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RESEARCH ARTICLE

Is there any effect of COVID-19 mRNA vaccination on electrocardiographic parameters in patients without apparent cardiovascular disease?

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ABSTRACT

Objective: Electrocardiographic alterations were investigated following the second dosage of COVID-19 mRNA vaccination. **Methods:** A total of 260 individuals after two doses of COVID-19 vaccine with Pfizer-BioNTech were included in the study. The electrocardiographic parameters recorded at baseline and approximately one week later after two doses of Pfizer-BioNTech vaccine were compared for all patients. **Results:** PR interval was increased and QTc maximum interval was decreased significantly after second dose COVID-19 mRNA vaccination. Baseline and post-second dose vaccination states regarding P wave dispersion and QT dispersion/Tp-e interval which have been recognized to imply inhomogeneous atrial conduction and heterogeneity in ventricular repolarization were similar between groups. **Conclusion:** Our findings suggest that there should be no concern related to asymptomatic involvement of the myocardium subsequent the second dose of COVID-19 mRNA vaccination.

Keywords: COVID-19, mRNA vaccine, myocarditis, electrocardiography, P wave dispersion, QT dispersion

ÖZET

Belirgin kardiyovasküler hastalığı olmayan hastalarda COVID-19 mRNA aşısının elektrokar-diyografik parametreler üzerinde herhangi bir etkisi var mı?

Amaç: Bu çalışmanın amacı, ikinci doz COVID-19 mRNA aşılamasından sonra elektrokardiyografik değişiklikleri değerlendirmektir. **Yöntem:** Çalışmaya Pfizer-BioNTech ile iki doz COVID-19 aşısı yapılan toplam 260 hasta dahil edildi. Başlangıçta ve iki doz Pfizer-BioNTech aşısından yaklaşık 1 hafta sonra kaydedilen elektrokardiyo-grafik parametreler tüm hastalar için karşılaştırıldı. **Bulgular:** İkinci doz COVID-19 mRNA aşılamasından sonra PR aralığı arttı ve QTc maksimum aralığı önemli ölçüde azaldı. Sırasıyla ventriküler repolarizasyonda homojen olmayan atriyal iletimi ve heterojenliği yansıttığı varsayılan P dalgası dispersiyonu ve QT dispersiyonu/Tp-e aralığı ile ilgili olarak başlangıç ve ikinci doz aşılama durumları arasında anlamlı bir fark yoktu. **Sonuç:** Bulgularımız, ikinci doz COVID-19 mRNA aşılamasından sonra miyokardın asemptomatik tutulumu ile ilgili herhangi bir endişe olmaması gerektiğini düşündürmektedir.

Anahtar kelimeler: COVID-19, mRNA aşısı, miyokardit, elektrokardiyografi, P dalga dispersiyonu, QT dispersiyonu

INTRODUCTION

The coronavirus disease 2019 (COVID-19) quickly became a pandemic. Adverse events, morbidity, and mortality from this pandemic are still enormous worldwide. The cardiovascular system has been suggested to be one of the main systems disturbed by the infection [1]. However, vaccination has a critical role to defend from COVID-19 disease [2]. Vaccines have been urgently approved prior the completion of clinical trials' all three phases for the prevention of the spread of COVID-19 infection [3]. A variety of adverse events related to vaccination have been reported with widespread usage of these vaccines and some of these adverse events have been suggested to be related to the cardiovascular system [4]. World Health Organization

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(WHO) database reported 103,954 adverse events for 30,523 patients from December 15th 2020 to January 24th 2021. Moreover, a total of 4863 cardiovascular adverse events were stated related to COVID-19 vaccines. Common reported cardiovascular adverse events were flushing, peripheral coldness, hyper- or hypotension, tachycardia [5]. A total of 1,068 myocarditis cases were reported following the various vaccines were administrated since 1991 by Centers for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System (VAERS). Among these, 778 (72.9%) cases were reported to be related to COVID-19 vaccination [6]. Several case reports also have been reported as myocarditis following COVID-19 mRNA vaccines [7]. Recently, Fatima et al. [7] reported that the merged occurrence of myocarditis and pericarditis inferred from current studies were 0.001% and 0.0004%. The direct causal relation-ship between these adverse events and vaccinations has yet to be established.

It is known that myocarditis may manifest as asymptomatic inflammation well as severe heart failure and death [8]. Electrocardiography (ECG) in patients with myocarditis has been reported to display a variety of abnormalities and has been suggested to represent a useful screening tool [8,9]. It was aimed to evaluate the probable effects of the COVID-19 mRNA vaccine on the myocardium by evaluating alterations in electrocardiographic parameters.

MATERIALS and METHODS

Patients and study design

A total of 260 patients who had undergone 2 consecutive doses of COVID-19 vaccination with Pfizer-BioNTech between July 2021 and September 2021 were included in the study. Cardiovascular risk factors, coexisting medications, and medical history of all patients were recorded. Twelve lead electrocardiographic recordings were obtained at baseline and nearly 1 week after the additional dose of the Pfizer-BioNTech vaccine. The electrocardiographic parameters were obtained at pre-vaccination and post-second vaccination and compared between groups.

Patients who had a history of COVID-19 infection within the previous 6 months, atrial fibrillation or flutter, pacemaker rhythm, and bundle branch block (complete or incomplete) at the time of vaccination were accepted as exclusion criteria. In addition, a history of coronary artery disease, any kind of cardiomyopathy, and heart failure. Patients with coexisting medications that may affect cardiac electrophysiology such as antiarrhythmic drugs were also excluded. The study was approved by the local ethics committee (2021/14/543).

Electrocardiography

A standard twelve-lead ECGs were taken before and after the vaccination for each patient using a recorder (GE Marquette Medical Systems, Milwaukee, WI) set with 25 mm/s paper speed and 1 mV/cm standardization. These ECGs were transferred to online analysis system by using the Cardio Calipers package (Version 3.3 for Windows). Three sequential cycles in each ECGs were measured in terms of aimed electrocardiographic parameters and mean value of these measurements were recorded. The initial point of the p wave was defined as the first deflection crossing the isoelectric line, and end of the P wave was considered to be the point where the final deflection of the P wave crossed the isoelectric line. P-wave duration with the longest interval was accepted as the P maximum (Pmax), whereas shortest duration in any leads was accepted as P minimum (Pmin). According to this definition, P wave dispersion was obtained by the following formula: Pmax- Pmin. If the initial and/or end part of the P wave could not be identified, patients were excluded from the study. The QT interval was defined as the between onset point of the QRS complex and T wave end point. Maximum QT duration was defined as the longest interval in any lead, whereas minimum QT was defined as the shortest interval in any lead. Bazett's formula ($QTc=QT/\sqrt{RR}$) was used to obtained corrected QT interval (QTc). QT dispersion was obtained by the following formula: QTmax-QTmin. In addition, T peak to Tend (Tp-Te) variable was obtained from V5 and V6 leads, and Tp-Te/QT ratio was calculated from obtained data.

Cardiovascular Risk Factors

Those who taking antidiabetic medication or whose blood glucose parameter is higher than 126 mg/dL in two consecutive determinations were accepted as diabetic. If fasting total serum cholesterol was found to be higher than 240 mg/dL or patients were taking the antihyperlipidemic agents were considered to had hyperlipidemia. In addition, hypertension diagnosis was made based on if patients were taking antihypertensive agents or whose systolic and/or diastolic blood pressure was higher than 140/90 mmHg. Smoking status was assessed as whether patients were smoking at least one cigarette in the last five years.

Statistical analysis

All statistical tests were performed with SPSS 22.0 version package program (SPSS Inc., Chicago, Illinois, United States). A significance level was set at $p<0.05$. Kolmogrov Smirnov test was carried to test the distribution of the variables. Parameters that distributed normally were expressed as mean±standard deviation scheme. Whereas non-normally distributed parameters

Table 1. Demographic characteristics and cardiovascular risk factors of the study population.

Age (years)	41.8±15.7
Gender (male)	140 (53.8%)
BMI (kg/m^2)	25.7±2.9
Obesity (BMI > 30) (n, %)	24 (9.2%)
Hypertension (n, %)	50 (19.2%)
Diabetes Mellitus (n, %)	33 (12.7%)
Hyperlipidemia (n, %)	31 (11.9%)
Smoking (n, %)	55 (21.2%)

BMI: body mass index.

were stated as medians with interquartile ranges scheme. Categorical variables were given as percentages and numbers. In addition, dependent variables were compared by using Wilcoxon rank test for non-normally distributed and dependent sample t test for normally distributed parameters. Reproducibility was assessed by reanalyzing 15 randomly selected patients, reported as intra-observer reliability and by calculating from a second independent observer, reported as inter-observer reproducibility.

RESULTS

A total of 260 subjects were used in the analysis. Demographic characteristics and cardiovascular risk factors of patients are presented in Table 1. Electrocardiographic parameters obtained at baseline and after second dose vaccination are displayed in Table 2. Mean heart rate, P wave terminal force, and maximum QTc interval were observed to decrease significantly after vaccination, and PR interval increased significantly after vaccination (Table-2).

DISCUSSION

PR interval was increased and QTc maximum interval was decreased significantly following the second dose of COVID-19 mRNA vaccination. Baseline and post-vaccination states regarding P wave dispersion and QT dispersion/Tp-e interval reflecting heterogeneous atrial conduction and ventricular repolarization did not differ be-tween groups.

There is accumulating data for myocarditis cases that might be related to COVID-19 mRNA vaccines. Recently, Woo et al. [2] have evaluated the clinical characteristics and prognostic factors related to myocarditis that seen following COVID 19 mRNA vaccination.

Authors have reviewed nine cases and 15 myocarditis case reports among a total of 74 patients following BNT162b2 or mRNA-1273 vaccines administration. They reported that 78.3% of the patients had administered the BNT162b2 vaccine, and 90.5% of them presented with myocarditis subsequently following the second dose of the vaccine. Most participants who developed myocarditis after vaccination were found to be male (94.6%) with 17.6 years median age (14-70). Younger patients (< 20 years of age) had presented with more severe systemic findings. However, myocardial involvement was more severe in older patients. Most patients resolved with conservative therapy but individuals with gastrointestinal symptoms requisite intensive care more frequently. Authors have reported that 87.8% of participants had unusual ECG findings with ST-segment deviations in 77.0%, T-wave abnormalities in 16.2%, and PR interval abnormality in 14.9%.

The pathogenesis of COVID-19 mRNA vaccines related myocarditis is not clear. Autoimmunity has been suggested to be a possible mechanism and the highest incidence after the second dosage seems to be in line with this hypothesis [10]. Furthermore, mRNA strands themselves have also been suggested to activate an autoimmune reaction against cardiomyocytes, exaggerate systemic reaction harmfully effecting the myocardium. In addition, a lipid nanoparticle sheath encapsulating the mRNA component has also been thought to be involved in the pathogenesis of myocardial damage [10]. The clinical manifestations of myocarditis have been known to be heterogeneous, ranging from virtually asymptomatic cases to cardiogenic shock due to severe myocardial destruction [10]. We tried to evaluate the electrocardiographic alterations after BNT162b2 vaccination, as vaccination may have an effect on the myocardium via the above-mentioned mechanisms in the current study. Subtle electrocardiographic alterations might be a reflection of asymptomatic involvement of the myocardium after vaccination due to myocardial edema/inflammation. We did not see any significant prolongation in QRS and QT intervals which have been implied to be associated with worse prognosis in

Table 2. Electrocardiographic parameters obtained before and after second vaccination.

	Pre-vaccination	Post-vaccination	Difference	95%CI	p
RR interval (ms)	785.9±135.5	802.5±124.8	-16.7±10.9	-29.9-3.3	0.014
Heart rate (beats/min)	78.7±13.9	76.6±11.9	2.1±11.2	0.7-3.5	0.003
P wave max (ms)	102.4±9.8	102.1±9.7	0.2±5.2	-0.4-0.9	0.473
P wave min (ms)	86.2±8.5	86.4±8.2	-0.2±5.2	-0.8-0.5	0.616
P dispersion (ms)	16.1±4.8	15.8±4.8	0.4±3.3	-0.01-0.8	0.06
P wave terminal force (ms)	46.7±7.3	46.2±6.7	0.5±4.1	0.001-0.99	0.046
PR interval (ms)	146±16.9	147±16.6	-1.0±7.1	-1.9-0.2	0.016
QRS duration (ms)	87.8±9.1	88.1±9.4	-2.9±4.4	-0.8-0.3	0.295
R wave peak time (ms)	39.4±3.8	39.2±3.2	0.2±2.1	-0.1-0.4	0.208
QTc interval max (ms)	432.7±25.3	428.6±34.1	4.1±31.5	0.2-7.92	0.038
QTc interval min (ms)	412.8±23.5	411.6±29.5	1.2±27.5	-2.1-4.6	0.484
Qtc dispersion (ms)	20±5.8	19.7±4.8	0.2±4.4	-0.3-0.8	0.394
V4 Tp-e (ms)	92.9±14.7	92.6±13.3	0.2±7.1	-0.6-1.1	0.586
V5 Tp-e (ms)	91.6±14	91.4±13.7	0.2±8	-0.8-1.2	0.66
V6 Tp-e (ms)	91.7±14.1	91.9±12.6	-0.2±5.8	-0.9-0.6	0.679
V4 Tp-e/QT	0.25±0.04	0.25±0.04	0.002±0.02	-0.0004-0.004	0.1
V5 Tp-e/QT	0.25±0.04	0.25±0.04	0.002±0.02	-0.0008-0.004	0.188
V6 Tp-e/QT	0.25±0.04	0.25±0.04	0.001±0.01	-0.0004-0.003	0.156

patients with acute myocarditis [11]. The cause of minimal but significant PR prolongation is not clear and both baseline and post-vaccination values were within normal limits.

Arrhythmias are a significant cause of adverse cardiovascular events including morbidity and mortality in patients with acute myocarditis and both brady- and tachyarrhythmias can be induced during the disease process [11]. We could not see any significant differences between baseline and post-vaccination states regarding parameters that are assumed to reflect the tendency for atrial and ventricular arrhythmias. A significantly higher heart rate at the baseline might be related to the anxiety before vaccination. The leading limitation of study is that we could not perform power analysis as there is no information related to the expected prevalence of asymptomatic myocarditis after COVID-19 mRNA vaccination. In conclusion, our analysis did not demonstrate any clinically important alterations in electrocardiographic parameters after BNT162b2 vaccination. Clinical acute myocarditis following COVID-19 mRNA vaccination was reported to be an adverse event related to the vaccine, but the reported incidence is quite low. Based on our findings it may be suggested that there should be no concern related to asymptomatic involvement of the myocardium after two doses of COVID-19 mRNA vaccination dose.

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