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Atrial electromechanical delay is impaired in patients with COVID-19

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ABSTRACT

Background: COVID-19 infection has the potential to affect the cardiovascular system. Intra/ interatrial electromechanical delay (EMD) demonstrated by P wave dispersion (PD) and tissue doppler echocardiography (TDE) is related to the development of atrial fibrillation. This study aimed to investigate atrial conduction time by PD and TDE in patients with COVID-19.

Material and Method: A total of 143 participants were selected in the current study. The COVID-19 group included 90 subjects and the control group included 53 individuals. Two groups were compared with each other, in terms of electrocardiographic P wave measurements, and atrial electromechanical coupling (AEC) parameters by TDE.

Results: Maximum P-wave duration (Pmax) and PD were significantly higher in COVID-19 patients compared to the control group ($p<0.001$, for both). Interatrial and intraatrial EMD were also longer in the COVID-19 patients compared to control group ($p<0.001$, for both). Correlation analysis revealed a significant and positive correlation between CRP with Pmax, PD, interatrial and intraatrial EMD ($r=0.608$, $p<0.001$; $r=0.708$, $p<0.001$; $r=0.692$, $p<0.001$; $r=0.697$, $p<0.001$, respectively). Besides, a positive and significant relationship was also found between the interatrial and intraatrial EMD with PD and Pmax ($p<0.001$, for all).

Conclusion: Atrial EMD parameters were prolonged in patients with COVID-19. The measurement of atrial EMD parameters might be used to determine the risk of AF development in patients with COVID-19.

Keywords: Atrial fibrillation, COVID-19, atrial electromechanical delay

INTRODUCTION

Although COVID-19 primarily presents with acute pneumonia and severe respiratory distress syndrome, cardiovascular involvement including new onset atrial fibrillation (NOAF) has also been reported extensively. Acute cardiovascular events such as arrhythmias that complicate the clinical course of SARS-CoV-2 may be one of the causes of poor survival (1-3).

The most common rhythm disorder in clinical practice, atrial fibrillation (AF), is critical owing to the associated hemodynamic disorders and thromboembolic events (4). Even though the exact mechanisms that cause AF are not fully understood, several risk factors including age, hypertension (HT), coronary artery disease (CAD), cerebrovascular disease, and diabetes are supposed to play roles in the development of AF (5). Moreover, accumulating evidence has shown that inflammation and inflammatory factors, the autonomic nervous system, and oxidative stress play a significant role in AF pathogenesis (6,7).

COVID-19 infection can cause direct myocardial cell injury, myocardial oxygen supply/demand mismatch, hypoxia, enhanced systemic inflammation and catecholamine surge, increased thrombosis, and oxidative stress imbalance, which may all be related to the occurrence of AF (8-10). Therefore, the risk of NOAF due to all these mentioned mechanisms may increase in COVID-19.

The atrial conduction time (ACT) represents the interval between sinus impulses and atrial mechanical contraction. A noninvasive alternative to invasive electrophysiological measurements is tissue Doppler echocardiography (TDI) (11). Prolonged intraatrial and interatrial conduction time, called atrial electromechanical delay (EMD), is associated with a higher risk of AF (12). It has also been shown that P wave dispersion (PD) and maximum P wave duration (Pmax) can be electrocardiographically (ECG) noninvasive determinants of atrial fibrillation (13).

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To our knowledge, there is no study evaluating atrial conduction abnormalities in COVID-19 using noninvasive tests such as TDI and ECG. This study aimed to determine atrial conduction abnormalities and factors affecting atrial conduction time in COVID-19 patients.

MATERIAL AND METHOD

Approval for the study was granted by Kayseri City Hospital Clinical Researches Ethics Committee (Date: 25.06.2020, Decision No: 134). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All patients signed the free and informed consent form.

The present study is a prospective single-center study conducted in an institute that accepts patients diagnosed with COVID-19 with polymerase chain reaction (PCR) tests and designated as a 'COVID-19 Hospital' by the Turkish Ministry of Health.

According to the definitions in the "COVID-19 Diagnosis and Treatment Guide" printed by the Turkish Ministry of Health (14), the clinical definition of patients was as follows: Mild illness presents with features such as fever, muscle/joint pain, cough, sore throat, and nasal congestion without pneumonia. Severe illness is defined as widespread findings of pneumonia in computed tomography (CT). Critical illness defines the requirement of the Intensive Care Unit (ICU). The routine criteria for ICU admission at our center were as follows (according to Ministry of Health guidelines); Signs conclusive for severe respiratory failure, including having an SpO_2 of ≤ 90% in ambient air, need for ≥ 6 L O_2/min, need for non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV).

The first electrocardiogram (ECG) recording of patients at the time of hospital admission were analyzed and conventional echocardiographies were performed. At that time, no patient was receiving any medical treatment. The patients in our study group consisted of patients with severe illness, older than 18 years of age, and having sinus rhythm at admission according to 12-lead electrocardiogram (ECG). We excluded patients with mild illnesses and patients in requirement of ICU on admission. Patients were also excluded from the study if any of the following criteria applied: a history of coronary artery disease (CAD), heart failure, arterial hypertension (HT) and diabetes mellitus (DM), LV ejection fraction (EF) less than 50%, primary cardiomyopathy, valvular heart disease, a history of AF, dysrhythmia, bundle branch block, atrioventricular conduction abnormalities on ECG, thyroid dysfunction, anemia, electrolyte imbalance, renal failure, who have previously tested positive for covid-19 pcr and/or have a history of severe flu symptoms, who have positive troponin results during hospitalization and poor quality echocardiographic and ECG imaging. A total of 199 hospitalized patients with COVID-19 diagnosis between september and december 2020 in our hospital were evaluated. One hundred nine patients who met the exclusion criteria were excluded from the study. The remaining 90 patients were included in the study. Fifty-three age- and sex-matched healthy volunteers with no previous positive covid-19 pcr test and/or no history of severe flu symptoms were randomized for comparison.

In order to show the poor statistical power of arrhythmias in covid-19 studies, a number of studies were selected for post hoc testing on the sample size in order to determine the achieved power. Gpower 3.1.9.4 program was used for calculation (3). Significance level and statistical power were set at 0.05 and 0.80 respectively. In the power analysis, it was concluded that a total of 119 participants (study and control groups) were sufficient.

On admission, a detailed medical history, 12-lead electrocardiography, complete blood count, serum biochemistry and detailed transthoracic echocardiographic examination were obtained from all patients before starting medical treatment. Blood pressure and oxygen saturation values during the echocardiographic examination were recorded. The presence of pneumonia was confirmed by computerized tomography imaging (CTI) within 24 h of hospital admission for all patients. The radiological appearance on CTI of the patients was diffuse infiltration.

The standard SARS-CoV-2 infection treatment protocol recommended by the Science Advisory Board of the Turkish Ministry of Health, including Oseltamivir phosphate 75 mg twice daily, and azithromycin 250 mg once daily (following a 500 mg loading dose), were administered to all patients.

Electrocardiography

ECG recordings were performed simultaneously by a Philips brand machine electrocardiography (ECG) device, including at least 3 QRS complexes for each derivation, at 25 mm / sec speed, 1 mV amplitude, and standard 12 leads. P wave duration in all derivations was measured manually with calipers and magnifying lenses to reduce error in measurements. P wave origin was taken as the point where the P wave crosses the isoelectric line. The endpoint was taken as the intersection of the isoelectric line and the end point of the P wave. The maximum P wave duration was accepted as the longest P wave and the longest atrial conduction time. The difference between the longest p wave (Pmax) and the shortest p wave (Pmin) was considered as P wave dispersion (PD=Pmax-Pmin) (15,16). All calculations were evaluated separately by two different cardiologists, who were unaware of the patients' clinical characteristics, in a single-blind fashion. The average of these two values was accepted as P wave dispersion and maximum P wave duration.

Echocardiography

Conventional echocardiography was performed with 2-dimensional, M-mode, pulsed wave, continuous color Doppler and tissue Doppler imaging using a Vivid 7 pro ultrasound system (Vivid 7 pro, GE, Horten, Norway, 2-4 MHz phased array transducer ultrasound system). Simultaneous ECG recording was done. All patients were in sinus rhythm at the time of examination. Conventional echocardiographic images were obtained from the parasternal and apical views according to the guidelines of the American Society of Echocardiography (17). Left ventricular (LV) diameters and wall thickness were measured from the para- sternal views by M-mode echocardiography. The Simpson's method was used for the calculation of LV ejection fraction. Right ventricular (RV) systolic function was determined by measuring tricuspid annular plane systolic excursion (TAPSE) using the M-mode technique. While the left atrial area (LAA) was measured from the apical 4-chamber view at the end-ventricular systole, LA diameter was measured from the parasternal long axis view. While the maximal LA volume was performed by applying Simpson's rule from apical 4 chamber imaging, the maximal right atrial (RA) volume was calculated by apical 4-chamber views using the area -length method. LV end-systolic and diastolic volumes were also calculated by 4-chamber views using the area - length method. Mitral inflow velocities were measured from apical views.

Atrial Electromechanical Time Measurement

TDI was performed using transducer frequencies of 3.5–4.0 MHz. The spectral pulsed Doppler signal filters were adjusted until a Nyquist limit of 15–20 cm/s was obtained. The minimal optimal gain was used. Myocardial TDI velocities [peak systolic (S'), early diastolic (E'), and late diastolic velocities (A')] were measured with a spectral pulsed Doppler from the apical 4-chamber view. The PW Doppler measurements were evaluated separately from the LV lateral mitral and LV septal mitral, RV tricuspid annulus.

The ultrasound beam slope did not exceed 15% in acquiring the optimal angle of imaging. The monitor sweep speed was adjusted at 50–100 mm/s to optimize myocardial velocities' spectral display. Atrial EMD was defined as the time interval from the onset of atrial electrical activity (P wave on surface ECG) to the beginning of mechanical atrial contraction (late diastolic A wave) (**Figure 1**). All values were averaged over three consecutive beats. Atrial EMD was measured from the lateral mitral annulus called 'PA lateral,' from the septal mitral annulus, called 'PA septal,' and from the right ventricle tricuspid annulus, called 'PA tricuspid.' Interatrial EMD was calculated as the difference between PA lateral and PA tricuspid, right intraatrial EMD was calculated as the difference between PA septum and PA tricuspid and left intraatrial EMD was calculated as the difference between PA lateral and PA septum (11).

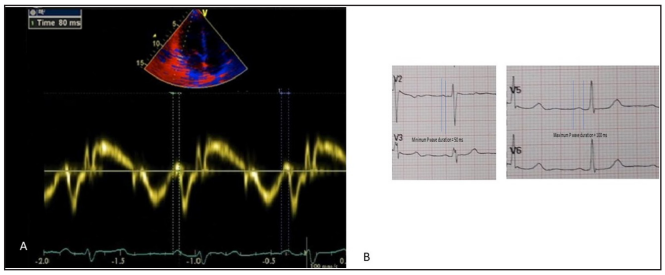

Figure 1. Operational duration according to the groups

A total of 20 participants, 10 from the patient group and 10 from the control group, were randomly selected to evaluate the intra-observational variability. Measurements were repeated under the same baseline conditions. Intra-observer variability was 3.2% for lateral PA, 3.6% for septal PA, and 4.3% for tricuspid PA, respectively.

Statistical Analysis

Statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) software for Windows. The distribution of quantitative variables was checked with the Kolmogorov-Smirnov test. Descriptive data were given as mean ± standard deviation, depending on the normality of distribution. Median and interquartile ranges were given when the variable did not follow a normal distribution. The independent sample t-test was used to compare normally distributed quantitative variables, and the Mann-Whitney U test was used to compare non-normally distributed quantitative variables. Categorical variables were compared with the chi-square test. The relationship between the variables was analyzed by Spearman correlation analysis. A P-value less than 0.05 was considered significant.

RESULTS

A total of 143 participants were selected in the current study. The COVID-19 group consisted of 90 subjects (63 male), and the control group included 53 individuals (34 male).

Baseline laboratory measurements and demographic features of the study groups are presented in **Table 1**. The study population was similar regarding sex distribution and age and there were no significant differences between the patients and the control group ($p > 0.05$).

Table 1. Baseline clinical and laboratory measurements of the study groups

Variables	Control Group (n=53)	Covid Group (n=90)	p value
Age (years)	54 (41-62)	52 (44-66)	0.568
Male/female	34 (64%)	63 (70%)	0.470
Glucose (mg/dL)	94 (83-116)	100 (88-113)	0.312
Creatinine (mg/dL)	0.82±0.16	0.87±0.25	0.200
AST (U/L)	22.5±5.7	21.4±7.8	0.119
ALT (U/L)	22.3±10	23.1±8.1	0.748
Total Bilirubin (mg/dL)	0.60±0.3	0.59±0.3	0.867
White Blood Cell (10^3/uL)	8.7 (7.14-9.83)	14.5 (9.3-19)	<0.001
Hemoglobin (g/l)	14.8±1.4	14.7±1.4	0.598
Platelet (/mm^3)	256 (199-300)	240 (215-295)	0.736
C-Reactive Protein (CRP)	3.2 (1.6-5.4)	16.6 (6.9-55.9)	<0.001
Neutrophils/Lymphocytes ratio (NLR)	1.9 (1.3-3.1)	4.7 (2.9-8.0)	<0.001
Systolic blood pressure	120.1±11.8	123.8±11.7	0.157
Diastolic blood presure	75.2±6.9	76±7.6	0.556
Oxygen saturation	97±0.9	92.4±1.2	<0.001

Serum C-reactive protein (CRP), white blood cell (WBC) levels and neutrophils/lymphocytes ratio (NLR) were significantly higher in COVID-19 patients (CRP; 16.6 (6.9-55.9) vs. 3.2 (1.6-5.4), p<0.001, WBC; 14.5 (9.3-19) vs. 8.7 (7.1-9.8), p<0.001, NLR; 4.7 (2.9-8.0) vs 1.9 (1.3-3.1), p< 0.001, respectively). Other blood parameters were similar between groups. Troponin values in COVID-19 patients were within the normal range. There were no differences between the groups.

The electrocardiographic parameters of the groups are shown in **Table 2**. Pmax and PD were significantly higher in COVID-19 patients when compared to the control groups (Pmax ;106.3±10 ms vs. 98.8±10 ms, p<0.001, PD; 46±10 ms vs. 39±11 ms, p<0.001) (**Figure 2**). Pmin was similar between the groups (p=0.596).

Table 2. Electrocardiographic Characteristics of the study population

Variables	Control group (N=53)	COVID group (n=90)	value
Heart Rate (min)	76.7±9.3	77.3±8	0.657
P Max (ms)	98.8±10	106.3±10	<0.001
P Min (ms)	60.4±5.3	60.9±7.2	0.596
PD (ms)	39±11	46±10	<0.001

Min: Minute, ms=millisecond, Pmax=maximum P-wave duration, Pmin=minimum P-wave duration, PD=P-wave dispersion

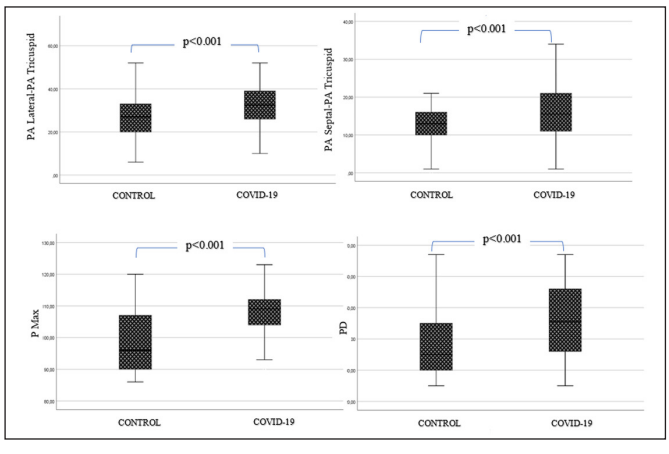

Figure 2. Change of PD, P max, PA Lateral -PA Tricuspid and PA Septal-PA Tricuspid between study groups

Echocardiographic and atrial electromechanical time parameters are shown in **Table 3**.

Table 3. Echocardiography Characteristics of the study population

Variables	Control group (N=53)	COVID group (n=90)	p value
LA Diameter, cm	3.37±0.28	3.43±0.29	0.230
LA area	21.8±2.1	22±2.2	0.729
LA volume, ml	36.4±3	37±3.1	0.230
LVED volume, ml	102.9±5.7	101.2±5.5	0.077
LVES volume, ml	34.4±4.5	35±5.4	0.519
LVEDD, cm	4.73±0.39	4.67±0.40	0.391
LVESD, cm	3.05±0.4	3.08±0.3	0.641
IVSD, cm	1.06±0.12	1.07±0.13	0.768
PWD, cm	1.03±0.9	1.04±0.1	0.598
LVEF, %	67.9±5.7	66.2±5.5	0.077
RA volume, ml	32.8±3.1	33±3.4	0.726
TAPSE, mm	23.4±2.1	23.5±2.2	0.729
PA Lateral, ms	61.4±9.3	64.6±12.3	0.110
PA Septum, ms	48.4±8.3	50.3±9.3	0.219
PA Tricuspid, ms	36.3±8.7	35.3±7.5	0.448
PA Lateral-PA Tricuspid (Interatrial delay)	26.6±10.3	32.3±11.5	<0.001
PA Septal-PA Tricuspid (Right intraatrial delay)	12.5±7.6	16.5±8.0	<0.001
PA Lateral-PA Septal (Left intraatrial delay)	13.2±9.1	14.4±9.3	0.448
E velocity	72±10	73±13	0.611
A velocity	56±16	60±16	0.249
DT,ms	182.6±37.1	183.8±33.1	0.851
Lateral (s') cm/s	11.5±3.3	11.5±2.7	0.997
Lateral (e') cm/s	13.8±3.3	13±2.7	0.109
Lateral (a') cm/s	9.8±2.3	10.2±2.3	0.410
Septal (s') cm/s	7.1±1.8	7.1±1.3	0.950
Septal (e') cm/s	7.9±3.4	8.2±2.2	0.546
Septal (a') cm/s	7.4±3.4	7.7±2.2	0.539
Tricuspid (s') cm/s	14.5±3.3	14±3.5	0.403
Tricuspid (e') cm/s	16.3±3.3	15.5±2.7	0.098
Tricuspid (a') cm/s	13.7±2	13.4±3.1	0.534

LA=Left atrium; LVEDD=LV end-diastolic dimension; LVESD=LV end-systolic dimension; IVSD=interventricular septum thickness; PWD=posterior wall thickness; LVEF=LV ejection fraction; RA=right atrium, TAPSE= tricuspid annular plane systolic excursion, DT=deceleration time. S': systolic myocardial flow; E': early myocardial diastolic flow; A': late myocardial diastolic flow. Interatrial delay: PA lateral – PA tricuspid. Right Intraatrial delay: PA septum – PA tricuspid. Left intraatrial delay: PA lateral – PA septum.

LV systolic and diastolic diameters, interventricular septum, LV posterior wall thickness, and LV ejection fraction were similar in all groups (p= 0.641, p=0.391, p=0.768, p=0.598, and p=0.077, respectively). No significant difference was observed between the groups between the left atrium diameters, and DT, one of the parameters showing left ventricular diastolic functions (p=0.230 vs. p=0.851, respectively). Moreover, other echocardiographic parameters were similar between groups (**Table 3**).

In tissue Doppler examination (TDI) and atrial electromechanical delay (AEMD) parameters (PA lateral, PA septum, and PA tricuspid) were similar between groups (PA lateral; 64.6±12.3 ms vs. 61.4±9.3 ms, p=0.110, PA septum; 50.3±9.3 ms vs. 48.4±8.3 ms, p=0.219, PA tricuspid; 35.3±7.5 vs. 36.3±8.7, p=0.448).

Interatrial EMD (PA Lateral–PA Tricuspid) and right intraatrial EMD (PA Septum–PA Tricuspid) were longer in the COVID-19 patients when compared to the control group (interatrial: 32.3±11.5 ms vs. 26.6±10.3 ms, p<0.001; right intraatrial: 16.5±8.0 ms vs 12.5±7.6 ms, p<0.001) (**Figure 2**). Left intraatrial EMD time was similar between groups (p=0.448). Correlation analysis revealed a significant and positive correlation between CRP with Pmax, PD, interatrial and right intraatrial EMD (r=0.608, p <0.001; r=0.708, p<0.001; r=0.692, p<0.001; r=0.697, p<0.001, respectively) (**Figure 3**). A similar relationship was also observed between NLR and Pmax, PD, and interatrial and intraatrial EMD (r=0.567, p<0.001; r=0.676, p<0.001; r=0.687, p<0.001; r=0.681, p<0.001, respectively).

In addition, a positive and significant relationship was found between the interatrial EMD with PD and Pmax (r=0.660, p<0.001 vs. r=0.623, p<0.001, respectively). A similar relationship was also observed between intraatrial EMD with PD and Pmax (r=0.706, p<0.001 vs. r=0.574, p<0.001, respectively) (**Figure 4**) .

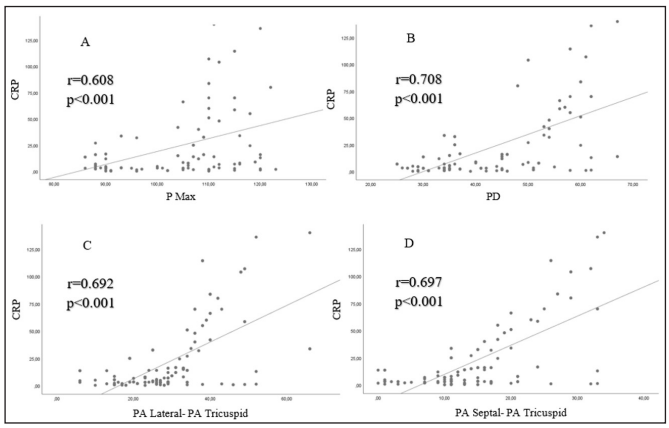

Figure 3. (A) Correlation between P max and CRP count. (B) Correlation between CRP and PD. (C) Correlation between CRP and PA Lateral- PA Tricuspid, (D) Correlation between CRP and PA Septal- PA Tricuspid

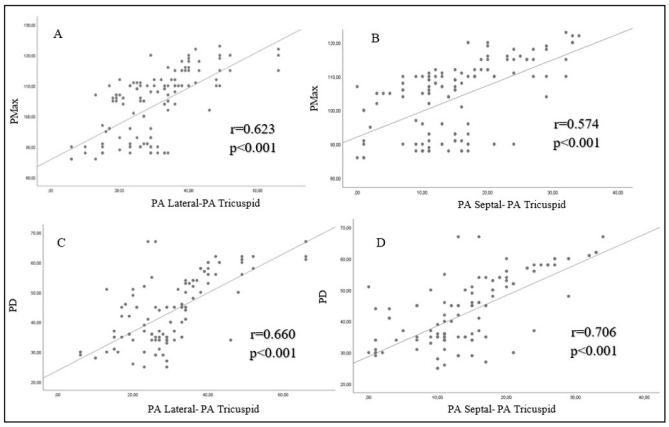

Figure 4. (A) Correlation between P max and PA lateral-PA Tricuspid (B) Correlation between P max and PA Septal- PA Tricuspid (C) Correlation between PD and PA Lateral- PA Tricuspid, (D) Correlation between PD and PA Septal- PA Tricuspid

In eight of the patients included in the study, the need for ICU developed during the follow-up. In six of these patients, non-invasive mechanical ventilation was required due to decreased oxygen saturation during follow-up. Two patients were also intubated because of ARDS and multiple organ failure. These two patients died during follow-up. However, none of these patients developed cardiac complications, including NOAF.

NOAF was observed in five COVID-19 patients with pneumonia during hospitalization. Three of these patients were male, and two were female, and their mean age was 60.4 (53, 58, 61, 64, 66 respectively). NOAF developed in these patients in the first three days of hospitalization. In these patients, initial ECG had present prolonged Pmax (128 ms, 126 ms, 120 ms, 119 ms, 115 ms respectively), PD (68 ms, 66 ms, 60 ms, 56 ms, 58 ms, respectively), interatrial EMD (43 ms, 39 ms, 40 ms, 36 ms, 34 ms, respectively) and intraatrial EMD (25 ms, 23 ms, 27 ms, 21 ms, 18 ms, respectively). All of these patients returned to sinus rhythm when discharged from the hospital.

DISCUSSION

In this study, the four crucial findings detected in COVID-19 patients can be listed as follows: (1) Pmax and PD on the 12-lead superficial ECG were significantly higher in COVID-19 patients. (2) Both interatrial and intraatrial EMD detected by TDI were longer in COVID-19 patients. (3) Pmax and PD times were significantly positively correlated with both interatrial and intraatrial EMD. (4) PD and Pmax durations and interatrial and intraatrial EMD were significantly positively correlated with C-Reactive Protein (CRP).

Even though COVID-19 is an infection that predominantly affects the lungs, cardiovascular involvement has also been reported extensively (1). Indeed, in Covid-19, after the respiratory system,

the most affected is the cardiovascular system. Many processes that affect the cardiovascular system directly and indirectly, work together. Direct myocardial cell injury, myocardial oxygen supply/demand mismatch, acute plaque rupture leading to the acute coronary syndrome as a part of systemic inflammation and catecholamine surge, increased thrombosis, and potential side effects of the current medications used for the treatment of COVID-19 have been considered to play a role in the presentation of cardiac manifestations (8, 18). For this reason, some authors accept the disease as "Acute Covid-19 Cardiovascular Syndrome" because of the frequent occurrence of acute myocarditis, acute coronary syndrome, and increased thromboembolic events in the course of the disease (19).

Atrial fibrillation is the most common arrhythmia in the population that causes increased cardiovascular mortality and morbidity (20). One of the most common rhythm disturbances encountered by clinicians, especially in patients with severe medical illnesses such as pneumonia, is AF. COVID-19 is a novel coronavirus infection, which predominantly affects the lungs, and pneumonia findings have become prominent and determinant in the disease's clinical course (21). The risk of NOAF in patients hospitalized for pneumonia has been investigated in several studies (22,23). A recent study performed by Pieralli et al. (22) showed that 10.3% of hospitalized patients for community-acquired pneumonia (CAP) experienced NOAF during hospitalization. Similarly, Cangemi et al. (23) found an increase in the incidence of NOAF within three days after hospitalization in patients hospitalized for community-acquired pneumonia. In our very recent study, we showed a significant increase in the incidence of NOAF in patients hospitalized for COVID-19 pneumonia (3). These findings suggest that patients hospitalized for pneumonia, regardless of the cause, may have a higher risk of developing new-onset AF. In particular, the development of AF has been shown to have a five-fold risk of stroke, a three-fold increased risk of heart failure, and a two-fold increased risk of death (24). Because of these undesirable effects, it is essential to determine in advance the risk of developing AF in patients. Therefore, some non-invasive methods have been described to predict the development and recurrence of AF.

Electromechanical delay (EMD), which can be easily measured non-invasively by TDI, is defined as the time interval between the onset of cardiac electrical activity and myocardial contraction. Prior studies have found that delays in interatrial and intraatrial conduction times, are significantly associated with new or recurrent AF (25,26). Also, it has been shown in previous studies that atrial EMD is also prolonged in several inflammatory clinical disorders such as psoriasis, and Inflammatory Bowel Disease (27, 28). Besides, the incidence of AF in these diseases has increased significantly compared to the normal population. In conclusion, atrial EMD is prolonged in paroxysmal AF and is considered a predictor of new-onset AF. P Max and PD are non-invasive markers showing the heterogeneous and unstable distribution of impulses from the sinus node in the atrial wall on standard ECG. Pmax and PD have been used as non-invasive markers to estimate AF's risk in various diseases, just like atrial EMD parameters (29-31). Especially, PD≥40 ms is associated with paroxysmal AF development (16).

In present study, we found that Pmax, PD, intraatrial and interatrial EMD, which are values that the noninvasive techniques TDI and ECG can easily measure, is significantly longer in patients with COVID-19. In other words, we have shown that the risk of developing AF increased in COVID-19 patients. Possible mechanisms between COVID-19 infection and increased risk of AF observed in this study can be listed as here.

Increased inflammation and serum inflammatory cytokines, have played an essential role in the initiation and persistence of AF independent of traditional risk factors, including HT and CAD (32-34). In particular, inflammatory mediators including CRP, interleukin-6, and tumor necrosis factor-alpha secreted during the inflammatory process have been demonstrated to trigger AF development in patients (35-37). Extensive data reveal that an inflammatory state and cytokine storm accompanies pneumonia in a subset of patients with COVID-19. In addition to the increased serum CRP levels, circulating TNF-alfa, IL-6, and IL-1β have been shown to increase in patients with COVID-19 infection (38). Serum CRP and NLR levels were high in our patient group, as in many inflammatory diseases. Moreover, we found that PD and Pmax durations and atrial EMD (interatrial and intraatrial) parameters were significantly positively correlated with CRP and NLR levels. These findings confirm previous studies' results, which underline the role of inflammation in AF' pathogenesis.

Apart from the increased inflammatory condition, increase in endogenous catecholamine release and hemodynamic breakdown might also form AF. In addition to those, widespread lung infiltration may cause ventilation / perfusion imbalance that precipitate hypoxemia, which could be another explanation for the development risk of NOAF in COVID-19 patients. Indeed, Radiological findings on CTI of the COVID-19 patients with pneumonia were diffuse infiltration in our study. As aresult, this study suggested that COVID-19 patients should be monitored for AF. The measurement of atrial EMD can be used to determine the high-risk population for AF development in COVID-19.

To the best of our knowledge, this study is the first in the literature to investigate intraatrial and interatrial EMD, Pmax, and PD in patients with COVID-19. We found that atrial conduction times were prolonged in COVID -19 patients. In light of the findings mentioned above, an increase in inflammatory load or inflammatory markers in COVID-19 patients seems to be a risk factor for AF occurrence. Indeed, recent research from Kelesoglu et al. (3) demonstrating that COVID-19 is independently associated with new-onset AF supports our findings. Moreover, extensive data have shown that COVID-19 patients have an increased risk of ischemic stroke. According to the findings presented here, the probability of NOAF should be kept in mind when COVID-19 patients complain of palpitations or suffer an ischemic stroke. Further research is needed to clarify the predictive role of atrial EMD, Pmax, and PD in evaluating AF's development in COVID-19 patients. Recent studies claim that the electromechanical delays measured on echocardiography differ from those measured in the electrophysiology study (39). Nevertheless, since echocardiographic electromechanical delay parameters represent the atrium's electromechanical integrity, we speculate that it can still be used non-invasively in determining the risk of AF.

CONCLUSION

COVID-19 disease has had an effect on cardiac functions by triggering arrhythmias and atrial fibrillation as the most important side effect. However, it is not clear in which patients it does this. In this study, we showed that this situation can be predicted in advance by evaluating the p wave, with the analyzes we performed on the p wave that best evaluates the atrial findings.

Limitations

This study's main limitations are the relatively small number of patients in the study group, to see if prolonged atrial EMD, Pmax, and PD develop AF in COVID-19 patients and the lack of follow-up in terms of possible future NOAF. Moreover, Because a follow-up study is required in these patients to show whether these changes are permanent or transient, we can never tell whether these parameters change over time. Unfortunately, we could not call these patients back for a follow-up, due to the COVID-19 pandemic. Therefore, Large-scale long-term follow-up is needed to evaluate the relationship between atrial EMD and AF occurrence accurately. Parameters with potential role in the pathophysiology, such as TNF-alfa, IL-6, and IL-1β levels were not measured, and these measurements might have been beneficial in finding the relationship between atrial EMD and COVID-19. Another limiting factor is the evaluation of CRP and NLR levels with only one measurement. We did not evaluate follow-up period. Also, since the echocardiographic examination was not performed again during the follow-up, we cannot speculate how the drugs used affect these parameters.

We looked at atrial EMD, a good marker for AF development, but the AF development has not been directly investigated. Although we found NOAF in five patients, lack of Holter monitoring or long-term ECG monitoring for all patients is also one of the study's main limitations and, silent AF may likely have been undetected.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was granted by Kayseri City Hospital Clinical Researches Ethics Committee (Date: 25.06.2020, Decision No: 134).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. J Infect 2020; 80 :388-93.
2. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res 2020; 116: 1666-87.
3. Keleşoglu S, Yılmaz Y, Özkan E, et al. New onset atrial fibrilation and risk faktors in COVID-19. J Electrocardiol 2021; 21; 65: 76-81.
4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64: e1-e76.
5. Miller JD, Aronis KN, Chrispin J, et al. Obesity, exercise, obstructive sleep apnea, and modifiable atherosclerotic cardiovascular disease risk factors in atrial fibrillation. J Am Coll Cardiol 2015; 66: 2899-906.
6. Boos CJ, Anderson RA, Lip GY. Is atrial fibrillation an inflammatory disorder? Eur Heart J 2006; 27: 136-49.
7. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. J Am Coll Cardiol 2007; 50: 2021-8.
8. Xiong T-Y, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. Eur Heart J 2020; 41:1798-800.

9. De Flora S, Balansky R, La Maestra S. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. FASEB J 2020; 34: 13185-93.
10. Keleşoglu S, Yılmaz Y, Özkan E, et al. Usefulness of C-reactive protein/albumin ratio as a predictor of new-onset atrial fibrillation in SARS-COV-2. Biomark Med 2021; 15: 1167-75.
11. Deniz A, Sahiner L, Aytemir K, et al. Tissue Doppler echocardiography can be a useful technique to evaluate atrial conduction time. Cardiol J 2012; 19: 487–93.
12. Daubert JC, Pavin D, Jauvert G, Mabo P. Intra and interatrial conduction delay: implications for cardiac pacing. Pacing Clin Electrophysiol 2004; 27: 507-25.
13. Tukek T, Akkaya V, Demirel S, et al. Effect of Valsalva maneuver on surface electrocardiographic P-wave dispersion in paroxysmal atrial fibrillation. Am J Cardiol 2000; 85: 896–99.
14. T. C. Ministry Of Health General Directorate Of Public Health, Covid-19 (Sars-Cov2 Infection) Directory, Coronavirus Scientific Advisory Board, Turkey 2020
15. Kawano S, Hiraoka M, Sawanobori T. Electrocardiographic features of p waves from patients with transient atrial fibrillation. Jpn Heart J 1988; 29: 57-67.
16. Dilaveris PE, Gialafos EJ, Sideris S, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J 1998; 135 :733–38.
17. Cheitlin MD, Armstrong WF, Aurigemma GP, et al: ACC/AHA/ASE 2003 guideline up- date for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Circulation 2003; 108:1146- 62.
18. Keleşoğlu Ş, Yılmaz Y. Assessment of Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios, in patients with COVID-19 infected with or without pneumonia. J Health Sci Med 2021; 4: 615-21.
19. Hendren NS, Drazner MH, Bozkurt B, Cooper LT. Description and proposed management of the acute COVID-19 cardiovascular syndrome. Circulation 2020; 141: 1903-14.
20. Brand FN, Abbott RD, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the Framingham Study. JAMA 1985; 254: 3449-53
21. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8: 420-2.
22. Pieralli F, Biondo B, Vannucchi V, et al. Performance of the CHA(2) DS(2)-VASc score in predicting new onset atrial fibrillation during hospitalization for community-acquired pneumonia. Eur J Intern Med 2019; 62: 24-8.
23. Cangemi R, Calvieri C, Taliani G, et al. SIXTUS study group. Left atrium dilatation and left ventricular hypertrophy predispose to atrial fibrillation in patients with community-acquired pneumonia. Am J Cardiol 2019; 124: 723-8.
24. Benjamin EJ, Wolf PA, D'Agostino RB, et al: Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998; 98: 946–52
25. Pytkowski M, Jankowska A, Maciag A, et al. Paroxysmal atrial fibrillation is associated with increased intra-atrial conduction delay. Europace 2008; 10: 1415–20.
26. Cui QQ, Zhang W, Wang H, et al. Assessment of atrial electromechanical coupling and influential factors in nonrheumatic paroxysmal atrial fibrillation. Clin Cardiol 2008; 31: 74-8.
27. Calapkorur B, Kelesoglu B, Sarli B, et al. Atrial electromechanical delay is impaired in patients with psoriasis. Med Princ Pract 2015; 24: 30–5.
28. Efe TH, Cimen T, Ertem AG, et al. Atrial Electromechanical Properties in Inflammatory Bowel Disease. Echocardiography 2016; 33: 1309-16
29. Yılmaz R, Demirbağ R. P-wave dispersion in patients with stable coronary artery disease and its relationship with severity of the disease. J Electrocardiol 2005 Jul; 38: 279-84.
30. Ozer N, Aytemir K, Ataler E, et al. P wave dispersion in hypertensive patients with paroxysmal AF. Pacing Clin Electrophysiol 2000; 23: 1859-62.
31. Aytemir K, Ozer N, Atalar E, et al. P wave dispersion on 12-lead electrocardiography in patients with paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 2000; 23:1109-12.
32. Boos CJ, Anderson RA, Lip GY. Is atrial fibrillation an inflammatory disorder? Eur Heart J 2006; 27: 136-49.
33. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. J Am Coll Cardiol 2012; 60: 2263-70.
34. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. J Am Coll Cardiol 2007; 50: 2021-8.
35. Marcus GM, Whooley MA, Glidden DV, Pawlikowska L, Zaroff JG, Olgin JE. Interleukin-6 and atrial fibrillation in patients with coronary artery disease: data from the Heart and Soul Study. Am Heart J 2008; 155: 303-9.
36. Amdur RL, Mukherjee M, Go A, et al. Interleukin-6 is a risk factor for atrial fibrillation in chronic kidney disease: findings from the CRIC study. PLoS One 2016; 11: e0148189.
37. Ren M, Li X, Hao L, Zhong J. Role of tumor necrosis factor alpha in the pathogenesis of atrial fibrillation: A novel potential therapeutic target? Ann Med 2015; 47: 316-24.
38. Henderson LA, Canna SW, Schulert GS, et al. On the Alert for Cytokine Storm: Immunopathology in COVID-19. Arthritis & rheumatology (Hoboken, NJ) 2020; 72: 1059-63.
39. Bozorgi A, Khoshnevis M, Hosseinsabet A. Agreement between electrophysiology study and tissue doppler imaging regarding the measurement of total atrial conduction time and left atrial conduction delay. Ultrasound Med Biol 2020; 46: 544-56.