RESEARCH ARTICLE / *Araştırma Makalesi*

Ventricular Repolarization Variability in Children Diagnosed with COVID-19

Covid-19 Tanısı Alan Çocuklarda Ventriküler Repolarizasyon Değişkenliği

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Abstract

Introduction	Although the childhood clinic of COVID-19 is more innocent than adults, its unknown aspects continue to cause concern among pediatricians. One of these unsettling aspects is the cardiovascular system effects. We investigate the role of ventricular repolarization parameters in predicting arrhythmia risk in pediatric COVID-19.
Materials and Methods	Twelve-channel surface electrocardiograms of a total of 166 participants, including children diagnosed with COVID-19 and healthy controls, were analyzed. The QT interval, corrected QT interval, QTc dispersion, Tpeak-Tend, Tp-e dispersion, Tp-e / QT and Tp-e / QTc ratio were calculated. The correlations between ventricular repolarization parameters and laboratory values were examined.
Results	In our study, the COVID-19 patients had a significantly longer Tpeak-Tend (64.51 ± 8.64 and 57.62 ± 7.96; p < 0.001), Tp-e dispersion (21.77 ± 6.4 and 18.01 ± 6.78; p < 0.001), and corrected QT interval (393.18 ± 20.06 and 380 ± 22.3; p < 0.001) duration than the control group. There was a significantly higher Tp-e / QT ratio (0.17 ± 0.02 and 0.15 ± 0.02; p < 0.001), Tp-e / QTc ratio (0.16 ± 0.02 and 0.15 ± 0.02; p < 0.001) in group with COVID-19 than the controls. In addition a positive correlation was found between Tpeak-Tend interval, Tp-e dispersion and white blood cells in the group with SARS CoV2 infection.
Conclusion	Evaluating these ventricular repolarization parameters in pediatric SARS CoV2 infection may be useful in predicting the risk of ventricular arrhythmia.
Keywords	COVID-19; child; ventricular repolarization abnormality

Öz

Amaç	*COVID-19'un çocukluklardaki kliniği, yetişkinlere kıyasla daha masum seyretse de bilinmeyen yönleri pediatristler arasında endişe yaratmaya devam ediyor. Bu tedirgin edici yönlerinden biri de kardiyovasküler sistem etkileridir. Biz de bu çalışmada pediyatrik COVID-19'da aritmi riskini tahmin etmede ventriküler repolarizasyon parametrelerinin rolünü araştırmayı amaçladık.*
Yöntem ve Gereçler	*COVID-19 teşhisi konan çocuklar ve sağlıklı kontroller dahil olmak üzere toplam 166 katılımcının on iki kanallı yüzey elektrokardiyogramı analiz edildi. Tp-e intervali, Tp-e dispersiyonu, Tp-e / QT oranı, Tp-e / QTc oranı, QT intervali, QTc intervali ve QTc dispersiyonu değerleri hesaplandı. Ventriküler repolarizasyon parametreleri ile laboratuvar değerleri arasındaki korelasyonlar incelendi.*
Bulgular	*Çalışmamızda, COVID-19 hastalarında kontrol grubuna göre anlamlı derecede uzamış Tpeak-Tend (64.51 ± 8.64 ve 57.62 ± 7.96; p < 0.001), Tp-e dispersionu (21.77 ± 6.4 and 18.01 ± 6.78; p < 0.001), ve corrected QT intervali (393.18 ± 20.06 ve 380 ± 22.3; p < 0.001) saptandı. COVID-19 olan grupta kontrol grubuna göre anlamlı derecede yüksek Tp-e / QT oranı (0.17 ± 0.02'ye ve 0,15 ± 0,02; p <0,001) ve Tp-e / QTc oranı (0,16 ± 0,02'ye ve 0,15 ± 0,02; p <0,001) vardı. Ayrıca SARS CoV2 enfeksiyonu olan grupta Tpeak-Tend aralığı, Tp-e dispersiyonu ve beyaz kan hücreleri arasında pozitif korelasyon bulundu.*
Sonuç	*Pediyatrik COVID-19 hastalarında bu ventriküler repolarizasyon parametrelerinin değerlendirilmesinin ventriküler aritmi riskini tahmin etmede faydalı olabileceğine inanıyoruz.*
Anahtar Kelimeler	*COVID-19; çocuk; ventriküler repolarizasyon anormalliği*

INTRODUCTION

A new type of coronavirus infection emerged in China. In a very short period of time, this disease spread to almost all countries of the world. Like other members of the coronaviridae family, the SARS-CoV-2 virus enters the cell through the angiotensin converting enzyme 2 receptor (ACE-2). After viral replication, ACE-2 receptor is down-regulated and increased angiotensin 2 release causes clinical symptoms such as pulmonary edema and respiratory distress. We observed that SARS-CoV-2 affected adults more than children and the clinical course progressed more seriously. It is thought that the milder course of the disease in children compared to adults may be due to higher ACE-2 activity than adults.[1] Although the main targets of COVID-19 are the airways and lungs, significant cardiac involvement has been reported with an impact on prognosis. In one study, cardiac involvement was reported 12% in adults with COVID-19 and in another study, arrhythmia and myocardial damage were reported as 16.7% and 7.2%.[2,3] Studies have shown that pre-existing cardiovascular disease in people have higher mortality with COVID-19. Therefore, there has been a growing awareness of the cardiovascular symptoms of COVID-19 and the negative impact of cardiovascular involvement on prognosis. Some electrocardiographic changes have been reported in COVID-19 patients. There are not many pediatric studies showing the true prevalence of these abnormalities. Ventricular repolarization is one of the important mechanisms of mortality in ventricular arrhythmias. QT interval, corrected QT interval (QTc) and QT dispersion (QTd) are used to determine ventricular repolarization abnormalities. In addition Tpeak-Tend (Tp-e), Tp-e / QT ratio, Tp-e / QTc ratio and Tp-e dispersion (Tp-ed) which are new parameters indicating the presence of ventricular repolarization, may also be used.[4-7] This study investigated the role of new ventricular repolarization indicators in predicting the risk of arrhythmia in pediatric COVID-19.

MATERİALS and METHODS

This study is a cross-sectional descriptive study. The study included total 83 children aged 0-18 years who were positive for COVID-19 RT-PCR and the same number, gender and age of children who were found healthy according to their examinations. The physical examinations of the participants were performed and blood samples were taken for biochemical values. Complete blood count, coagulation parameters, serum troponin value, aspartate aminotransferase and alanine aminotransferase values were analyzed from the blood samples. The vital signs were recorded. Twelve-channel surface electrocardiograms (ECGs) of all patients were evaluated. The exclusion criteria for study were history of cardiac surgery, congenital anomalies, ventricular dysfunction, heart failure, presence of arrhythmia, electrolyte abnormalities. This study was designed in accordance with the Declaration of Helsinki Principles and received approval from the Sakarya University Faculty of Medicine Ethics Committee on 22 September 2020. (Ethics no:71522473/050.01.04/485)

Electrocardiography

All children rested for ten minutes. The ECGs were recorded in 12 channels, at a speed of 50 mm/s and standardization of 1 mV/cm. The recordings were magnified in photoshop and than analyzed. From these records ventricular repolarization parameters were interpreted by the same specialist. The QT interval was defined as the distance between the beginning of the QRS complex and the point where the T wave returns to the isoelectric line. The QTc interval was set arighted according to the Fridericia formula.[8] The difference between the maximum QT interval and the minimum QT interval was measured as QTd.[9] The Tp-e interval was calculated from the distance from the peak of the T wave to the end of the T wave. The peak of the T wave was described as the highest point of the T wave. The end of the T wave was defined as the tangent intersecting the downslope of the T wave and the isoelectric line. Tp-ed was the difference between the maximum Tp-e interval and minimum Tp-e interval.[10] For all parameters, the average of three measurements were used in the analysis.

Statistical analysis

Descriptive statistics were used to elucidate the general features of the participants. The distribution of numerical variables was determined with the Kolmogorov-Smirnov test. If the data were normally distributed, comparison was made using independent group t tests, but if the data were non normally distributed, the Mann-Whitney test was used. The chi-square test was used for comparison of groups consisting of categorical variables. The pearson correlation coefficient for numerical variables with normal distribution; the spearman correlation coefficient was used for non-normal distribution. In all analyzes, the statistical significance was accepted as p <0.05.

RESULTS

The group with COVID-19 had 59% girls and 41% boys, while the control group had 56% girls and 44% boys. The mean age of the group with COVID-19 was 9.57 (± 5.74) year and the mean age of the controls was 9.3 (± 5.54) year. The control group had a statistically significantly lower QTc interval than the group with COVID-19 (380 ± 22.3 and 393.18 ± 20.06; p < 0.001), but there was no statistically significant difference in the QT interval between the two groups (369.35 ± 18.4 and 368.84 ± 21.78; p = 0.874) and QTc dispersion (34.55 ± 11.58 and 32.2 ± 9.67; p = 0.168). Tp-ed (18.01 ± 6.78 and 21.77 ± 6.4; p < 0.001), Tp-e interval (57.62 ± 7.96 and 64.51 ± 8.64; p < 0.001), Tp-e/QT ratio (0.15 ± 0.02 and 0.17 ± 0.02; p < 0.001), and Tp-e/QTc ratio (0.15 ± 0.02 and 0.16 ± 0.02; p < 0.001) were statistically significantly lower in the controls compared to the group with SARS CoV2 infection (Table 1). There was a significant positive correlation between Tp-e interval, Tp-ed, and white blood cells (r = 0.248, p = 0.024 and r = 0.289, p = 0.008). In addition, there was a correlation between lymphocyte, aspartate aminotransferase, alanine aminotransferase, troponin and Tp-e, Tp-ed, Tp-e/QT ratio, and Tp-e/QTc ratio. Prothrombin time and international normalized ratio were correlated with Tp-e/QT ratio, Tp-e/QTc ratio and Tp-e interval. These correlation results are shown in Table 2, and the hematological parameters and laboratory findings in the COVID-19 population are shown in Table 3.

Table 1. The demographic and ECG characteristics of the groups

	COVID-19(n = 83)	Control (n = 83)	p value
Gender (M/F)	44/39	47/36	0.960
Age (year)	11.20 (11.13)	12 (10.88)	0.720
QT, ms	369.35 ± 18.4	368.84 ± 21.78	0.874
QTc, ms	393.18 ± 20.06	380 ± 22.3	<0.001
cQTd, ms	34.55 ± 11.58	32.2 ± 9.67	0.168
Tp-e interval, ms	64.51 ± 8.64	57.62 ± 7.96	<0.001
Tp-e dispersion, ms	21.77 ± 6.4	18.01 ± 6.78	<0.001
Tp-e/QT, ms	0.17 ± 0.02	0.15 ± 0.02	<0.001
Tp-e/QTc, ms	0.16 ± 0.02	0.15 ± 0.02	<0.001

Parameters were expressed as mean ± Standart deviation and median.
Student's t, Mann-Whitney U tests and x2 were performed.
Data are given as mean ± SD, median (IQR), M=Male; F=Female; 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.

Table 2. The results of the correlation analyses between new VR indicators and hematological, biochemical parameters

	Tp-e interval, ms		Tp-e/QT, ms		Tp-e/QTc, ms		Tp-e dispersion, ms	
	r	p	r	p	r	p	r	p
WBC 10^3 uL	0.248	0.024	0.203	0.066	0.210	0.056	0.289	0.008
LYM 10^3 uL	0.363	<0.001	0.311	0.004	0.352	<0.001	0.268	0.014
AST, IU/L	0.416	<0.001	0.400	<0.001	0.402	<0.001	0.432	<0.001
ALT, IU/L	0.279	0.011	0.335	0.002	0.310	0.005	0.347	<0.001
Troponin ng/L	0.218	0.050*	0.267	0.015*	0.219	0.048*	0.361	<0.001
PT sec	0.240	0.036	0.301	0.008	0.279	0.014		
INR	0.229	0.044	0.269	0.017	0.249	0.028		

Pearson and Spearman correlation tests were performed and p value<0.05 was considered significant.
*Spearman correlation
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; LYM, lymphocyte count; PT, prothrombine time; VR, ventricular repolarization ;WBC, white blood count

Table 3. Descriptive statistics of laboratory findings in the pediatric COVID-19 population.

Parameters	COVID-19 (n = 83)
WBC, 10^3 uL	6.34 (14.58)
LYM, 10^3 uL	2.16 (13.29)
AST, IU/L	27.50 (83.00)
ALT, IU/L	12.50 (35.00)
Troponin ng/L	0.40 (53.40)
PT, sec	11.47 ± 2.60
APTT, sec	26.86 ± 3.49
INR	1.12 ± 0.26

Data are given as mean ± standart deviation and median (inter quartile range)
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; APTT activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombine time; LYM, lymphocyte count; WBC, white blood count

DISCUSSION

The SARS-CoV-2 infection, which entered our lives in December 2019, spread rapidly all over the world and there are many unknown aspects. Serious fatal cardiovascular complications have been shown in SARS-CoV-2 infection, which reveal the association between cardiac involvement and poor prognostic outcomes. Our knowledge of SARS-CoV-2 is based on our experiences with other members of the family. Malignant arrhythmias are common in SARS-CoV infection.[11] In a recent SARS-CoV-2 study, arrhythmia was present in 16.7% of patients. Arrhythmias in COVID-19 may complicate the clinical course of the disease and worsen its prognosis.[3] Ventricular repolarization abnormalities play an important role in malignant arrhythmias. Parameters such as the T wave, QT, QTc interval analysis are widely used to evaluate ventricular repolarization. Clinical studies show that heterogeneity in ventricular repolarization may trigger ventricular arrhythmias and this is very important for prognosis.[12,13] The Tp-e interval is effective in demonstrating variability of ventricular repolarization in people with a normal QT interval.[13] There are studies on the new myocardial repolarization index in structurally normal hearts in children.[14] However, there have not been any studies on the association between pediatric COVID-19 and ventricular repolarization variability. COVID-19 is thought to have a good prognosis in children, but mortality has also been reported. Based on this unknown aspect, we investigated the variability of ventricular repolarization in children with SARS-CoV-2 infection. In our study, the TP-e / QT, Tp-e / QTc, Tp-e and Tp-ed were lower in healthy controls compared to group with SARS-CoV-2. Therefore, we thought that children with COVID-19 infection may be at proarrhythmic risk. In fact, SARS-CoV-2 infection, like other similar viral infections, may cause proarrhythmic environment due to fever, stress, electrolyte disturbances. Especially systemic inflammation may cause arrhythmias by lowering the arrhythmogenic threshold. In many studies has been shown that inflammatory cytokines lead to prolongation of the QT interval by extending the action potential times of cardiomyocytes, especially through potassium and calcium channels.[15-17] In addition, it has been reported that systemic inflammation may cause arrhythmia by disrupting the oxidative balance and triggering cell death.[18] We showed a positive correlation between the Tp-e and Tp-e dispersion and white blood cells, we also showed a positive correlation between the Tp-e, Tp-ed, Tp-e/QT, Tp-e/QTc ratio and lymphocyte values. Similar to our study in a study with adults COVID-19, repolarization parameters were significantly longer compared to the healty controls.[19] Studies have shown that leukocytosis and lymphopenia / lymphocytosis are among common laboratory abnormalities in COVID-19 patients and also showed that the poor prognosis was in patients with leukocytosis.[20]

The possible causes and mechanisms of arrhythmias due to inflammation are not fully understood yet. Myocardial dysfunction has been shown to trigger arrhythmia in different mecanism. It may be assumed that the inflammation seen in COVID-19 patients may impair myocardial function and result of this causing arrhythmia. Severe systemic inflammation, including infections, is known to cause reversible myocardial damage, leading arrhythmia. However, it is remains to be established that mild to moderate

systemic inflammation may cause reversible myocardial damage and increase arrhythmia.[21-23]

We showed our study that a positive correlation between the Tp-e interval, Tp-e/QT and Tp-e/QTc ratios and PT and INR in COVID-19 patients. Activation of the coagulation response may result in a predisposition to a variety of cardiac arrhythmias. A large-scale study demonstrated a strong and independent association of various hemostatic markers. Endothelial dysfunction and oxidative stress are thought to be potential indirect mechanisms underlying this relationship.[24]

In our study no patient had a critical course, none of patient observed with arrhythmia and mortality. However the TP-e / QT and Tp-e / QTc ratio were higher, Tp-e and Tp-ed were longer in group with SARS-CoV-2 compared to the healthy control and a positive correlation was found between new ventricular repolariztaion parameters such as Tp-e interval, Tp-ed, Tp-e/QT, Tp-e/QTc and laboratory parameters such as AST, ALT, troponin levels.

In conclusion, pediatric COVID-19 is generally not critical, but we thought there might be ventricular repolarization abnormalities. Therefore, careful electrocardiographic monitoring might be used to detect arrhythmia. It is difficult to find exact results in the presence of all these uncertainties. We believe that evaluating these electrocardiographic repolarization parameters in addition to the QTc interval in pediatric COVID-19 will be useful in predicting the risk of ventricular arrhythmia. A large prospective study is needed to determine the usefulness of these parameters.

Highlights: Pediatric COVID-19 remains uncertain. Cardiovascular system disorders associated with mortality and morbidity. In these children, abnormalities were found in parameters indicating ventricular repolarization. We think that ventricular repolarization abnormalities may pose an arrhythmia risk in pediatric COVID-19.

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Conflicts of Interest

None declared.

Informed consent

Informed consent was obtained from all parents and individual participants.

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Ethical approval

Ethics committee approval was given for this study from the Sakarya University Faculty of Medicine Ethics Committee on 22 September 2020 (Ethics no:71522473/050.01.04/485)

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