Myocardial performance index increases at long-term follow-up in patients with mild to moderate COVID-19

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Abstract

Background: The long-term cardiovascular effects of Coronavirus disease-2019 (COVID-19) are not yet well known. Myocardial performance index (MPI) is a non-invasive, inexpensive and reproducible echocardiographic parameter that reflects systolic and diastolic cardiac functions. The aim of the study was to compare MPI with a healthy control group in patients with mild or moderate COVID-19 infection who subsequently had unexplained cardiac symptoms.

Methods: The study included 200 patients aged 18–70 years who were diagnosed with COVID-19 infection at least 2 months ago and defined cardiac symptoms in their follow-up. Patients with mild or moderate symptoms, no history of hospitalization, and no other pathology that could explain cardiac symptoms were included in the study. As the control group, 182 healthy volunteers without COVID-19 were evaluated. Echocardiographic examination was performed on the entire study group. Isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT), and ejection time (ET) were measured by tissue Doppler imaging. MPI was calculated with the IVCT + IVRT/ET formula.

Results: The mean age of the study group was 44.24 ± 13.49 years. In the patient group the MPI was significantly higher (.50 ± .11 vs .46 ± .07, p < .001), IVRT was longer (69.67 ± 15.43 vs 65.94 ± 12.03 ms, p = .008), and ET was shorter (271.09 ± 36.61 vs 271.09 ± 36.61 ms, p = .028). IVCT was similar between groups (63.87 ± 13.66 vs 63.21 ± 10.77 ms, p = .66). Mitral E and mitral A wave, E', A', and E/A were similar in both groups.

Conclusions: Our study showed that conventional diastolic function parameters were not affected in patients who survived COVID-19 with mild symptoms but had symptoms in the long term. However, MPI measurements showed left ventricular dysfunction. To our knowledge, this is the first echocardiographic follow-up study to evaluate left ventricular systolic and diastolic functions with MPI in COVID-19 patients. We think that when cardiac involvement assessment is required in patients who have survived COVID-19, MPI should be measured alongside other echocardiographic measurements.
1 | INTRODUCTION

COVID-19 pneumonia, reported in the Wuhan region of China in the last months of 2019, spread rapidly and turned into a pandemic that caused the death of 5.4 million people worldwide.1,2 The most common symptoms of the disease are respiratory system-related symptoms such as shortness of breath and cough.3 Therefore, most of the previous studies focused on damage to the respiratory system.5–6 However, it was soon seen that COVID-19 infection is a disease that can show widespread systematic involvement and is accompanied by multiorgan pathologies.7,8 Another important organ involvement is heart involvement like myocarditis, acute coronary syndrome, cardiomyopathy, and arrhythmias.9–11 The main parameters used to determine heart damage caused by COVID-19 in clinical practice are electrocardiography (ECG), increased serum ischemia biomarkers, and ventricular dysfunction in transthoracic echocardiography.12–14

Myocardial performance index (MPI) is a useful predictor of global myocardial performance, which provides the opportunity to evaluate both systolic and diastolic functions of the heart.15 MPI, which was first defined by Tei et al., is also known as the Tei index.16 This index is obtained by the echocardiographic tissue Doppler method. It is calculated by dividing the sum of isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT) by ejection time (ET) (MPI = IVCT + IVRT/ET). The fact that it is not affected by the geometric structure of the ventricle and is relatively unaffected by the heart rate is an important advantage compared to other classical echocardiographic parameters.17

In the literature, there are many studies with conventional echocardiographic parameters in the investigation of cardiac dysfunction in COVID-19 patients. In most of these studies, patients in the active disease who had an asymptomatic course and had a general condition disorder, and needed intensive care were investigated.18 In addition, the pathophysiological process is not yet clear in patient groups whose cardiac symptoms persist in the long term after infection and no pathology is detected in classical cardiac diagnostic methods.

Our current study aim is to compare MPI with a healthy control group in patients with mild or moderate COVID-19 infection who have unexplained cardiac symptoms in the later period.

2 | MATERIALS AND METHODS

2.1 | Study population

The study was designed as a single-center cross-sectional and prospective. We enrolled patients aged 18–70 years who applied to the cardiology outpatient clinic between March 2021 and November 2021 and had COVID-19 at least 2 months ago. Patients with mild or moderate symptoms of the disease, no history of hospitalization, and no other pathology that could explain cardiac symptoms were included in the study. Patients presenting with complaints such as exertional dyspnea, chest pain, and palpitation were evaluated as having cardiac symptoms. According to the World Health Organization interim guidance, the diagnosis of COVID-19 should be based on real-time reverse transcription-polymerase chain reaction (RT-PCR). The disease history of the patients who said they had COVID-19 infection was scanned in the hospital system, and those with positive RT-PCR tests were accepted as a previous COVID-19 infection. The patient group that made up the study was 200 people. The control group consisted of 182 age- and sex-matched individuals who did not have COVID-19.

A complete physical examination was performed by taking the medical history of all individuals in the study group. Clinical, demographic characteristics, and drug use histories were questioned and recorded. Surface ECGs were taken and laboratory analyzes were performed. All participants were informed about the study and their written consent was obtained. The approval of the Turkish Ministry of Health was obtained for the study and the approval of the local ethics committee was obtained.

2.2 | Exclusion criteria

- Those with a history of hospitalization or intensive care series due to COVID-19.
- Those with similar cardiac symptoms before the infection.
- History of the acute coronary syndrome after COVID-19 infection.
- Those with pulmonary sequelae due to COVID-19 infection on computerized tomography (CT).
- Those with inadequate respiratory function tests.
- Heart failure with reduced ejection fraction (LVEF \(\leq 40\%\)), and heart failure with mid-range ejection fraction (LVEF between 41% and 49%)
- Those who have rapid weight gain after COVID-19 (as it can cause exertional dyspnea).
- History of previous pulmonary embolism.
- Active infection.
- Pregnancy.
- Presence of pathological Q wave or left bundle branch block on ECG.
- Moderate and severe heart valve disease.
- Severe anemia (Hg < 11 gr/dl).
- Endocrine disorders (thyroid dysfunction, diabetes mellitus type I and type II).
- Pulmonary hypertension (SPAB > 20 mm-Hg).
- Poor echogenicity and poor image quality.
2.3 | Echocardiographic evaluation

Philips brand EPIQ seven device (Philips, Amsterdam, Netherlands) was used for transthoracic echocardiographic evaluation. ECG electrodes were connected to evaluate cardiac cycles before echocardiographic evaluation. Measurements were made in the left lateral decubitus position as recommended by the American Society of Echocardiography. All measurements were recorded by a different cardiologist blinded to the patient data, averaging three to five cardiac cycles. Aortic diameter left atrial diameter, LV systolic and diastolic diameters, right ventricular diameter, LV wall thickness was measured in parasternal imaging. Modified Simpson and Teichholz methods were used to calculate LVEF. The presence of pericardial fluid and valve dysfunction was also checked in the measurements. Tricuspid annular plane systolic excursion (TAPSE) was recorded in M-mode at the junction between the right ventricular lateral wall and the tricuspid annulus in the apical four-chamber view.

LV tissue Doppler imaging was performed from the apical four-chamber view. Myocardial velocity profiles of the lateral mitral annulus were obtained by placing the sample volume at the junction of the mitral valve annulus and the lateral myocardial wall. Early diastolic mitral flow (E), late diastolic mitral flow (A) waves were measured by pulse wave (PW) Doppler from the apical four-chamber windows. E/A ratios of the patients were calculated using these values. Mitral annular velocities were obtained by tissue Doppler imaging (TDI) using pulsed-wave mode. Early diastolic mitral annular (E'), late diastolic (A'), systolic peak velocities (S) were measured at the level of the annulus of the lateral margins of the left ventricle. Mitral annular IVRT, IVCT, ET was measured. MPI was calculated by dividing the sum of IVCT and IVRT by ET (Figure 1).

2.4 | Statistics

The statistical analyses were given as mean ± standard deviation (SD). Unpaired T-test (one-sided p-value) was utilized to check the cardiac echocardiographic parameters of the COVID-19 patient (1) group against the healthy (2) group. The Kolmogorov–Smirnov test was used to analyze the normality of the data. All statistical tests were conducted using the Statistical Package for the Social Sciences 21.0 for Windows (SPSS Inc., Chicago, IL, USA). p < .05 was accepted as statistical significance.

3 | RESULTS

The mean age in the study group was 44.24 ± 13.49 years. There was no statistically significant age difference between the groups. In conventional echocardiographic measurements, aortic diameter, LVDD, RV diameter, and wall thicknesses were similar between groups. Mitral E wave and mitral A wave indicators of diastolic function did not differ between the groups. There was no significant difference in mitral E' and A' and S waves in both groups. E/A and E'/A' ratios were similar between groups.

While the measurements obtained in tissue Doppler were similar between the IVCT groups, it was statistically significantly prolonged in the IVRT patient group (69.67 ± 15.43 vs. 65.94 ± 12.03, p = .008). ET was significantly shorter in the patient group compared to the healthy control group (271.09 ± 36.61 vs. 278.35 ± 27.55, respectively, p = .028). In the evaluation of right ventricular functions, while the RVE patient group was significantly lower (8.72 ± 3.16 vs 10.2 ± 8.82, p = .033), there was a similarity between the RVA groups.
The most important new finding of this study is the determination of statistically significantly increased MPI in patients with persistent cardiac symptoms after COVID-19 infection but without any other explainable pathology compared to healthy control subjects. Again, we determined that IVRT, which is used to calculate MPI, is high in people who have had COVID-19. These results provide important evidence that may explain the cause of long-term symptoms in individuals who have had COVID-19. This is also the first study in the literature to report an increase in MPI in those with COVID-19.

The number of admissions to hospitals with cardiac symptoms after COVID-19 infection has been increasing recently. Despite the absence of any underlying pathology, the persistence of symptoms made it necessary to conduct this study. The findings of our study provide fundamental insights into how COVID-19 can cause subclinical myocardial damage in later stages, even in such a low-risk, asymptomatic, and outpatient population. This demonstrates the importance of long-term clinical follow-up of these patients in terms of cardiology.

|                         | Patients group (n = 200) | Healthy group (n = 182) | p-value |
|-------------------------|------------------------|------------------------|---------|
| Aortic diameter (mm)    | 33.49 ± 4.21           | 33.59 ± 3.89           | .804    |
| LVEDD (mm)              | 44.43 ± 5.13           | 44.53 ± 5.05           | .848    |
| Interventricular septum (mm) | 9.49 ± 1.53       | 9.61 ± 1.67           | .465    |
| Posterior wall (mm)     | 9.44 ± 1.49            | 9.34 ± 1.46            | .713    |
| RV (mm)                 | 26.9 ± 13.6            | 26 ± 5.6               | .446    |
| Mitral E wave (cm/s)    | 66.94 ± 19.05          | 66.19 ± 16.1           | .682    |
| Mitral A wave (cm/s)    | 61.47 ± 15.92          | 59.09 ± 15.11          | .137    |
| E (cm/s)                | 11.76 ± 3.72           | 11.42 ± 3.27           | .343    |
| A' (cm/s)               | 10.01 ± 3.17           | 9.60 ± 2.73            | .186    |
| E/A                     | 1.17 ± .5              | 1.21 ± .47             | .458    |
| E'/A'                   | 1.32 ± .65             | 1.31 ± .58             | .875    |
| S                       | 9.79 ± 2.46            | 9.69 ± 2.63            | .691    |
| IVCT (msn)              | 63.87 ± 13.66          | 63.21 ± 10.77          | .66     |
| IVRT (msn)              | 69.67 ± 15.43          | 65.94 ± 12.03          | .0001***|
| ET (msn)                | 271.09 ± 36.61         | 278.35 ± 27.55         | .028*   |
| MPI                     | .50 ± .11              | .46 ± .07              | .0001***|
| RV, E wave (cm/s)       | 8.72 ± 3.16            | 10.2 ± 8.82            | .033*   |
| RV, A wave (cm/s)       | 8.97 ± 3.05            | 8.67 ± 3.06            | .332    |
| RV, S wave (cm/s)       | 8.09 ± 2.74            | 7.40 ± 2.25            | .008****|
| TAPSE (cm)              | 2.09 ± .31             | 2.15 ± .31             | .043**  |

Abbreviations: LVEDD, left ventricular end diastolic diameter; RV, right ventricle; IVCT, isovolumetric contraction time; IVRT, isovolumetric relaxation time; ET, ejection time; MPI, myocardial performance index; TAPSE, Tricuspid annular plane systolic excursion; ns, non-significant. The degree of significance was denoted as: *p < .05, **p < .01, ***p < .001, and ****p < .0001.
Evidence of cardiac damage in COVID-19 patients has been reported in several previous studies.\textsuperscript{19–21} Myocardial inflammation has been reported in 60% of patients with recent (<3 months) COVID-19 infection, regardless of pre-existing conditions.\textsuperscript{22} Myocardial inflammation triggers a progressive fibrotic remodeling of the heart, which will lead to hardening of the cardiac tissue and altered cardiac relaxation. As a result, systolic and diastolic functions may be adversely affected. Studies showing that biventricular diastolic functions are adversely affected in COVID-19 patients are included in the literature.\textsuperscript{23–25}

In a recent study, cardiac performance was followed for 6 months in hospitalized patients with COVID-19, and evidence of myocardial injury, and diastolic dysfunction was reported to be common. However, they reported that diastolic dysfunction was not affected in the 6-month follow-up of COVID-19 patients without cardiac involvement.\textsuperscript{26} The difference in our study was that our patient group was not followed up in the hospital and did not have severe symptoms. Another difference is that we evaluated TDI and IVCT, IVRT, and ET, apart from echocardiographic parameters showing conventional diastolic functions. Again, we calculated MPI using these parameters. Similarly, parameters showing conventional diastolic functions were not affected in our study. However, MPI showing both systolic and diastolic functions of the heart was significantly greater in the group with the disease.\textsuperscript{23–25}

MPI is not significantly affected by preload, afterload, sample volume location, age, or rhythm.\textsuperscript{17,27} Therefore, it is a reliable index.

In a single-center retrospective study, Huang et al. surveyed 26 patients who had recovered from COVID-19. Study populations consisted of patients with no evidence of cardiac involvement who described chest discomfort or palpitations during their initial treatment and other nonspecific cardiac symptoms one to three months after discharge (mean 47 days). The authors reported 54% of participants with evidence of myocardial edema using T2-weighted magnetic resonance imaging (MRI).\textsuperscript{28} Puntmann et al. found that 78% of the patients had cardiac involvement and 60% of the patients had ongoing myocardial inflammation on MRI. The patients in the study consisted of hospitalized, outpatient, and cardiovascular risk factors, and a few patients had new or persistent symptoms.\textsuperscript{22}

Baycan et al. showed that left ventricular global longitudinal strain and right ventricular longitudinal strain were significantly reduced in COVID-19 patients compared to the control group, using the speckle tracking echocardiography method.\textsuperscript{29} In this method, important information about the systolic and diastolic functions of the heart is obtained. However, it is not a method that can be performed in every cardiology clinic and its application requires experience.

Another important finding in our study was that TAPSE, which is an indicator of right ventricular functions, was found to be significantly lower in the group who had the disease. This was consistent with other studies in the literature.\textsuperscript{20} Unlike these studies, the patients in our study were not in the active infection period. TAPSE is a reliable, easily applicable, and reproducible method for determining right ventricular functions.\textsuperscript{31}

**5 | CONCLUSION**

As a result, we determined that MPI, which allows the evaluation of both systolic and diastolic functions of the heart, is prolonged in patients who have had the disease but whose cardiac symptoms have persisted for a long time. MPI can be easily calculated by echocardiography and can provide information in patients with COVID-19 infection but with unexplained symptoms, which may help guide the management of this patient group.

**6 | LIMITATIONS**

First, data were obtained from a single center. Second, while investigating the presence of cardiac involvement in patients, coronary angiography was not performed in all patients. In patients with suspected coronary ischemia, it was investigated whether there was ischemia by exercise test or myocardial perfusion scintigraphy. As is known, these tests are not standard diagnostic methods like coronary angiography in the diagnosis of coronary artery disease.

**CONFLICT OF INTEREST**

There is no conflict of interest to be declared.

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No financial support was received from any person or institution in the study.

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