The RT-PCR assay was performed using a SARS-CoV-2 (2019-nCoV) qPCR Detection Kit according to the manufacturer's protocol (Bioesken R & D Technologies Co Ltd). Cases with SARS-CoV-2 RNA in RT-PCR method were accepted as COVID-19.

Study population and procedure

This cross-sectional, single-centre study was performed in University of Health Sciences Samsun Training and Research Hospital, which was determined to treat COVID-19 patients by Turkish Republic Ministry of Health, between March 20th and April 10th 2020. The data was collected from the pre-treatment COVID-19 patients diagnosed according to the Turkish Republic Ministry of Health COVID-19 Treatment guideline [8–9]. Patients with myocardial injury, coronary artery disease, heart failure (left ventricular ejection fraction $\leq 50\%$ or heart failure with preserved ejection fraction), severe chronic renal and liver failure, abnormal serum electrolyte values, atrial fibrillation, complete or incomplete branch block, pace rhythm and patients using QT interval lengthening drugs were not included in the study. Demographical data, baseline cardiovascular risk factors, medical history, drugs used, smoking habits and laboratory values recordings were obtained using the hospital's medical database. Height and weight measurements and body mass index (BMI) were calculated. A total of 75 sex- and age-matched healthy subjects were randomly selected as the control group. Written informed consent was obtained from the patients and healthy individuals. The research procedures were revised and approved by the local hospital's ethics committee (GOKA/2020/6/5) and Ministry of Health Scientific Research Platform (2020-05-04T18_29_21), according to the ethical considerations stipulated in the Helsinki Declaration.

Definitions

Myocardial injury was defined if the serum levels of cardiac biomarkers (troponin I) were above the 99th percentile upper reference limit or new abnormalities were shown in electrocardiography and echocardiography [10]. Hypertension was defined by a previous

diagnosis of hypertension or the presence of SBP of ≥ 140 mmHg or DBP of ≥ 90 mmHg (mean of two consecutive measurements). Diabetes mellitus was defined as the use of anti-diabetic medication or fasting glucose level ≥ 126 mg/dL in at least two measurements, or HbA1c $\geq 6.5\%$. Hyperlipidaemia was defined as low-density lipoprotein (LDL) cholesterol levels of ≥ 160 mg/dL or statin usage. Chronic renal failure (CRF) was defined as estimated glomerular filtration rate (GFR) of < 60 mL/min/1.73 m² according to the Modification of Diet in Renal Disease (MDRD) formula. Smokers were current smokers and had been using at least 10 cigarettes per day for at least 5 years continuously.

Electrocardiography

Twelve lead electrocardiograms (ECG) of the patients were recorded before the treatment for COVID-19 was started at the resting and supine position, at a rate of 50 mm/s (Nihon Kohden, Page-writer, Japan). All of the ECGs were scanned and transferred to a personal computer to decrease error measurements, and then used for 400% magnification by Adobe Photoshop software. All of the measurements were performed on screen by manual method. All patients were in sinus rhythm. No patient had fewer than nine measurable leads and all precordial derivations were included in the measurements. The Tp-e interval was defined from the peak of T wave to the end of T wave. Measurements of Tp-e interval were performed from precordial leads and the longest Tp-e interval was recorded. Tp-e dispersion was defined as the difference between the maximum and minimum Tp-e interval in the precordial leads V1 to V6 during a single beat. The QT interval was defined as the interval from the onset of the QRS complex to the end of the T wave. Measurements of QT interval were performed from all leads and the longest QT interval was recorded. QT dispersion (QTd) was determined as the difference between the maximum and minimum QT interval in different leads. The R-R interval was measured and used to compute the heart rate. Corrected QT dispersion (QTdc) and correct QT interval (QTc) were calculated using Bazett's formula: $QTc = QT\sqrt{R-R \text{ interval}}$ [11]. Tp-e/QT ratios were calculated from these measured values. ECG data of the patients were performed by two cardiologists. For each study patient, these values were calculated on average three times. Intraobserver and interobserver variations for measurements were less than 4%.

Echocardiography

Echocardiographic evaluation was performed using a VIVID 7-dimensional cardiovascular ultrasound system (Vingmed-General Electric, Horten, Norway) with a 3.5 MHz transducer. To minimize the risk of exposure, echocardiography was performed only to patients with heart failure or any doubt for myocardial injury. Parasternal long and short axis views and apical views were used as standard imaging windows. Left ventricular dimensions were measured from the parasternal long axis. The ejection fraction was calculated from the apical window using the modified Simpson method.

Blood samples

Peripheral venous blood samples were drawn from the antecubital vein after 12-h of fasting in the morning. Blood samples were taken into standardized tubes containing dipotassium ethylene dinitro tetra acetic acid (EDTA) for complete blood count (CBC). Plasma levels of creatinine, serum electrolytes were evaluated using an automated chemistry analyser (Abbott Aeroset, USA) using commercially available kits (Abbott, USA). Plasma level of C - reactive protein (CRP) was measured using a turbidimetric immunoassay method.

Statistical analysis

In all statistical analysis SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used. In order to test normality of distribution Kolmogorov–Smirnov test was used. Quantitative variables with a normal distribution were specified as the mean \pm standard deviation and non-normally distributed variables were specified as median (interquartile range). Categorical variables were shown as number and percentage values. Differences between groups were evaluated by using Student's *t*-test and Mann Whitney *U* test. Categorical variables were compared with Chi-square test. Spearman correlation analysis was performed to examine the relationship between Tp–e interval, Tp–e/QTc and CRP. A *p* value of <0.05 was accepted as statistically significant.

Results

Baseline clinical characteristics and laboratory parameters of the study groups are summarized in Table 1. The mean age of the participants 55.3 ± 16.5 years and 53.3% were male. There were no significant differences between the two groups in terms of baseline demographic characteristics and medical history. In their laboratory findings, white blood cell ($7.9 \pm 3.3 \times 10^3$ uL vs. $6.2 \pm 1.6 \times 10^3$ uL; *p* = .002), neutrophil ($6.0 \pm 2.3 \times 10^3$ uL; vs. $4.4 \pm 2.3 \times 10^3$ uL; *p* = .02) and CRP (32 mg/L (12–42) vs. 5 mg/L (3–7); *p* < .001) levels were significantly higher in the COVID-19 group than the control group. Lymphocyte counts ($1.1 \pm 0.6 \times 10^3$ uL vs. $1.4 \pm 0.5 \times 10^3$ uL; *p* = .034) were significantly lower in the COVID-19 group than the control group. In addition, there was no difference between the groups in terms of other laboratory findings (*p* > .05).

ECG and echocardiography findings are presented in Table 2. Heart rate (74.9 ± 8.5 vs. 77.7 ± 6.2 ; *p* = .128), QT interval (364.7 ± 11.5 vs. 365.1 ± 14.3 ; *p* = .652), QTc interval (411.1 ± 23.9 vs. 410.6 ± 23.9 ; *p* = .594), QT dispersion (15.4 ± 6.5 vs. 15.1 ± 3.1 ; *p* = .491) and corrected QT dispersion (19.9 ± 3.2 vs. 19.2 ± 3.1 ; *p* = .678) were not different between the two groups. Tp–e interval (80.7 ± 4.6 vs. 70.9 ± 4.8 ; *p* < .001), Tp–e dispersion (20.1 ± 3.4 vs. 16.2 ± 4.1 ; *p* < .001), Tp–e/QT ratio (0.21 ± 0.01 vs. 0.19 ± 0.01 ; *p* < .001) and Tp–e/QTc ratio (0.19 ± 0.01 and 0.17 ± 0.01 ; *p* < .001) were significantly higher in the COVID-19 patients compared to control group. There

Table 1
Baseline characteristics and laboratory findings of the study population.

Parameters	COVID-19 (n = 75)	Control (n = 75)	p value
Age, years	55.5 \pm 17.1	50.2 \pm 16.6	0.053
Gender, male, n (%)	39 (52)	41 (54)	0.777
HTN, n (%)	39 (52)	41 (54)	0.885
DM, n (%)	27 (36)	25 (33)	0.273
Hyperlipidemi, n (%)	14 (18)	15 (20)	0.527
Smoking, n (%)	28 (37)	30 (40)	0.478
Body mass index, kg/m ²	24.1 \pm 3.5	24.6 \pm 3.1	0.222
White blood cell, 10 ³ uL	7.9 \pm 4.3	6.2 \pm 1.6	0.002
Neutrophil, 10 ³ uL	6.0 \pm 2.3	4.4 \pm 2.3	0.020
Lymphocyte, 10 ³ uL	1.1 \pm 0.6	1.4 \pm 0.5	0.034
Monocyte, 10 ³ uL	0.6 \pm 0.3	0.6 \pm 0.3	0.727
Platelet, 10 ³ uL	243 \pm 77	232 \pm 79	0.239
Hemoglobin, g/dl	12.7 \pm 1.7	13.2 \pm 1.6	0.076
Glucose, mg/dl	98.0 \pm 11.5	95.5 \pm 12	0.667
Aspartate aminotransferase, IU/l	27.9 \pm 8.6	23.7 \pm 9.7	0.124
Alanine aminotransferase, IU/l	29.5 \pm 8.4	26.2 \pm 15	0.375
Creatinin mg/dl	0.87 \pm 0.21	0.86 \pm 0.21	0.857
Sodium, mEq/L	136.7 \pm 3.1	136.8 \pm 2.9	0.920
Calcium, mg/dl	9.40 \pm 0.25	9.45 \pm 0.57	0.699
Magnesium, mg/dl	1.9 \pm 0.2	1.95 \pm 0.2	0.623
Potassium, mmol/L	4.1 \pm 0.3	4.2 \pm 0.3	0.071
CRP, mg/L	32 (12–42)	5 (3–7)	<0.001

Data are given as mean \pm SD, median (interquartile range) or n (%), DM: Diabetes Mellitus; HTN: Hypertension; CRP: C-reactive protein.

Table 2
Electrocardiographic and echocardiographic characteristics of study population.

Parameters	COVID-19 (n = 75)	Control (n = 75)	p value
LVEF, %	59.9 \pm 2.0	60.9 \pm 2.1	0.073
Heart rate, bpm	74.9 \pm 8.5	77.7 \pm 6.2	0.128
QT, ms	364.7 \pm 11.5	365.1 \pm 14.3	0.652
QTc, ms	411.1 \pm 23.9	410.6 \pm 23.9	0.594
QTd, ms	15.4 \pm 6.5	15.1 \pm 3.1	0.491
cQTd, ms	19.9 \pm 3.2	19.2 \pm 3.1	0.678
Tp–e interval, ms	80.7 \pm 4.6	70.9 \pm 4.8	<0.001
Tp–e dispersion, ms	20.1 \pm 3.4	16.2 \pm 4.1	<0.001
Tp–e/QT, ms	0.218 \pm 0.008	0.195 \pm 0.014	<0.001
Tp–e/QTc, ms	0.191 \pm 0.013	0.173 \pm 0.014	<0.001

Data are given as mean \pm SD or (%), Bpm: beats per minute; LVEF: left ventricular ejection fraction; ms: milliseconds; QTc: corrected QT interval; QTd: QT dispersion, the difference between the maximum and minimum QT intervals; cQTd: corrected QT dispersion; Tp–e: T-peak to T-end interval.

was no difference between the groups in terms of left ventricular ejection fraction (59.9 ± 2 and $60.9 \pm 2.0\%$; *p* = .073). There was a significant positive correlation between Tp–e interval and CRP levels (*r* = 0.332, *p* = .005) (Fig. 1A) and Tp–e/QTc ratio and CRP levels in patients with COVID-19 infection (*r* = 0.397, *p* < .001) (Fig. 1B).

Among these 75 patients, 11 were followed-up in the ICU afterwards. Two of them developed ventricular tachycardia in the ICU unit. Both of them were taking hydroxychloroquine (HCQ), azithromycin and favipiravir treatment. These patients had increased Tp–e intervals (82 ms and 80 ms respectively), and Tp–e/QTc ratios (0.195 and 0.192, respectively), but normal QTc (415 ms and 410 ms) intervals before treatment. After treatment these values were as follows: Tp–e intervals (95 ms and 90 ms respectively), QTc (460 ms and 455 ms) and Tp–e/QTc ratios (0.20 and 0.197, respectively).

Discussion

In this study, longer Tp–e interval and elevated Tp–e/QT and Tp–e/QTc ratios were detected before the treatment was started in patients with COVID-19 infection when compared to the control group. We also demonstrated that the Tp–e interval and Tp–e/QTc ratios were also positively correlated with serum CRP levels. This is the first study in the literature in which these repolarization parameters were investigated in patients with COVID-19 infection.

Ever since the first case was reported at the end of 2019, the SARS-CoV-2 virus and associated COVID-19 has spread throughout the world and has become a pandemic. In particular, the high transmission rate of the virus has made it a threat to public health globally. Currently, there is no proven effective therapy against the virus. This infection mainly affects the respiratory system, but acute and chronic cardiovascular complications of COVID-19 are also common and result from various mechanisms. Much of our current knowledge of SARS-CoV-2 comes from previous historical outbreaks such as SARS-CoV, MERS-CoV and H1N1 influenza outbreaks. In these outbreaks, a significant relationship was observed between the underlying cardiovascular disease, cardiac involvement and poor prognostic results. Cardiovascular complications of influenza infection, including myocarditis, acute myocardial infarction, malignant arrhythmias and exacerbation of heart failure have been well-recognized during previous historical epidemics and make a significant contribution to mortality [12]. Hypotension, tachycardia, bradycardia, arrhythmia, or even sudden cardiac death are common in patients with SARS disease [13]. In the largest published clinical cohort of COVID-19 to date, acute cardiac injury, shock, and arrhythmia were present in 7.2%, 8.7%, and 16.7% of patients, respectively [14]. These results show that cardiac involvement may be associated with poor results in patients with COVID-19 and arrhythmias are not uncommon.

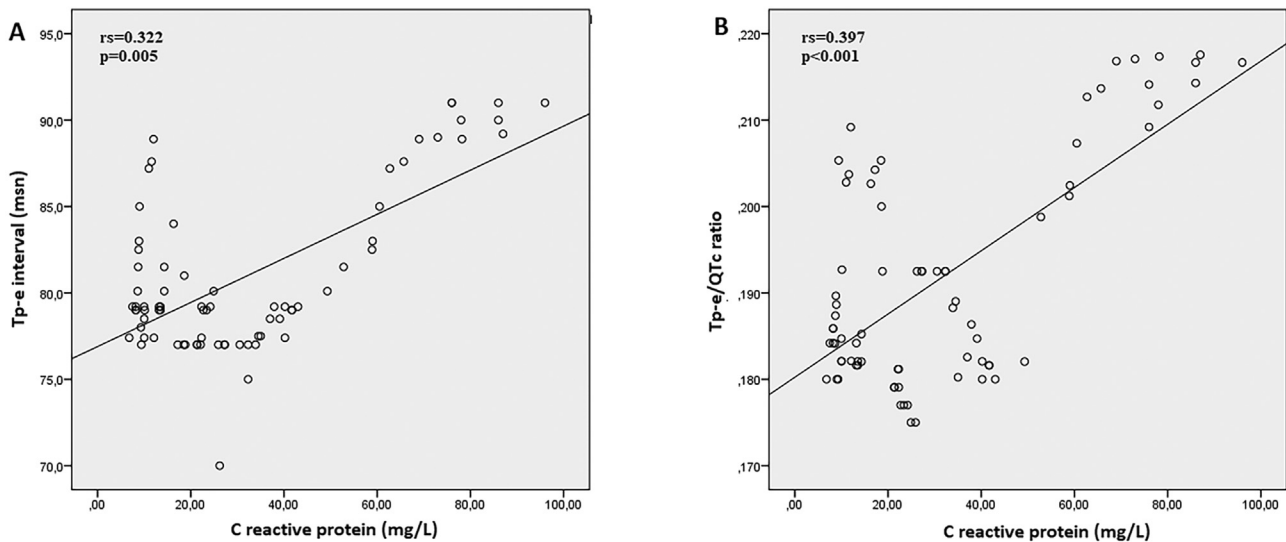


Fig. 1. (A) Correlation between CRP and Tp-e interval. (B) Correlation between CRP and Tp-e/QTc ratio. rs indicates correlation coefficient.

SARS-CoV-2 specifically binds to cells expressing angiotensin converting enzyme 2 (ACE2) [15]. Angiotensin converting enzyme 2 is also expressed in the heart and provides a link between the coronaviruses and the cardiovascular system. Human autopsy samples show that SARS-CoV can downregulate myocardial and pulmonary ACE2 pathways, thereby mediating myocardial inflammation, pulmonary edema and acute respiratory failure [16]. In their study, Pan et al. tried to explain the occurrence of cardiac arrest in 15 SARS patients and proposed some cardiovascular mechanisms of action; myocardial stress caused by damage, hypoxia, increased endogenous catecholamine release, increased oxygen demand and inflammation directly in myocardial cells and/or delivery system [17]. In their study, Wang et al., observed arrhythmia in 16.7% of patients hospitalized with COVID-19 [14] and Guo et al. found 5.2% of malignant ventricular arrhythmia in COVID-19 patients with normal troponin levels [18]. Considering all these pathophysiological mechanisms and clinical research results, the risk of ventricular arrhythmia and mortality may increase in COVID-19 patients.

Ventricular repolarization parameters are thought to play an important role in the formation of ventricular arrhythmia. Increased dispersion of repolarization showing heterogeneity of repolarization is a marker of important ventricular arrhythmias. QT/QTc interval and T wave analyses are commonly used for ventricular repolarization assessment. The increase in the distribution of ventricular repolarization is associated with malignant arrhythmias and has a prognostic significance in terms of mortality and sudden cardiac death [19]. Tp-e interval is a relatively new ECG parameter showing ventricular repolarization. It has been associated with ventricular arrhythmias and sudden death, even in patients with normal QTc [20–21]. Whereas, both QT and Tp-e intervals may vary according to the body weight and heart rate that makes these indices less sensitive for predicting arrhythmogenesis. Tp-e/QT ratios has also recently been used as a new electrocardiographic marker for ventricular repolarization [21] and it has been reported to be associated with malignant ventricular arrhythmias [22]. In this context, using the Tp-e/QTc ratio is more favoured compared to a single assessment of either Tp-e or QT intervals because this ratio remains steady regardless of the dynamic variations in heart rate [23]. Our study is the first study to evaluate Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio which were found to be increased in SARS-CoV-2 infected patients. The prolongation of Tp-e interval and Tp-e/QT ratios may contribute significantly to the mechanism underlying sudden cardiac death in pre-treatment COVID-19 patients. Furthermore, QT prolonging drugs such as HCQ and azithromycin for COVID-19 infection

are being started to these patients and these agents may contribute to ventricular arrhythmias by further deranging the ventricular repolarization. In our study, two patients who were followed-up in the ICU (both were taking HCQ, azithromycin and favipiravir) developed ventricular tachycardia had both increased Tp-e interval and Tp-e/QTc ratio despite normal QTc intervals before treatment. This finding may also show that pre-treatment Tp-e/QTc ratio and Tp-e interval may predict the development of ventricular arrhythmias better than the QTc interval alone in COVID-19 patients.

Cardiac arrhythmias can occur due to myocardial ischemia, heart failure, increased catecholamine exposure, electrolyte disturbances, scar formation, hypoxia, autonomic dysfunction and inflammation. The re-entry and acquired automaticity may initiate arrhythmogenesis at the cellular level [24]. Systemic inflammation has important effects on arrhythmogenesis. Systemic inflammation plays an important role in inducing arrhythmias by providing a decrease in arrhythmogenic threshold in patients prone to arrhythmia. CRP, which is an indicator of inflammation, may have direct arrhythmogenic properties by inducing oxidative stress and apoptosis [25]. Huang et al. stressed that the imbalance of patients with COVID-19 T helper 1 and T helper 2 results in an inflammatory storm that may contribute to myocardial injury [26]. In a study investigating the early stage of COVID-19, CRP levels were found to reflect disease severity and should be used as a key indicator for disease monitoring [27]. Similarly, in their study, Oudit et al. showed that CRP levels were high in patients with COVID-19 [28]. In many studies, CRP has been shown to be associated with ventricular arrhythmia predictors, Tp-e interval and Tp-e interval / QT rates [6,29–30]. In our study, CRP was significantly higher in patients with COVID-19 than in control group. Also, CRP and Tp-e interval, Tp-e/QT and Tp-e/QTc ratios showed positive correlation. According to these results, inflammation occurring in patients with COVID-19 may cause an increase in ventricular repolarization parameters, leading to the development of ventricular arrhythmias.

Limitations

Our study has some limitations. First, only 75 COVID-19 patients were included and a larger cohort study is needed to confirm our results. Second, as a retrospective study, other inflammation parameters such as cardiovascular complications, detailed echocardiographic measurements, and interleukin-6, erythrocyte sedimentation rate (ESH), and ferritin were not presented in the study due to limited operating conditions, the possibility of virus infection, and the urgency of the

COVID-19 pandemic. Third, the data in this study allow for only pre-treatment evaluation of patients with COVID-19. The most important limitation of this study was the absence of control (before COVID-19 infection) and/or recovery data. We can never tell whether they were already prolonged before COVID-19 infection or prolonged due to COVID-19 infection.

Conclusions

The TP-e interval, Tp-e/QT and Tp-e/QTc ratios that evaluate ventricular repolarization are easily accessible, inexpensive and non-invasive ECG parameters. To our knowledge, this is the first study to evaluate the ventricular repolarization using the Tp-e interval and Tp-e/QT ratios in patients with COVID-19. In our study, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were found to be increased in COVID-19 patients before treatment. In addition, a significant correlation was found between repolarization parameters and CRP. We believe that pre-treatment evaluation of these electrocardiographic repolarization parameters of in patients with newly diagnosed COVID-19 in addition to QTc interval would be beneficial for predicting ventricular arrhythmia risk. Large-scale long-term studies are needed to support our data.

Declaration of Competing Interest

None.

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