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Hidden enemy of pulmonary arteries: COVID-19

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Abstract

It has been reported that COVID-19 may cause severe endothelial damage. Pulmonary Artery Stiffness (PAS) is a strong predictor of right ventricular function. PAS can reveal important information about the endothelial functions of the pulmonary bed. In this study, we aimed to elucidate the possible effect of COVID-19 on PAS. The study was performed by measuring PAS values with transthoracic echocardiography in 130 patients, 60 of whom had COVID-19 and 70 were controls. COVID-19 patients with positive polymerase chain reaction (PCR) test results were included in the study 3-6 months after their positivity. When the Maximal frequency shift (MFS) (Hz) results were examined, no significant difference was observed between the patient and control groups (2764±279.24 and 2664.8±673.91 p=0.340, respectively). There was a significant difference between the patient and control groups in favor of the patient group in pulmonary acceleration time (PAT) (msec) results (93.18±14.99 and 126.1±17.58, respectively, p<0.001). There was a significant difference between the patient and control groups in favor of the patient group in PAS (Hz/msec) results (30.28±5.07 and 21.57±7.04, respectively, p<0.001). It is possible that COVID-19 may have adverse effects on the pulmonary artery wall and bed. As a result of endothelial damage due to COVID-19, an increase in PAS values can be observed.

Keywords: COVID-19, pulmonary arterial stiffness, pulmonary hypertension

Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic accounted by violent acute respiratory syndrome coronavirus 2 (SARS-CoV-2), characterized by marked pulmonary damage [1]. The clinical presentation of COVID-19 is broad and can be order from asymptomatic manifestations to severe pneumonia needing hospitalization, oxygen and intubation/mechanical ventilation.

Pulmonary fibrosis is a condition characterized by irregular remodeling of the lung parenchyma, and post-mortem studies on patients with COVID-19 have shown diffuse parenchymal changes with the development of pulmonary fibrosis [2,3]. Parenchymal changes (interstitial fibrosis, diffuse alveolar damage, honeycomb appearance, etc.) were also observed more frequently in COVID-19 patients who were followed up for a long time compared to the healthy population [4,5].

Pulmonary Artery Stiffness (PAS) is an important parameter for evaluating the condition and functions of the pulmonary bed by echocardiographic method and its height is a negative indicator [6]. PAS can be an important marker for right ventricular functions, pulmonary hypertension and pulmonary fibrosis [7]. In a study confirmed with right heart catheterization (RHC), it was predicted that it could give an idea about the state of the pulmonary bed as an effective parameter [8]. The need for invasive methods to detect early remodeling of the pulmonary arteries limits serial measurements. Recently, non-invasive imaging methods have been demonstrated to investigate pulmonary artery stiffness and right ventricular function by focusing on fluid hemodynamic indices of the proximal pulmonary bed [9]. Endothelial damage in COVID-19 patients may result from the direct effect of Sars-Cov 2 virus or indirectly from cytokine and complement activation [10]. It has been shown that endothelial dysfunction may lead to arterial systemic stiffness [11].

Our aim in the study is to investigate the relationship between COVID-19 infection and PAS.

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Material and Methods

The study was conducted in Çanakkale Onsekiz Mart University cardiology outpatient clinic between 01.07.2020 and 01.04.2021. A total of 130 individuals 60 of whom had disease and 70 were control group have been enrolled within the scope of this research (Table 1). Patient and control groups were selected according to PCR results. In the patient group, those with COVID-19 pneumonia were included in the study. The control group consisted of those who had been examined with suspicion of COVID-19 in the last 1-3 months, had a negative PCR result, had no previous history of COVID-19, and had a cardiology examination. 60 of the patients were vaccinated. Approval of this study has been granted from Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (Date: 3 November 2022, Decision No: 2022/13-3). The study was conducted in accordance with the Declaration of Helsinki, and both verbal and written informed consent was obtained from the participants.

Table 1. Demographic, biochemical and echocardiographic characteristics of the patient and control groups

	Patient (60)	Control (70)	P values
Age (year)	52.17±15.69	46.06±13.99	**0.044***
Smoking	11 (18.3%)	14 (20%)	0.801
Alcohol	3 (5%)	4 (5.7%)	0.650
Hypertension	14 (23.3%)	11 (15.7%)	0.224
Diabetes Mellitus	6 (10%)	8 (11.4%)	0.769
CAD	10 (18%)	11(15.7%)	0.723
Urea (mg/dl)	31.047±10.43	30.988±9.29	0.978
Creatinine (mg/dl)	0.85±0.25	0.77±0.17	0.099
Glucose(mg/dl)	97.56±25.01	93.4±21.58	0.521
ALT (U/L)	19.63±8.61	20.81±9.78	0.524
AST (U/L)	22.73±6.82	20.3±6.86	0.525
Hemoglobin (g/dl)	13.9±1.45	14±1.45	0.684
Leukocyte	7.87±1.94	8±2.05	0.742
TSH	3.03±2.75	2.29±1.79	0.155
Sodium (mEq/L)	139.4±2.3	139.4±1.8	0.891
Potassium (mEq/L)	4.38±0.31	4.5±0.41	0.714
LVEF%	59.49±3.92%	60.84±4.67%	0.124
TAPSE	24.02±3.04	23.06±3.22	0.162
PASP (mmHg)	23.07±4.5	21.29±5.5	0.175
MFS (khz)	2.76±0.279	2.66±0.673	0.339
PAT (msec)	93.18±14.99	126.1±17.58	**0.000***
PAS (hz/msec)	30.28±5.07	21.57±7.04	**0.000***
EDD	46.76±3.24	46.78±3.39	0.980
ESD	30.3±4.22	30.53±3.06	0.800
IVS	10.58±1.02	10.45±1.45	0.688
PW	10.32±1.1	9.81±1.16	0.079
mit E	0.86±0.26	0.77±0.24	0.243
E'	0.07±0.009	0.07±0.014	0.464
A	0.66±0.21	0.4±0.15	0.683

PAS was measured with doppler echocardiography. The control group was formed from a similar age group and a similar sample size. The control group consisted of patients with no history of COVID-19 and no contact with positive subjects. COVID-19 patients with positive real time polymerase chain reaction (RT-PCR) test results were included in the study 3–6 months after their positivity. Combined throat/nose swabs for polymerase chain reaction tests were taken in accordance with the guidelines of the Ministry of Health of the Republic of Türkiye and the World Health Organization.

Laboratory results were obtained from the hospital automation system. Biochemical and demographic parameters of the patients were noted.

Patients with left ventricular (LV) systolic dysfunction, obstructive sleep apnea syndrome, drug or substance use, chronic kidney and liver failure, atrial fibrillation, congenital heart disease, history of prosthetic valve, ascending aorta >40 mm, bicuspid aortic valve, poor echocardiography window, cerebrovascular disease, portal hypertension, <18 years of age, connective tissue

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disease, advanced valve insufficiency or stenosis, patients with myocardial infarction in the last 6 months, patients with right heart failure, diagnosis of pulmonary hypertension, history of pulmonary embolism were excluded from the study.

Doppler echocardiography

Echocardiography was performed on patients 3-6 months after PCR positivity. In this time period selection, we chose previously published literature data as referances [12-14]. Two-dimensional transthoracic doppler echocardiography (Vivid 7, GE Vingmed, 2.5 MHz, USA) was used for measurements. Blood pressure (BP) levels were measured just before the start of echocardiographic imaging. Measurements were made in the echocardiography laboratory in a quiet environment, after resting for 15 minutes in a sitting position, on the right and left arms. Echocardiographic examinations were performed following BP measurements. Echocardiographic measurements were taken while the patients were lying in the left lateral position. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's formula. Left and right heart chamber measurements were calculated according to the recommendations of the American and European Heart Association [15].

PAS was obtained by imaging the pulmonary artery from the parasternal axis while the patients were in the left lateral position, and by placing a pulse wave (PW) Doppler 1 cm below the pulmonary valve, maximum frequency shift (MFS) and pulmonary flow acceleration time (PAT) were measured, and then the MFS was calculated by dividing it to PAT. Pulmonary flow peak velocity was evaluated as MFS, and the time from the onset of pulmonary flow to the peak duration was evaluated as PAT. To obtain the most accurate measurement, the procedure was repeated in at least three shots [6] (Figures 1 and 2).

$$PAS = \frac{Maximum Frequency Shift (MFS) Hz}{Pulmonary Flow Acceleration Time (PAT) msec}$$

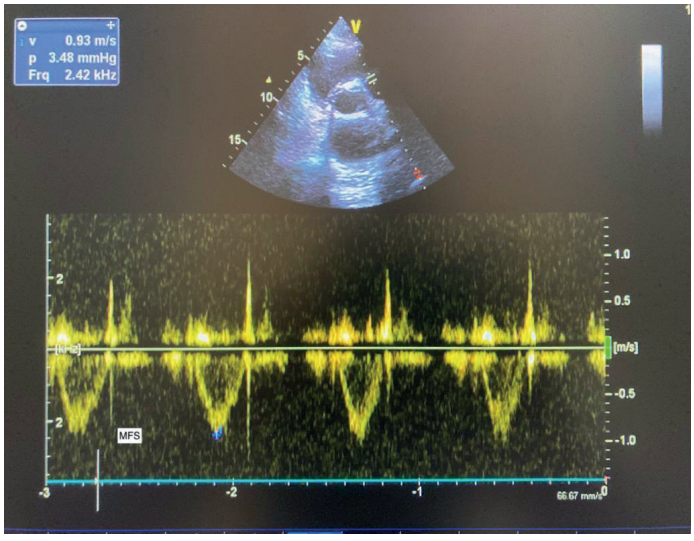

Figure 1. Echocardiographic image of MFS measurements

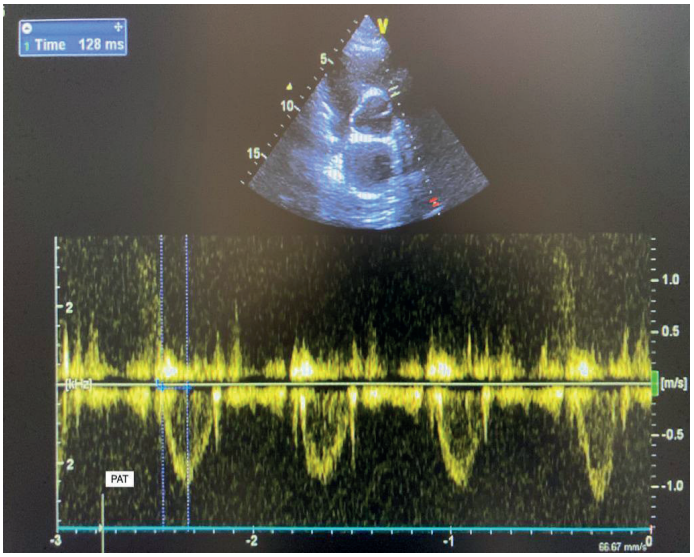

Figure 2. Echocardiographic image of PAT measurements

Statistical analysis

SPSS 19.0 (SPSS Inc, Chicago, IL, USA) program was used for statistical analysis and normal distributions of variables were analyzed using Kolmogorov-Smirnov test. While continuous variables are expressed as mean±standard deviation, categorical variables were expressed as percentages and numbers. Independent samples t-test and Mann-Whitney U-test were used to compare parameters with and without normal distribution, respectively. A p value of <0.05 was accepted for statistical significance.

Results

The data of our study were obtained by prospective analysis using retrospective data. A total of 130 individuals have been enrolled within the scope of this research. Sixty cases had a history of COVID-19 RT–PCR positivity (30 males, 30 females). The control group consisted of 70 subjects (32 females, 38 males). The mean age of the patient group was 52.17±15.69 years, and the mean age of the control group was 46.06±13.99 years.

Tricuspid annular plane systolic excursion (TAPSE), pulmonary artery pressure (sPAP), LVEF and heart chamber measurements did not differ significantly between the two groups. When the MFS (Hz) results were examined, no significant difference was observed between the patient and control groups (2764±279.24 and 2664.8±673.91 p=0.340, respectively) (Graphic 1).

PAT (msec) results showed a significant difference between the patient and control groups in favor of the patient group (93.18±14.99 and 126.1±17.58 p<0.001, respectively) (Graphic 2). In PAS (Hz/msec) results, there was a significant difference between the patient and control groups in favor of the patient group (30.28±5.07 and 21.57±7.04 p<0.001, respectively) (Graphic 3).

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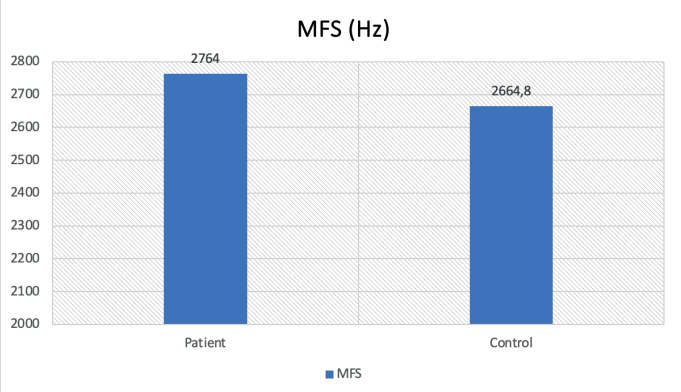
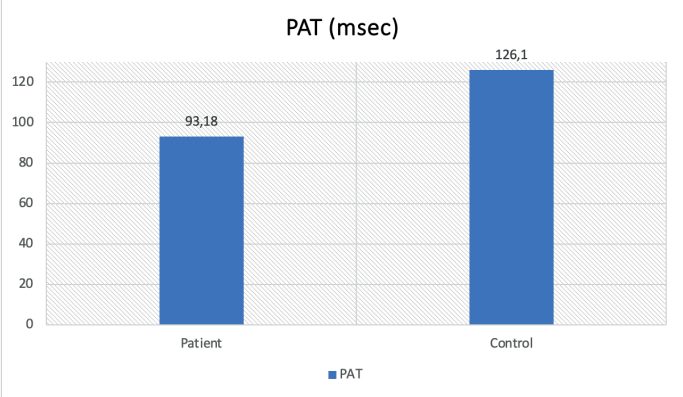
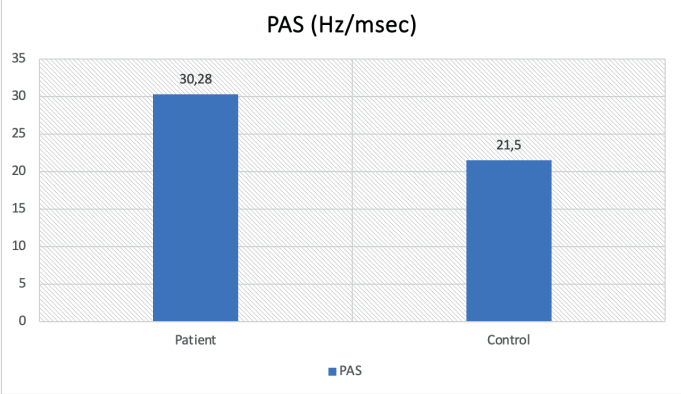


Graphic 1. MFS values of groups



Graphic 2. PAT values of the groups



Graphic 3. PAS values of the groups

Discussion

In this study, we purposed to investigate the intercourse between COVID-19 and PAS by interpreting the difference between the PAS values of the patients who had COVID-19 and the control group. As a result of this study, it was observed that there was a significant difference in PAS values between COVID-19 patients and the control group.

COVID-19 is a disease with a wide spectrum that primarily affects lung functions and progresses to acute respiratory distress syndrome. However, it has been shown that it affects not only lung functions but also many organs due to endothelial dysfunction and causes organ damage [16,17]. The evolving clinical, laboratory, and post-mortem findings of COVID-19 suggest a crucial role for altered endothelial function in its pathophysiology that contributes to multi-organ dysfunction. Studies have revealed that it causes varying degrees of diffuse alveolar damage in the lungs, as well as venous and arterial inflammation of different organs [18-20]. Endothelial damage and subsequent atherosclerotic processes cause arterial stiffness by causing thickening and hardening of the tunica media layer as the prevalence and severity of atherosclerosis increases [21]. Pulmonary vascular endothelium is affected in the course of COVID-19. The increased accumulation of proinflammatory molecules and activated immune cells results in a cytokine storm, which makes the pulmonary endothelium leaky, hypoxic, and dysfunctional and causes endothelial inflammation [22]. The mechanical properties of pulmonary arteries, particularly stiffness, are linked to the composition and structure of extracellular matrix (ECM) proteins. ECM proteins that are dominant in the pulmonary arteries, such as elastin and collagen, have a strong relationship with PAS [23].

Remodeling of the distal pulmonary arteries in pulmonary hypertension (PH) is characterized by intimal thickening, fibrosis, and medial hypertrophy [24]. PAS is an echocardiographic parameter that evaluates the status and functions of the pulmonary bed. In studies involving conditions that may play a role in the etiology of PH such as obstructive sleep apnea syndrome, cirrhosis, HIV virus carriers, congenital heart disease (CHD), chronic obstructive pulmonary disease (COPD), and systemic lupus erythematosus (SLE), an increase in PAS value was found to be associated with PH [25,26]. Gorgulu et al. In a study by 33 patients with CHD, RHC and doppler echocardiography results were compared and pulmonary vascular resistance was found to be correlated with PAS. At the end of the study, it was predicted that PAS could give an idea about the functions of the pulmonary bed [8]. In the study of Coldea et al., magnetic resonance imaging (MRI) was used to evaluate PAS and right ventricular functions in COPD patients with a secondary cause of PH, and a significant relationship was found between PAS and PH in the study [27]. PAS can be used non-invasively to show the remodeling and pulmonary vascular dysfunction that develops with the decrease in the effect of elastin and the predominance of collagen. It can be measured with MRI and doppler echocardiography as a diagnostic method, especially in patients with PH in the early period [28].

The development of PH and right ventricular dysfunction after COVID-19 has been shown in some studies [29,30]. This endothelial dysfunction and arterial stiffness seen in patients with COVID-19 may also negatively affect the functions of the pulmonary bed, resulting in PH and right ventricular dysfunction. Our study aimed to evaluate echocardiographically the pulmonary artery stiffening caused by COVID-19. Pulmonary artery evaluation should be performed, especially in patients with COVID-19 pneumonia. The important advantage is that the

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procedure is non-invasive and practical. It is possible to obtain findings that may be clues for possible diseases such as PHT.

In our study, it was observed that there was a significant difference in PAS values in the patient group. This suggested that the negative effect of COVID-19 on pulmonary endothelial damage and pulmonary vascular bed can be demonstrated indirectly with a non-invasive method. COVID-19, which has been proven to cause both pulmonary endothelial damage and fibrosis, may eventually increase the risk of PAS. In order to evaluate the condition of the pulmonary bed, measurement with echocardiographic seems more appropriate in terms of use because it is both non-invasive and inexpensive. In long-term studies, evaluation of the pulmonary bed may have clearer results in surviving patients with the contribution of interventional methods. PAS values measured by doppler echocardiography can be used as a precursor as in other diseases affecting right ventricular functions. In our study, it was determined that the pulmonary artery was affected. Treatment strategy and prophylactic medical treatment studies can be planned in prospective long follow-up studies. Our study will shed light as a guide for these new studies.

One of the limitations of this study was the lack of a follow-up study. The second is; The reason for our study was that RHC was not applied to the patients. Conducting long-term follow-up studies using the PAS index can increase our knowledge of long-term complications in COVID-19 survivors.

Conclusion

Regarding the results of this research one can say that COVID-19 might have adverse effects on the pulmonary artery wall and bed. As a result of endothelial damage due to COVID-19, an increase in PAS values can be observed.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study has been approved at 03/11/2022 by the Ethics Committee of Clinical Research of Çanakkale Onsekiz Mart University with protocol number 2022/13-3.

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