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ARAŞTIRMA / RESEARCH

Evaluation of association between asymptomatic COVID-19 and ventricular arrhythmias

Asemptomatik COVID-19 ve ventriküler aritmiler arasındaki ilişkinin belirlenmesi

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Abstract

Purpose: Electrocardiography (ECG) is the first-line diagnostic tool to evaluate cardiac involvement in any disease and COVID-19 patients. The objective of this study is to investigate the ventricular arrhythmia forming effect of COVID-19 and to guide the treatment.
Materials and Methods: A total of 74 patients (mean age 52.63±17.85 years) under follow-up for asymptomatic COVID-19 and 74 healthy volunteers (mean age 50.71±6.02 years) were enrolled in the study. Heart rate, QRS duration, QT distance, T-wave morphology (Tp-e interval), Tp-e/QT ratio, and index of cardio-electrophysiological balance (iCEB) were analyzed and compared to both groups.
Results: The heart rate was higher, and the QT interval was shorter on ECG in the COVID-19 group. QTc interval, Tp-e intervals, and Tp-e/QT ratio were not different between groups. Furthermore, iCEB and iCEB-c values were not different between groups. A significant positive but weak correlation was observed between CRP and troponin values in patients with COVID-19. Moreover, there was no correlation between troponin levels and Tp-e/QT ratio and iCEB in patients with COVID-19.
Conclusion: The chronic cardiac effects of the COVID-19 have not been elucidated. Prospective clinical trials with long-term and a high number of patient populations are needed to reveal this. Notably, patients with significantly elevated troponin values should be followed up for long-term development of cardiomyopathy and arrhythmias.
Keywords: Arrhythmia, COVID-19, Electrocardiography, iCEB, Tp-e/QT

Öz

Amaç: Elektrokardiyografi (EKG), herhangi bir hastalıkta ve COVID-19 hastalarında kardiyak tutulumu değerlendirmek için ilk seçenek tanı aracıdır. Bu çalışmanın amacı, COVID-19'un ventriküler aritmilere yatkınlık oluşturan etkisini araştırmak ve tedaviye rehberlik etmektir.
Gereç ve Yöntem: Asemptomatik COVID-19 nedeniyle takip edilen 74 hasta (ortalama yaş 52.63 ± 17.85 yıl) ve 74 sağlıklı gönüllü (ortalama yaş 50.71 ± 6.02 yıl) çalışmaya dahil edildi. Kalp hızı, QRS süresi, QT mesafesi, T dalgası morfolojisi (Tp-e aralığı), Tp-e / QT oranı ve kardiyak elektrofizyolojik denge indeksi (iCEB) analiz edildi ve her iki grup arasında karşılaştırıldı.
Bulgular: COVID-19 grubunda EKG'de kalp hızı daha yüksekti ve QT aralığı daha kısaydı. QTc aralığı, Tp-e aralıkları ve Tp-e / QT oranı açısından gruplar arasında farklılık yoktu. Ayrıca, iCEB ve iCEB-c değerleri gruplar arasında farklı değildi. COVID-19'lu hastalarda CRP ve troponin değerleri arasında anlamlı ancak zayıf pozitif bir korelasyon gözlendi. COVID-19'lu hastalarda troponin seviyeleri ile Tp-e / QT oranı ve iCEB arasında korelasyon yoktu.
Sonuç: COVID-19'un kronik kardiyak etkileri aydınlatılamamıştır. Bunu ortaya çıkarmak için uzun vadeli ve çok sayıda hasta popülasyonu içeren prospektif klinik araştırmalara ihtiyaç vardır. Özellikle, troponin değerleri önemli ölçüde yüksek olan hastalar, uzun süreli kardiyomiyopati ve aritmi gelişimi açısından izlenmelidir.

Anahtar kelimeler: Aritmi, COVID-19, Elektrokardiyografi, iCEB, Tp-e/QT

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new beta coronavirus that was first described in a group of patients presenting with symptoms of pneumonia in Wuhan, China, in December 2019 [1]. The disease was named COVID-19, which means "Coronavirus Disease 2019". The virus spread rapidly in many countries and caused a global pandemic [2]. The most common clinical features reported at the beginning of the disease are fever (99 percent), fatigue (70 percent), dry cough (59 percent), anorexia (40 percent), myalgia (35 percent), dyspnea (31 percent) and sputum (27 percent). The most common serious infection in this disease is pneumonia, which is primarily presented with cough, fever, shortness of breath and bilateral infiltrates in chest imaging [3]. SARS-CoV-2 enters the cell by binding to the surface Angiotensin-converting enzyme 2 (ACE2) receptor. The SARS-CoV-2 spike protein binds directly to the cell ACE2 surface receptor of the host cell, thereby facilitating the virus's entry and replication into the cell [4]. ACE2 is a membrane-bound protein expressed in many human cells, such as alveolar epithelial cells, cardiovascular tissue, vascular endothelium, kidney tissue, and small intestinal epithelium [5]. The expression of ACE2 from various organs can explain the multiple organ damage that can be seen due to the SARS-CoV-2, which can enter the cell by binding to this receptor[6].

Cardiovascular system involvement during COVID-19 is a significant problem for the management of the disease. Myocardial injury may be seen with an estimated 17% rate, which documented with elevated troponin levels and has also been speculated that a quarter of patients may develop heart failure[7]. Unfortunately, complications such as acute heart failure acute respiratory distress syndrome, renal injury and malignant ventricular arrhythmias have been reported to occur more frequently in patients with high troponin[8]. In addition, atrial arrhythmias may be the first clinical finding of COVID-19 infection[9]. It was reported that arrhythmia developed in 16.7 % of hospitalized patients due to COVID-19 and 44.4 % of those followed in the intensive care unit[3]. Myocardial infarction, heart failure, myocarditis due to COVID-19 infection or proinflammatory effects, and finally, an increased sympathetic stimulation may be causes of cardiac arrhythmias[10].

Electrocardiography (ECG) is the first-line diagnostic tool to evaluate cardiac involvement in any disease and COVID-19 patients, and several waves and intervals have been identified on electrocardiography to predict cardiac arrhythmias. QT interval prolongation is the most known ECG finding that is a marker for electrical instability and sudden cardiac death[11].

Tp-Te interval on ECG is considered as an index of transmural dispersion of left ventricular repolarization, and Tp-Te/QT ratio is also used as a novel electrocardiographic index of ventricular arrhythmogenesis. Previously published studies demonstrated that a prolonged Tp-Te interval and higher Tp-Te/QT ratio had been associated with an increased risk of ventricular arrhythmias[12]. Index of cardio-electrophysiological balance (iCEB), estimated as QT interval divided by QRS duration, is a novel risk indicator for predicting malignant ventricular arrhythmias. An elevated iCEB level is accepted as a predictor of torsades de pointes (TdP) ventricular arrhythmias whereas decreased iCEB level is linked with non-torsades de pointes ventricular arrhythmias[13,14].

In this study, we aimed to investigate the isolated pro-arrhythmogenic effect of COVID-19 infection in patients with asymptomatic or mildly symptomatic with using QT interval, iCEB, Tp-e and Tp-e/QT ratio. Especially in similar studies from literature, the patient population with COVID-19 was selected from older and more comorbid patients than the control groups.

As can be guessed at the end of these studies, it was emphasized that COVID-19 is associated with cardiac arrhythmias. In our study, COVID-19 patients who were similar in terms of age and comorbid diseases with the control group were evaluated. Thus, the effect of advanced age and comorbid diseases that may be associated with ventricular arrhythmias on the study result was tried to be minimized. As a result, the effect of COVID-19 on the development of ventricular arrhythmia has been clearly explained without confounding factors.

MATERIALS AND METHODS

This study was conducted according to the Declaration of Helsinki 1975. The study was approved by Necmettin Erbakan University Meram Medical Faculty Medicine and Non-Medical Device Research Ethics Committee at its 106th meeting on 17 April 2010 and with the number 2020/2449.. All patients have provided informed consent before participating into study.

The study was conducted in patients with COVID-19 hospitalized in the Necmettin Erbakan University Meram Faculty of Medicine Hospital, Infectious Diseases and Clinical Microbiology service and Chest Diseases service, located in an area with a high prevalence of COVID-19, is accepted as a reference center for COVID-19 care.

Sample

A total of 74 patients (33 male; mean age 52.63±17.85 years) under follow-up for asymptomatic COVID-19 (laboratory-confirmed cases, SARS-CoV-2 RNA detected by molecular method) were retrospectively reviewed and 74 healthy volunteers (38 male; mean age 50.71±6.02 years) were enrolled in the study. The study population was categorized as the control group, COVID-19 group, and compared the parameters between groups.

Patients with a history of coronary revascularization or myocardial infarction (via coronary artery bypass graft operation or percutaneous coronary intervention), those who documented atrial fibrillation, cardiac pacemaker implantation, sick sinus syndrome, any kind of bundle branch blocks, pre-excitation syndromes, atrioventricular block, left ventricular hypertrophy and valvular heart disease (moderate-to-severe), renal insufficiency (creatinine levels > 1.5 or glomerular filtration rate below 50), electrolyte hemostasis disorders, heart failure who need medical treatment were excluded from the study.

Procedure

Electrocardiograms and serum biochemistry test results of COVID-19 patients taken at the time of hospitalization were obtained from patient files. If anyone has received a drug that affects the myocardial conduction system (azithromycin or hydroxychloroquine, etc.) in the COVID-19 group was not included in the study. And also, patients or healthy individuals who were taking beta-blockers, diltiazem or verapamil, antiarrhythmic drugs, and inhaler therapy for any reason were excluded from the study. Patients with lung involvement in thorax computed tomography were not included in the study.

The routine transthoracic echocardiography was performed in the control group and it was revealed that the left ventricular systolic function was normal. Given the high risk of transmission of COVID-19 for health-care workers, routine transthoracic echocardiography could not be performed, as this group of patients was not needed. It was tried to determine whether there were any possible cardiac problems in the physical examination by questioning the symptoms of patients before COVID, evaluating their electrocardiograms, evaluating the anteroposterior Chest X-ray. In the COVID-19 group, patients with possible ischemic findings on the electrocardiogram and cardiomegaly on chest X-ray were not included the study.

Electrocardiographic examinations

Heart rate, QRS duration, QT distance, and T-wave morphology were analyzed. All ECG samples were examined on a digital platform, and measurements were then taken using specialized software (Adobe Photoshop) to provide necessary magnification.

The QT interval was conventionally obtained by manually measuring from the onset of the QRS complex to the crossing point of the T wave and isoelectric line. The heart rate-corrected QT interval was calculated using Bazett's formula ($cQT = QT\sqrt{}$ (R–R interval)). QT interval measurements were taken by examining recordings from leads D2 and precordial V5, and the longer lead was recorded for statistical analysis[15]. The distance from the peak of the T-wave (T peak) to the endpoint of the T-wave (T end) (T peak-end or Tp-e) was obtained from the chest leads. The Tp-e/QT ratio was obtained by dividing the Tp-e duration by the QT interval in the precordial V5 lead [15, 16]. The index of cardiao-electrophysiological balance (iCEB) was obtained by dividing the QT interval by the QRS duration in the same lead (D2 or V5)[13,14].

Statistical analysis

SPSS version 20.0 statistical package software (SPSS Inc., Chicago, IL, United States) was used for statistical analyses. The normally distributed quantitative variables (age, hemoglobin levels and other hemogram parameters, serum biochemistry markers, electrocardiographic data) were demonstrated as mean ± standard deviation, while categorical variables (gender, comorbid diseases, smoking) have shown in numbers and percentages. Kolmogorov–Smirnov test was used for evaluating the normality of distribution. Mean values of continuous variables were compared between independent groups using the Student's T-test, one-

way ANOVA test, or Kruskal-Wallis test as appropriate. The chi-square test was performed to compare the study groups in terms of categorical variables. Spearman Correlation test was used for assessment of the correlation between CRP or troponin and electrocardiographic findings (Tpe/QT ratio and iCEB). The threshold for significance was defined at $p < 0.05$.

RESULTS

A total of 148 patients with a mean age of 51.17±14.44 years and 74 (53.6%) of whom were women, constituted the study population. There was no statistically significant difference between COVID-19 group and control group in terms of gender, age, and laboratory parameters except fasting blood glucose and CRP. CRP levels were higher in the COVID-19 group as expected (p= 0.001).

The study groups were comparable in terms of electrocardiographical parameters. Although the heart rate was higher, and the QT interval was lower on ECG in the COVID-19 group, QTc interval, Tp-e intervals, and Tp-e/QT ratio were not different between groups (p = 0.21). Furthermore, iCEB and iCEB-c values were not different between groups (p = 0.27). The demographic features, laboratory parameters, and electrocardiographic characteristics and comparison between groups are summarized in Table 1 and 2.

Table 1. Demographical characteristics of the study population

Variables	All cohort (n = 148)	Control group (n = 74)	COVID-19 group (n= 74)	p value
Age (year) (mean±std)	51.17±14.44	50.71±6.02	52.63±17.85	0.382
Female (n, %)	74 (53.6)	36 (48.6)	41 (55.4)	0.411
Hypertension (n, %)	48 (34.8)	20 (27)	16 (21.6)	0.566
Diabetes mellitus (n,%)	27 (19.6)	11 (14.8)	8 (10.8)	0.624
Smoking (n, %)	25 (18.1)	9 (12.1)	6 (8.1)	0.582
Hemoglobin (g/dL)	13.57±1.57	13.77±1.68	13.39±1.47	0.149
WBC (10^3/mL)	7.46±1.98	7.69±1.68	7.23±2.22	0.165
PLT (10^3/mL)	260.47±73.48	267.83±76.16	252.77±70.34	0.213
Creatinine (mg/dL)	0.81±0.17	0.78±0.18	0.84±0.16	0.054
Potassium (mmol/L)	4.87±0.92	4.92±0.71	4.83±0.84	0.889
Calcium (mg/dL)	9.47±1.21	9.82±1.35	9.71±1.44	0.754
SGPT (U/L)	22.4±18.77	20.51±9.84	24.25±24.54	0.360
SGOT (U/L)	23.32±9.78	22.58±7.92	24.06±11.32	0.229
Glucose (mg/dL)	106.73±31.38	100±21.26	113.10±37.74	0.012 *
CRP (mg / L)	25.23±40.98	4.86±19.1	45.60±46.66	0.001 *
Troponin (ng/L)	-	-	3.63±6.51	-
CK-MB (µg/L)	-	-	8.36±10.1	-

WBC: White blood cells; PLT: Platelets; SGPT: Serum glutamic pyruvic transaminase; SGOT: Serum glutamic oxaloacetic transaminase; CRP: C-reactive protein; CK-MB: Creatine kinase myocardial band

Table 2. Electrocardiographic alternations of the study population

Variables	All cohort	Control group	COVID-19 group	p value
Heart rate (mean±std)	77.91±14.09	73,41±12.06	82.41±14.61	0.001*
QT interval (mean±std)	376.83±33.22	383.51±33.50	370.16±31.78	0.014*
QTc interval (mean±std)	421.29±32.42	421.01±30.20	421.56±34.71	0.918
QRS interval (mean±std)	87.07±16.08	88.45±17.59	85.68±14.40	0.296
Tp-e interval (mean±std)	79.54±19.37	78.91±19.27	80.17±19.59	0.695
iCEB (mean±std)	4.45±0.83	4.44±0.79	4.44±0.88	0.875
iCEB-c (mean±std)	4.97±0.85	4.89±0.79	5.05±0.91	0.279
Tp-e/QT (mean±std)	0.21±0.05	0.21±0.04	0.21±0.05	0.216
Tp-e/QTc	0.18±0.04	0.18±0.04	0.19±0.04	0.653

QTc: Corrected QT interval; Tp-e: The interval from the peak to the end of the electrocardiographic T wave; iCEB: Index of cardio-electrophysiological balance; iCEB-c: Corrected index of cardio-electrophysiological balance

We did not detect a significant positive or negative correlation between CRP and iCEB and Tpe / QT ratio in the study group (respectively, r = 0.06, p = 0.441 and r = 0.06, p = 0.417). As expected, a significant positive but weak correlation was observed between CRP and troponin values in patients with COVID-19 (r = 0.293, p = 0.014). Moreover, there were no correlation between troponin levels and Tpe/QT ratio and iCEB in patients with COVID-19 (respectively, r = -0.085, p = 0.489 and r = 0.185, p = 0.129).

DISCUSSION

In the current study, our results indicate that Tp-e interval, Tp-e / QT ratio, or index of cardiac electrophysiological balance value, knowns as predictors of the development of arrhythmia which can measure on standard 12-lead surface ECG, were not different during asymptomatic or mild symptomatic COVID-19 than healthy controls.

COVID-19 is associated with various pro-inflammatory processes that can play an important role in the pathophysiology of cardiac complications. In a study by Shi S et al., 82 (19.7%) of 416 patients hospitalized with COVID-19 diagnosis had heart damage. The mortality rate was 51.2% in COVID-19 patients with cardiac complications, and 4.5% in the non-cardiac group (p <.001) [17]. However, in this study, COVID-19 patients with cardiac complications were older than those without (median [range] age, 74 [34-95] vs. 60 [21-90] years; P < .001), and more comorbid diseases were present.

Hypoxia, acidosis, intravascular volume imbalances, neurohormonal, catecholaminergic stress, metabolic derangements, or directly infected myocardium are accepted as multifactorial reasons for arrhythmias in a COVID-19 patient [18]. It is also thought that the virus may have harmful effects on the cardiovascular system via the ACE2 pathway and cause myocardial damage [19]. Different values are reported in terms of cardiac involvement with an increasing number of publications. In a published study demonstrated that in patients with COVID-19, arrhythmias, acute cardiac injury, shock, and were present in 16.7%, 7.2%, and 8.7% of patients, respectively [3]. It has been speculated that elevated cardiac biomarkers levels are associated with poor prognosis during infection, so myocardial biomarkers should be evaluated in all patients with COVID-19 for risk stratification and prompt intervention. Especially, it has been stated that cardiac MR may be useful after infection control for the evaluation of the development of atrial or ventricular fibrosis, which is accepted a substrate for the development of arrhythmias in this group patient [20].

COVID-19, which is a new disease for the whole world, seems to affect many organs and systems. It attracts the attention of all the people of the world due to its rapid spread with high mortality rates. Despite medical developments, there is still no definitive treatment method. Its effects on the cardiovascular system are still among the problems that await answers. Due to the disease's high transmission rates, most information should be obtained in the shortest time from the patients. In this context, electrocardiography is the simplest and fastest method to predict myocardial performance and arrhythmias. Tp-e, Tp-e/QT ratio, QT interval, and index of cardio-electrophysiological balance (iCEB) are pro-arrhythmogenic markers that can be calculated from the surface electrocardiogram. Tpe and Tpe/QT ratio are thought to reflect of transmural dispersion of left ventricular repolarization. It has been demonstrated that Tp-e interval and Tp-e/QT ratio were increased in patients with chronic hepatitis B or human immunodeficiency virus infections [21, 22]. Nevertheless, we failed to demonstrate a similar situation in patients with COVID-19.

Besides, the index of cardiac electrophysiological balance (iCEB), estimated as QT interval divided by QRS duration, is a novel risk indicator for predicting malignant ventricular arrhythmias [13]. Moreover, it has been demonstrated that iCEB is equal to the cardiac wavelength λ (λ = effective refractory period (ERP) x conduction velocity) and that an increased or decreased ratio of iCEB might potentially predict TdP or non-TdP mediated VT/VF, respectively. Furthermore, authors have speculated that iCEB may reflect both of the depolarization and repolarization phases of the cardiac action potential. However, we have limited data about iCEB, according to literature. Sivri S et al. demonstrated elevated iCEB levels after hemodialysis that indicates the increased risk of TdP-mediated ventricular arrhythmia [23]. In another study, it has been shown that iCEB levels and Tpe/QT ratio were higher in patients with common variable immunodeficiency [24]. Nevertheless, we did not detect a relationship in patients with COVID-19 and ICEB. Also, this study failed to show an association between QTc interval and COVID-19. We have only found

that the heart rate was increased during infection, as expected.

The emergence of these results should not be surprising. Firstly, cardiac effects may not yet occur due to an acute infection. Secondly, the cardiac effects of the disease may not have occurred because of the inclusion of asymptomatic or mildly symptomatic patients. Thirdly, the absence of a significant increase in troponin values in our patient group may indicate that cardiac involvement is not evident. Fourthly, the absence of lung involvement in patients may prevent the development of arrhythmia. Finally, the levels of pro-inflammatory markers may be considered lower in the patient group, which are associated with cardiac arrhythmias. Our findings may have been different with the inclusion of moderate or severe COVID-19 patients into the study. However, the idea that arrhythmogenic effect may occur through direct cardiac involvement of the virus or damage to other organ systems (kidney failure, respiratory failure, liver dysfunction, etc.) may confuse when studying with severe COVID-19 patients groups.

It has been suggested that patients with severely impaired left ventricle function secondary to COVID-19 may need close follow-up for the development of malign arrhythmia, and even wearable, implantable cardiac defibrillators may be useful after discharge. This recommendation can be kept in mind for the course of this infection, because of our limited knowledge about the disease [10].

Our study has a few limitations. First one, this is a single-center, retrospective study with a low number of participants. Secondly, the patients were not followed up for malignant ventricular arrhythmia, sudden cardiac death, and their ECG changes. Thirdly, the lack of 24-hour electrocardiographic Holter monitoring to detect arrhythmic conditions in these patients may be considered as a limitation. Finally, although patients with known cardiovascular disease were excluded from the study, it is a significant limitation that the echocardiographic findings of the COVID group are unknown.

We do not have enough information yet about the chronic cardiac effects of the COVID-19. Prospective clinical trials with long-term and a high number of patient populations are needed to reveal this. Notably, patients with significantly elevated troponin values during the disease should be followed up for long-term development of cardiomyopathy and arrhythmias.

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