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Clinical Investigation

Effects of COVID-19 on the Autonomic Cardiovascular System: Heart Rate Variability and Turbulence in Recovered Patients

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Abstract

Background: COVID-19 may be a risk factor for developing cardiovascular autonomic dysfunction. Data are limited, however, on the association between heart rate variability, heart rate turbulence, and COVID-19. The aims of this study were to evaluate the effect of COVID-19 on the cardiovascular autonomic system in patients with persistent symptoms after recovering from COVID-19 and to determine whether these patients showed changes in ambulatory electrocardiography monitoring.

Methods: Fifty-one adults who had confirmed SARS-CoV-2 infection and presented with persistent symptoms to the cardiology outpatient clinic after clinical recovery between April and June 2021 were included. Patients were prospectively followed for 6 months. The patients were evaluated at the time of first application to the cardiology outpatient clinic and at 6 months after presentation. Ambulatory electrocardiography monitoring and echocardiographic findings were compared with a control group of 95 patients.

Results: Patients in the post–COVID-19 group had significantly higher mean (SD) turbulence onset (0.39% [1.82%] vs –1.37% [2.93%]; $P < .001$) and lower heart rate variability than those in the control group at both initial and 6-month evaluations. The post–COVID-19 group had no significant differences in echocardiographic findings compared with the control group at 6 months, except for right ventricle late diastolic mitral annular velocity ($P = .034$). Furthermore, turbulence onset was significantly correlated with turbulence slope ($r = −0.232$; $P = .004$), heart rate variability, and the parameters of left ($r = −0.194$; $P=.049$) and right ($r = 0.225$; $P = .02$) ventricular diastolic function.

Conclusions: COVID-19 may cause cardiovascular autonomic dysfunction. Heart rate variability and turbulence parameters can be used to recognize cardiovascular autonomic dysfunction in patients who have recovered from COVID-19 but have persistent symptoms.

Keywords: ambulatory electrocardiography monitoring; autonomic dysfunction; COVID-19; heart rate

Introduction

Cases of pneumonia of unknown origin were reported in Wuhan City, Hubei Province, China, on December 31, 2019. It was caused by a new coronavirus now known as SARS-CoV-2. The resulting disease was named COVID-19, and the outbreak was characterized as a pandemic by the World Health Organization on March 11, 2020.[1] To date, more than 300 million patients have had confirmed SARS-CoV-2 infection, and more than 5 million deaths have been reported worldwide.[2] During this pandemic, various persistent symptoms have been observed in patients recovering from COVID-19—most notably, fatigue, dyspnea, weakness, chest pain, cough, insomnia, palpitation, and headache.[3] How common these symptoms are and why they appear or persist in some people after the acute period remain unclear, but these persistent symptoms have been thought to

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involve multiple tissues and organs. Currently, research is being conducted to understand these long-term effects of COVID-19.

Studies demonstrating cardiac involvement and the persistence of patients' symptoms after COVID-19 have led to research into the possible causes, including heart failure, rhythm disturbances, sudden cardiac death, impaired coronary flow, hypertension, and inappropriate blood pressure and heart rate responses.[4] The mechanism behind the autonomic dysfunction seen in COVID-19 cases is complex and involves many interconnected mechanisms. Sudden activation of the sympathetic system is 1 of the mechanisms responsible for autonomic dysfunction, causing a cytokine storm by inducing proinflammatory cytokine release.[5] Another mechanism could be related to virus- or immune-mediated neuropathy.[6] Furthermore, the diffuse endotheliitis and vascular injury observed in patients with COVID-19 may lead to impaired arterial baroreflex sensitivity, resulting in autonomic dysfunction.[7]

In healthy individuals with normal sinus rhythm, the intervals between heartbeats constantly change. Currently, heart rate variability (HRV), heart rate turbulence (HRT), baroreflex sensitivity, and heart rate recovery are used to assess autonomic function because they can indicate autonomic effects on the sinus node. *Heart rate variability* refers to variability in the interval between consecutive heart beats, whereas *HRT* refers to fluctuations in heart rate following a premature ventricular contraction (PVC). Heart rate variability derived from 24-hour electrocardiography monitoring is measured using time- and frequency-domain methods. Among the time-domain methods, the SD of all NN intervals (SDNN), SD of average NN intervals (SDANN), average of the SD of all NN intervals for all 5-minute segments in 24-hour recordings, the root mean square of successive differences (rMSSD), and the percentage of pairs of adjacent NN intervals differing by more than 50 milliseconds (pNN50, which can be calculated directly from the NN interval or differences between NN intervals) are the most commonly used metrics. The pNN50 and rMSSD measures predominantly reflect parasympathetic activity, whereas SDNN indicates the general state of autonomic nervous system balance.[8] Among the frequency-domain methods, the low-frequency (LF), high-frequency (HF), and very low-frequency bands are used. The HF band predominantly represents parasympathetic activity, whereas the LF band represents sympathetic and parasympathetic activity.[9] Reduced HRV induces impaired autonomic balance and is a significant risk factor for all highly mortal and morbid diseases.[10] Meanwhile, HRT provides important data regarding cardiac autonomic function.[11] Heart rate turbulence is evaluated by using the following parameters: (1) turbulence onset (TO), which reflects the initial increase in heart rate following a premature ventricular beat, and (2) turbulence slope (TS), which reflects heart rate deceleration.[12] Impaired HRT is associated with many diseases, including cardiac autonomic dysfunction.[13]

COVID-19 can cause persistent myocarditis, potentially causing cardiac fibrosis or scarring in the long term.[14] In their cardiac magnetic resonance imaging study, Puntmann et al[15] observed cardiac involvement in 78% of patients who recovered from COVID-19. In contrast, Huang et al[16] reported a rate of 58%. Considering the findings of subclinical myocarditis in patients with COVID-19, SARS-CoV-2 infection could be a risk factor for heart failure later in life.[17] Echocardiography is used to assess patients with cardiac involvement. The most common echocardiographic parameters to assess left ventricular (LV) systolic and diastolic functions are LV ejection fraction (LVEF), the ratio of early peak of mitral inflow velocity (E) to early diastolic mitral annular velocity (Em) (E/Em), the ratio of early (E) to late (A) peak of mitral inflow velocity (E/A),

Abbreviations and Acronyms

A	late peak of mitral inflow velocity
BMI	body mass index
E	early mitral inflow velocity
EF	ejection fraction
Em	early diastolic mitral annular velocity
HF	high-frequency
HRT	heart rate turbulence
HRV	heart rate variability
LF	low-frequency
LV	left ventricular
MPI	Myocardial Performance Index
PCC	post–COVID-19 condition
pNN50	percentage of adjacent NN interval pairs differing by more than 50 ms
PVC	premature ventricular contraction
rMSSD	root mean square of successive differences in NN intervals
RV	right ventricular
SDANN	SD of average NN intervals
SDNN	SD of all NN intervals
TO	turbulence onset
TS	turbulence slope

deceleration time, and left atrial volume index. Among these parameters, the E/Em ratio can more accurately reflect LV relaxation and diastolic dysfunction.[18] The right ventricle Myocardial Performance Index (MPI) is a representative marker of global right ventricular (RV) function. The right ventricle MPI is independent of volume status, heart rate, and arterial pressure and has prognostic value for many cardiac conditions.[19,20]

Although COVID-19 is not a new entity, data on long-term autonomic cardiovascular outcomes in recovered patients are limited. Monitoring cardiac autonomic function and evaluating HRV and HRT in patients with COVID-19 may help identify those at risk of adverse cardiovascular outcomes. Therefore, the present study aimed to evaluate HRT and HRV as autonomic dysfunction markers in patients who have recovered from COVID-19.

Patients and Methods

Study Populations

Adult patients with COVID-19 who presented to the cardiology outpatient clinic directly or were referred from the post–COVID-19 condition (PCC) outpatient clinic with postrecovery symptoms between April and June 2021 were included. All patients had SARS-CoV-2 infection, as confirmed by reverse transcriptase–polymerase chain reaction on nasopharyngeal or oropharyngeal swabs. Patients were followed for 6 months. This prospective cohort study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of İzmir Tınaztepe Üniversitesi. Informed consent was obtained from each patient before enrollment.

Exclusion Criteria

The exclusion criteria were as follows: (1) presence of diabetes, hypertension, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, asthma, anemia, hyperthyroidism, hypothyroidism, goiter, or other thyroid diseases; (2) receiving treatment with β-blockers, inhaled or oral β-mimetics, theophylline, steroids, or other drugs with potential chronotropic effects; and (3) having a history of severe COVID-19 (requiring hospitalization or intensive care admission).

An age-matched and sex-matched group, which included some employees of the hospital who met the previously mentioned selection criteria and tested negative for SARS-CoV-2, served as the control. Figure 1 shows the study flowchart.

The demographic and clinical data of patients in the study group were obtained. After allowing the patients to rest for 5 to 10 minutes in the sitting position, 3 blood pressure measurements were obtained (1 per minute) and averaged using an oscillometric monitor (Omron M3 Comfort; Omron Healthcare). The patients underwent routine cardiologic evaluation, including height and weight measurements, followed by 12-lead electrocardiography. Transthoracic echocardiography and 24-hour Holter tests were performed at initial presentation and 6-month control evaluation.

Holter Monitoring

Cardiac rhythm was monitored for 24 hours using validated devices (GE HealthCare SEER 1000 Holter Recorder). The following parameters were measured: SDNN, SDANN, rMSSD, pNN50, LF, HF, ratio of LF power to HF power, TO, and TS. Turbulence onset was calculated by subtracting the sum of 2 R-R intervals immediately before a PVC from the sum of 2 R-R intervals after PVC following a compensatory pause and dividing the result by the sum of 2 R-R intervals before the PVC.[20] Turbulence slope was defined as the maximum positive regression slope assessed over any 5 consecutive sinus R-R intervals within the first 15 R-R intervals following a PVC.[21] Heart rate TO or TS was considered abnormal if the onset was at least 0% or the slope was at or below 2.5 ms/beat.

Echocardiography

Transthoracic echocardiographic examination was performed at initial presentation and the 6-month control evaluation. A standard 2-dimensional echocardiographic examination was performed using color Doppler echocardiography (Vivid PRO 7, General Electric) with a 2.5- to 3.5-MHz transducer from the parasternal long-axis and short-axis and apical 2-, 3-, and 4-chamber views. The LV systolic and diastolic diameters, left atrial diameter, aortic diameter, and LVEF (Simpson method) were measured, and mitral inflow E and A were obtained from the apical 2- and 4-chamber views. Pulsed wave tissue Doppler imaging was performed from the apical 4-chamber view on the medial wall of the mitral annulus. Mitral Em, late diastolic mitral annular velocity, and peak tissue Doppler systolic velocity were obtained, and the

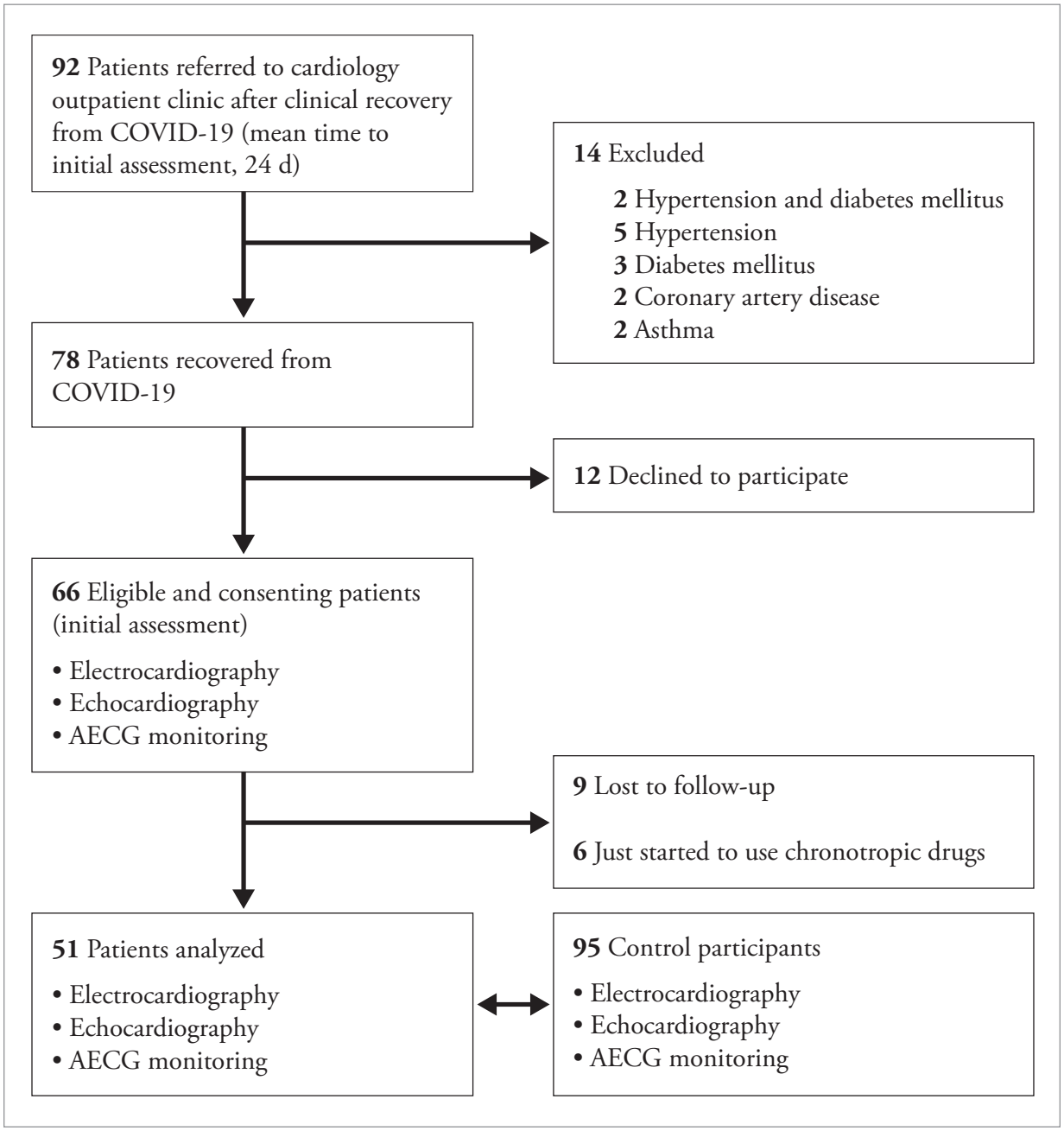

Fig. 1 Participant flow diagram.

AECG, ambulatory electrocardiogram.

E/Em ratio was calculated. The left atrial volume was calculated using the biplane area length method at end systole, and the left atrial volume index was determined. The right ventricle diameter and tricuspid annulus plane systolic excursion were measured from right ventricle–focused 4-chamber views, and the isovolumic relaxation time, isovolumic contraction time, ejection time, and MPI were also determined. The MPI was calculated as follows: (isovolumic contraction time + isovolumic relaxation time) / RV ejection time.[22]

Statistical Analysis

All statistical analyses were performed using SPSS, version 24.0 (SPSS Inc). Categorical data were expressed as absolute number and percentage, and continuous data were expressed as mean (SD) and median. The normality of variables was checked using the Kolmogorov-

Smirnov test. Differences between categorical data were assessed using the χ^2 test. The independent *t* test and Mann-Whitney *U* test were used to compare continuous variables between groups. The paired *t* test and Wilcoxon signed-rank test were performed for pre-post comparisons within the same group. The Pearson correlation coefficient (*r*) was used to examine correlations between 24-hour electrocardiographic monitoring, echocardiographic findings, age, body mass index (BMI), and sex. Partial correlation was used to control the effect of confounding factors, including BMI and age. Binary logistic regression analysis was performed using age, BMI, sex, smoking, heart rate, systolic blood pressure, glucose, total cholesterol, triglyceride, and high-density and low-density lipoprotein levels. $P<.05$ was considered statistically significant.

Results

Baseline Characteristics

The study included a total of 146 patients (51 in the post–COVID-19 group and 95 in the control group), with a predominance of female participants (89 women [60.9%]). The mean (SD) age was 48.6 (13.2) years (range, 21-81 years). The baseline heart rate was significantly higher in the post–COVID-19 group than in the control group ($P<.001$), whereas all other baseline characteristics were similar (Table I). Patients in the post–COVID-19 group reported persistence of at least 1 symptom at 6-month follow-up: palpitation (31 of 51 [60.8%]), chest pain (22 of 51 [43.1%]), fatigue (24 of 51 [47.1%]), and dyspnea (14 of 51 [27.5%]). The mean (SD) time to cardiology outpatient clinic application after clinical recovery from COVID-19 was 24.1 (5.7) days. A comparison of the symptoms, HRV and HRT findings, and echocardiographic findings of the post–COVID-19 group at initial presentation and 6-month evaluation are shown in Table II.

Initial Evaluation

Those in the post–COVID-19 group who initially presented to the outpatient cardiology clinic had significantly higher TO ($P=.007$) and lower pNN50 ($P=.006$), rMSSD ($P=.009$), LF bands ($P=.006$), very low-frequency bands ($P=.04$), and HF bands ($P<.001$) compared with those in the control group. Furthermore, the rate of abnormal TO was significantly higher in the post–COVID-19 group than in the control group. No significant differences were observed in other HRV and HRT parameters between groups. A comparison of the HRV and HRT findings of the post–COVID-19 group at initial presentation and the control group is shown in Table III.

The post–COVID-19 group had significantly higher LV E/Em ($P=.001$) and RV MPI ($P<.001$), significantly lower LV E/A ($P=.01$), and significantly longer RV isovolumetric relaxation time ($P<.001$) at initial presentation compared with the control group. No significant differences were observed in

TABLE I. Baseline Clinical and Demographic Characteristics

Characteristic	Post–COVID-19 (n = 51)	Control (n = 95)	*P* value[a]
Female sex, No. (%)	29 (56.9)	60 (63.1)	.42[b]
Age, mean (SD), y	50.8 (13.6)	46.3 (12.4)	.08[c]
BMI, mean (SD)	29.0 (4.3)	28.8 (4.2)	.86[c]
Heart rate, mean (SD), bpm	90.5 (10.6)	80.1 (12.6)	<.001[c]
Systolic blood pressure, mean (SD), mm Hg	128.9 (10.3)	130.4 (7.6)	.41[c]
Diastolic blood pressure, mean (SD), mm Hg	79.3 (9.4)	80.5 (8.0)	.49[c]
Smoker, No. (%)	15 (29.4)	31 (32.6)	.67[b]

BMI, body mass index; bpm, beat per minute.
[a]$P < .05$ was considered statistically significant.
[b]χ^2 test.
[c]Independent *t* test.

TABLE II. Symptom Profile, Heart Rate Turbulence and Variability Findings, and Echocardiographic Findings at Initial Assessment and 6 Months in the Post–COVID-19 Group (n = 51)

Symptom or characteristic	Initial assessment	6 Mo	*P* value[a]
Palpitation, No. (%)	35 (68.6)	31 (60.8)	.40[b]
Chest pain, No. (%)	28 (54.9)	22 (43.1)	.23[b]
Fatigue, No. (%)	19 (37.3)	24 (47.1)	.32[b]
Dyspnea, No. (%)	17 (33.3)	14 (27.5)	.52[b]
Joint pain, No. (%)	15 (29.4)	17 (33.3)	.67[b]
Cough, No. (%)	11 (21.6)	9 (17.6)	.62[b]
Headache, No. (%)	7 (13.7)	10 (19.6)	.42[b]
Insomnia, No. (%)	5 (9.8)	3 (5.9)	.46[b]
≥3 Symptoms, No. (%)	27 (52.9)	24 (47.1)	.55[b]
Time to initial assessment, mean (SD), d[c]	24.1 (5.7)	–	–
SDNN, median (IQR), ms	98.0 (30.0-222.0)	84.9 (40.0-128.0)	.005[d]
SDANN, median (IQR), ms	85.0 (28.0-256.0)	70.0 (31.0-128.0)	.001[d]
ASDNN, median (IQR), ms	44.0 (11.0-109.0)	40.0 (13.0-89.0)	.40[d]
rMSSD, mean (SD), ms	23.5 (9.6)	24.3 (13.3)	.70[e]
pNN50, mean (SD), %	5.1 (5.0)	6.4 (8.8)	.39[e]
Very low frequency, mean (SD), ms^2	24.4 (12.3)	23.7 (10.1)	.76[e]
LF, mean (SD), ms^2	14.4 (9.4)	14.9 (8.2)	.79[e]
HF, mean (SD), ms^2	8.0.0 (4.5)	9.3 (5.4)	.43[e]
LF/HF, mean (SD)	1.88 (0.67)	1.68 (0.51)	.08[e]
TO, mean (SD), %	0.47 (3.73)	0.39 (1.82)	.90[e]
TS, mean (SD), ms/R-R	9.25 (6.06)	6.14 (4.73)	.006[e]
Left arterial volume index, mean (SD), mL/m^2	36.3 (11.6)	37.4 (12.3)	.66[e]
LVEF, median (IQR), %	63.0 (58.0-69.0)	62.0 (56.0-66.0)	.11[d]
E/A ratio, mean (SD)	1.13 (0.29)	1.26 (0.21)	.01[e]
Right ventricle, mean (SD), cm	3.59 (0.74)	3.45 (0.49)	.24[e]
E/Em ratio, mean (SD)	11.9 (4.3)	10.0 (1.9)	.005[e]
Right ventricle MPI, mean (SD)	0.70 (0.30)	0.42 (0.02)	<.001[e]

ASDNN, average of the SD of all NN intervals for all 5-minute segments in the 24-hour recordings; E/A ratio, ratio of early (E) to late (A) peak of mitral inflow velocity; E/Em ratio, ratio of early peak of mitral inflow velocity (E) to early diastolic mitral annular velocity (Em); HF, high-frequency; LF, low-frequency; LVEF, left ventricular ejection fraction; MPI, Myocardial Performance Index; pNN50, percentage of pairs of adjacent NN intervals differing by more than 50 milliseconds; rMSSD, root mean square of successive differences of NN intervals; SDANN, SD of the average NN intervals; SDNN, SD of all NN intervals; TO turbulence onset; TS, turbulence slope.

[a]$P < .05$ was considered statistically significant.
[b]χ^2 test.
[c]The mean time to cardiology outpatient clinic presentation after clinical recovery from COVID-19.
[d]Wilcoxon signed-rank test.
[e]Paired *t* test.

other echocardiographic parameters between groups (Table IV).

Six-Month Evaluation

Those in the post–COVID-19 group at 6-month evaluation had significantly higher TO ($P<.001$) and lower HRV parameters than those in the control group. The rate of abnormal TO was significantly higher in the post–COVID-19 group than in the control group. No significant differences were observed in TS between groups. A comparison of HRV and HRT findings of the post–COVID-19 group at 6-month evaluation and the control group is shown in Table V.

The echocardiographic findings showed no significant differences between the post–COVID-19 group at 6-month evaluation and the control group, except for RV late diastolic mitral annular velocity ($P=.03$) (Table VI).

Correlations

A significant correlation was observed between TO and age ($r=0.328$, $P=.001$), BMI ($r=0.224$, $P=.02$), TS ($r=-0.232$, $P=.004$), SDNN ($r=-0.259$, $P=.001$), SDANN ($r=-0.203$, $P=.01$), rMSSD ($r=-0.170$, $P=.03$), pNN50 ($r=-0.184$, $P=.02$), HF ($r=-0.177$, $P=.03$), LV E/A ($r=-0.149$, $P=.049$), and right ventricle MPI ($r=0.225$, $P=.02$). Turbulence onset was not significantly correlated with any of the other parameters. When controlling for possible confounders (eg, age and BMI), the significant correlations with TO remained statistically significant, except for the SDANN and the LV E/A ratio (Table VII).

TABLE III. Heart Rate Variability and Turbulence Findings in the Post–COVID-19 Group at Initial Assessment and the Control Cases

Variable	Post–COVID-19 (n = 51)	Control (n = 95)	*P* value[a]
SDNN, median (IQR), ms	98.0 (30.0-222.0)	105.0 (47.0-202.0)	.37[b]
SDANN, median (IQR), ms	85.0 (28.0-256.0)	83.0 (41.0-263.0)	.98[b]
ASDNN, median (IQR), ms	44.0 (11.0-109.0)	50.0 (18.0-173.0)	.07[b]
rMSSD, mean (SD), ms	23.5 (9.6)	30.8 (17.1)	.009[c]
pNN50, mean (SD), %	5.1 (5.0)	10.1 (11.6)	.006[c]
Very low frequency, mean (SD), ms^2	24.4 (12.3)	31.0 (18.7)	.04[c]
LF, mean (SD), ms^2	14.4 (9.4)	20.5 (12.2)	.006[c]
HF, mean (SD), ms^2	8.0.0 (4.5)	12.5 (7.2)	<.001[c]
LF/HF, mean (SD)	1.88 (0.67)	1.72 (0.56)	.19[c]
TO, mean (SD), %	0.47 (3.73)	–1.37 (2.93)	.007[c]
TS, mean (SD), ms/R-R	9.25 (6.06)	7.34 (5.27)	.09[c]
Abnormal TO, No. (%)	19 (37.3)	9 (17.6)	.03[d]
Abnormal TS, No. (%)	9 (17.6)	7 (13.7)	.59[d]

ASDNN, average of the SD of all NN intervals for all 5-minute segments in the 24-hour recordings; HF, high-frequency; LF, low-frequency; pNN50, percentage of pairs of adjacent NN intervals differing by more than 50 milliseconds; rMSSD, root mean square of the successive differences of NN intervals; SDANN, SD of the average NN intervals, measured primarily reflects total circadian rhythms and for 5-minute segments during a 24-hour physical activity recording; SDNN, SD of all NN intervals; TO, turbulence onset; TS, turbulence slope.

[a]$P < .05$ was considered statistically significant.
[b]Mann-Whitney *U* test.
[c]Independent *t* test.
[d]χ^2 test.

TABLE IV. Echocardiography Findings in the Post–COVID-19 Group at Initial Assessment and in Control Cases

Echocardiographic characteristic	Post-COVID-19 (n = 51)	Control (n = 95)	*P* value[a]
Left atrial volume index, mean (SD), mL/m^2	36.3 (11.6)	36.0 (12.1)	.90[b]
LVEF, median (IQR), %	63.0 (58.0-69.0)	62.0 (58.0-66.0)	.29[c]
LV end-diastolic diameter, median (IQR), cm	4.1 (3.0-5.3)	4.2 (3.0-5.5)	.24[c]
LV end-systolic diameter, mean (SD), cm	2.78 (0.34)	2.75 (0.30)	.67[b]
E, mean (SD), cm/s	81.4 (17.8)	88.7 (13.3)	.02[b]
A, mean (SD), cm/s	74.3 (17.8)	71.1 (9.9)	.26[b]
E/A ratio, mean (SD)	1.13 (0.29)	1.26 (0.21)	.01[b]
Deceleration time, median (IQR), ms	165.0 (99.0-349.0)	155.0 (120.0-232.0)	.12[c]
Right ventricle, mean (SD), cm	3.59 (0.74)	3.38 (0.50)	.10[b]
Em, mean (SD), cm/s	7.76 (1.81)	9.43 (0.95)	<.001[b]
Am, mean (SD), cm/s	9.48 (2.10)	8.53 (0.74)	.003[b]
E/Em ratio, mean (SD)	11.9 (4.3)	9.5 (1.9)	.001[b]
RV Em, mean (SD), cm/s	11.08 (3.43)	12.83 (2.80)	.006[b]
RV Am, mean (SD), cm/s	12.59 (4.57)	9.09 (1.18)	<.001[b]
RV ejection time, median (IQR), ms	250.0 (70.0-505.0)	300.0 (214.0-505.0)	<.001[c]
RV isovolumic relation time, mean (SD), ms	86.7 (30.1)	67.3 (11.8)	<.001[b]
Right ventricle MPI, mean (SD)	0.70 (0.30)	0.41 (0.02)	<.001[b]
Tricuspid annular plane systolic excursion, median (IQR), cm	2.2 (1.7-3.0)	2.3 (1.8-3.3)	.06[c]
Peak tissular Doppler systolic velocity, mean (SD), cm/s	7.6 (1.6)	7.5 (1.5)	.75[b]

A, late peak of mitral inflow velocity; Am, late diastolic mitral annular velocity; E, early peak of mitral inflow velocity; E/A ratio, ratio of early (E) to late (A) peak of mitral inflow velocity; Em, early diastolic mitral annular velocity; E/Em, ratio of early (E) peak of mitral inflow velocity to early (Em) diastolic mitral annular velocity; LVEF, left ventricular ejection fraction; MPI, Myocardial Performance Index; RV, right ventricular.

[a]*P* < .05 was considered statistically significant.
[b]Independent *t* test.
[c]Mann-Whitney *U* test.

Binary Logistic Regression Analysis

Logistic regression analysis was performed using age, BMI, sex, smoking, heart rate, systolic blood pressure, glucose, total cholesterol, triglyceride, and high-density and low-density lipoprotein levels to identify a relationship between these independent variables and the presence of abnormal TO. Age, heart rate, and smoking were found to be independently associated with the presence of abnormal TO (Table VIII).

TABLE V. Heart Rate Variability and Turbulence Findings in the Post–COVID-19 Group at 6 Months and in Control Cases

Variable	Post–COVID-19 (n = 51)	Control (n = 95)	*P* value[a]
SDNN, median (IQR), ms	84.9 (40.0-128.0)	105.0 (47.0-202.0)	<.001[b]
SDANN, median (IQR), ms	70.0 (31.0-128.0)	83.0 (41.0-263.0)	<.001[b]
ASDNN, median (IQR), ms	40.0 (13.0-89.0)	50.0 (18.0-173.0)	.002[b]
rMSSD, mean (SD), ms	24.3 (13.3)	30.8 (17.1)	.03[c]
pNN50, mean (SD), %	6.4 (8.8)	10.5 (11.4)	.046[c]
Very low frequency, mean (SD), ms^2	23.7 (10.1)	31.0 (18.7)	.02[c]
LF, mean (SD), ms^2	14.9 (8.2)	20.5 (12.2)	.008[c]
HF, mean (SD), ms^2	9.3 (5.4)	12.5 (7.2)	.01[c]
LF/HF, mean (SD)	1.68 (0.51)	1.72 (0.56)	.74[c]
TO, mean (SD), %	0.39 (1.82)	–1.37 (2.93)	<.001[c]
TS, mean (SD), ms/R-R	6.14 (4.73)	7.34 (5.27)	.23[c]
Abnormal TO, No. (%)	24 (47.1)	9 (17.6)	.001[c]
Abnormal TS, No. (%)	12 (23.5)	7 (13.7)	.20[c]
Heart rate, mean (SD), bpm	87.3 (10.7)	80.1 (12.6)	.002[c]

ASDNN, average of the SD of all NN intervals for all 5-minute segments in the 24-hour recordings; HF, high-frequency; LF, low-frequency; pNN50, percentage of pairs of adjacent NN intervals differing by more than 50 milliseconds; rMSSD, root mean square of the successive differences of NN intervals; SDANN, SD of the average NN intervals, measured primarily reflects total circadian rhythms and for 5-minute segments during a 24-hour physical activity recording; SDNN, SD of all NN intervals; TO, turbulence onset; TS, turbulence slope.

[a]$P < .05$ was considered statistically significant.
[b]Mann-Whitney *U* test.
[c]Independent *t* test.

Discussion

The primary findings were as follows: (1) abnormal HRT was common in the post–COVID-19 group, even at 6 months after clinical recovery, and was associated with HRV, LV E/A ratio, and right ventricle MPI. (2) Sinus tachycardia and reduced HRV were also common in the post–COVID-19 group during admission to the cardiology outpatient clinic and 6 months after clinical recovery. (3) At 6-month follow-up, those in the post–COVID-19 group reported the persistence of at least 1 symptom (most frequently, palpitation, chest pain, fatigue, and dyspnea). (4) At the time of admission to the cardiology outpatient clinic, abnormal LV and RV diastolic function were common in the post–COVID-19 group. (5) At 6-month follow-up, although echocardiographic findings were recovered, HRV and HRT abnormalities persisted in the post–COVID-19 group.

COVID-19 causes systemic inflammatory activation that can affect the entire autonomic nervous and cardiovascular systems. According to Oudit et al,[23] SARS-CoV-2 may mediate myocardial inflammation and damage. Huang et al[16] retrospectively evaluated 26 patients who had recovered from COVID-19 and undergone cardiac magnetic resonance imaging because of cardiac symptoms. They found decreases in cardiac functions such as EF, cardiac index, and stroke volume in patients. In a recent study, Szekely et al[24] performed echocardiographic evaluation of 100 patients with COVID-19 within 24 hours of admission and found that LV diastolic function and RV function were

TABLE VI. Echocardiography Findings in the Post–COVID-19 Group at 6 Months and in Control Cases

Echocardiographic characteristic	Post–COVID-19 (n = 51)	Control (n = 95)	*P* value[a]
Left atrial volume index, mean (SD), mL/m²	37.4 (12.3)	36.0 (12.1)	.56[b]
LVEF, median (IQR), %	62.0 (56.0-66.0)	62.0 (58.0-66.0)	.46[c]
LVEDD, median (IQR), cm	4.2 (3.0-5.6)	4.2 (3.0-5.5)	.82[c]
LV end-systolic diameter, mean (SD), cm	2.76 (0.36)	2.75 (0.30)	.94[b]
E, mean (SD), cm/s	91.9 (17.8)	88.7 (13.3)	.22[b]
A, mean (SD), cm/s	74.0 (10.9)	71.1 (9.9)	.17[b]
E/A ratio, mean (SD)	1.26 (0.21)	1.26 (0.21)	.95[b]
Deceleration time, median (IQR), ms	165.0 (121.0-252.0)	155.0 (120.0-232.0)	.29[c]
Right ventricle, mean (SD), cm	3.45 (0.49)	3.38 (0.50)	.51[b]
Em, mean (SD), cm/s	9.32 (1.01)	9.43 (0.95)	.57[b]
Am, mean (SD), cm/s	8.53 (0.70)	8.53 (0.74)	.96[b]
E/Em ratio, mean (SD)	10.0 (1.9)	9.5 (1.9)	.23[b]
RV Em, mean (SD), cm/s	13.18 (2.39)	12.83 (2.80)	.50[b]
RV Am, mean (SD), cm/s	9.59 (1.16)	9.09 (1.18)	.03[b]
RV ejection time, median (IQR), ms	303.0 (214.0-505.0)	300.0 (210.0-455.0)	.64[c]
RV isovolumic relaxation time, mean (SD), ms	65.9 (10.0)	67.3 (11.8)	.52[b]
Right ventricle MPI, mean (SD)	0.42 (0.02)	0.41 (0.02)	.64[b]
Tricuspid annular plane systolic excursion, median (IQR), cm	2.2 (1.8-2.9)	2.3 (1.8-3.3)	.83[c]
Peak tissular Doppler systolic velocity, mean (SD), cm/s	7.3 (1.6)	7.5 (1.5)	.69[b]

A, late peak of mitral inflow velocity; Am, late diastolic mitral annular velocity; E, early peak of mitral inflow velocity; E/A ratio, ratio of early (E) to late (A) peak of mitral inflow velocity; Em, early diastolic mitral annular velocity; E/Em, ratio of early peak of mitral inflow velocity (E) to early diastolic mitral annular velocity (Em); LVEF, left ventricular ejection fraction; MPI, Myocardial Performance Index; RV, right ventricular.

[a]$P < .05$ was considered statistically significant.
[b]Independent *t* test.
[c]Mann-Whitney *U* test.

impaired, whereas LV systolic function was preserved. When there is cardiovascular system involvement in COVID-19, the disturbance in regulatory mechanisms may cause autonomic dysfunction, resulting in sympathetic hyperactivation or vagal impairment. Thus, sympathetic tonus also becomes dominant in the ventricular myocardium and decreases myocardial compliance. Although our study was not designed to answer questions of sequence or causation in relation to systolic and diastolic dysfunction of RV, LV, and sympathetic overactivity, those in the post–COVID-19 group had a higher incidence of impaired RV and LV diastolic function and impaired HRV and HRT during admission to the cardiology outpatient clinic than those in the control group. Moreover, a significant correlation was observed between HRT, HRV, and right ventricle MPI as a marker of RV diastolic dysfunction. Therefore, it is logical to suggest that COVID-19 may cause both of these conditions, although the cardiac involvement caused by COVID-19 was temporary in the present

TABLE VII. Correlation Analyses Between Heart Rate Turbulence and Variability Findings, With and Without Adjustment for Age, BMI, and Sex

	TO		TO adjusted for age, BMI, and sex	
Independent variable	***r* coefficient**	***P* value**	***r* coefficient**	***P* value[a]**
Age	0.328	.001	–	–
BMI	0.224	.02	–	–
Sex	0.044	.66	–	–
SDNN	−0.259	.001	−0.241	.01
SDANN	−0.203	.01	−0.146	.14
ASDNN	−0.130	.11	−0.137	.17
rMSSD	−0.170	.03	−0.209	.03
pNN50	−0.184	.02	−0.223	.02
Very low frequency	−0.053	.52	−0.042	.67
LF	−0.037	.65	−0.037	.71
HF	−0.177	.03	−0.218	.03
LF/HF	−0.029	.72	−0.009	.93
TS	−0.232	.004	−0.259	.009
LV E/Em	0.018	.85	0.029	.78
LV E/A	−0.194	.049	−0.170	.09
Right ventricle MPI	0.225	.02	0.211	.03

ASDNN, average of the SD of all NN intervals for all 5-minute segments in the 24-hour recordings; BMI, body mass index; HF, high-frequency; LF, low-frequency; pNN50, percentage of pairs of adjacent NN intervals differing by more than 50 milliseconds; LV E/A ratio, ratio of early (E) to late (A) peak of mitral inflow velocity of the left ventricle; LV E/Em, ratio of early peak of mitral inflow velocity (E) to early diastolic mitral annular velocity (Em) of the left ventricle; rMSSD, root mean square of the successive differences of NN intervals; MPI, Myocardial Performance Index; SDANN, SD of the average NN intervals, measured primarily reflects total circadian rhythms and for 5-minute segments during a 24-hour physical activity recording; SDNN, SD of all NN intervals; TO, turbulence onset; TS, turbulence slope.

[a]$P < .05$ was considered statistically significant.

TABLE VIII. Binary Logistic Analyses Between Abnormal TO and Independent Variables

Independent variable	Regression coefficient (β)	Wald (χ^2)	*P* value[a]	Dominance ratio (95% CI)
Age	0.05	4.40	.03	1.05 (1.00-1.15)
BMI	0.06	0.79	.37	1.06 (0.92-1.21)
Sex (male)	0.56	0.82	.36	1.74 (0.52-5.79)
Heart rate	0.04	4.28	.04	1.04 (1.00-1.08)
Systolic blood pressure	0.02	0.48	.49	1.02 (0.96-1.08)
Smoker	1.26	4.10	.04	3.54 (1.04-12.02)
Glucose	0.004	0.22	.63	1.00 (0.98-1.02)
HDL	−0.05	3.57	.06	0.94 (0.89-1.00)
Triglycerides	0.003	0.20	.65	1.00 (0.99-1.01)
LDL	0.007	0.09	.75	1.01 (0.96-1.05)
Total cholesterol	0.006	0.07	.79	1.01 (0.96-1.04)

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a]$P < .05$ was considered statistically significant.

study. Furthermore, no significant correlation was observed between HRT, HRV, and LV systolic and diastolic parameters. These findings are contrary to those of Skaluba et al,[25] who reported a significant inverse relationship between the LV E/Em ratio and slowed heart rate recovery. They also support the results reported by Arora et al,[26] who observed reduced HRV in patients with LV diastolic dysfunction, which may suggest a sympathetic-parasympathetic imbalance. COVID-19 is believed to involve the right ventricle both directly and indirectly and to have different effects on the lungs in the acute and chronic periods.[27] Changes in right ventricle size and function have also been associated with increased sympathetic tone and altered volume status because of the systemic inflammatory response. Lucrezotti et al[28] found that reduced HRV was significantly related to RV dysfunction indexes. These results are consistent with the data obtained in the present study. In another study, Tadic et al[29] speculated that RV diastolic function, RVEF, and RV longitudinal function were associated with decreased HRV. Unlike Tadic et al, no significant relationship between RV systolic function and HRV was observed.

The autonomic nervous system is another target of COVID-19. The basis of autonomic dysfunction in COVID-19 is complex and involves many interconnected mechanisms. One of the mechanisms responsible for autonomic dysfunction is diffuse endotheliitis and vascular injury.[3] Another explanation for cardiac involvement is that hyperinflammation syndrome and coagulopathy may cause dysautonomia on the micro and macro scales.[30] In addition, COVID-19 itself may cause myocardial damage and necrosis, and necrotic and noncontractile segments cause geometric changes during heartbeat, stimulating the sympathetic afferent nerve endings.

A substantial number of patients who recovered from COVID-19 with persistent symptoms present to outpatient clinics every day. In a study by Carfi et al,[31] approximately 55.2% of patients had at least 3 persistent symptoms, which is similar to the rate found in the present study (52.9%). The most common symptoms in the post–COVID-19 group were palpitation, chest pain, fatigue, dyspnea, joint pain, cough, headache, and insomnia. For these patients, 24-hour ambulatory electrocardiography monitoring can aid in determining the cause of their symptoms, if they have a cardiac origin. Heart rate variability and HRT obtained from 24-hour rhythm Holter are useful noninvasive parameters for determining the cardiovascular responses to autonomic dysfunction.[32] Although the vagal system is dominant, there is a balance between the vagal and sympathetic systems under resting conditions. Heart rate variability is the main representative marker of overall parasympathetic activity.[33] Reduced HRV has been associated with high levels of proinflammatory cytokines and worse outcomes in patients with coronary artery disease, heart failure, diabetes, hypertension, obesity, and autoimmune disease.[34,35] Regardless of the disease, however, reduced HRV is primarily associated with sympathetic overactivity or parasympathetic underactivity. In the present study, reductions in HRV parameters (including SDNN; pNN50; rMSSD; and LF, very low-frequency, and HF bands) were observed in patients who had recovered from COVID-19. These findings are consistent with a recent report by Shouman et al,[36] who found that many patients with PCCs had abnormal autonomic function test results and speculated that there may be a causal relationship between COVID-19 and autonomic symptoms. In another study, Barizien et al[37] determined that patients with PCCs and persistent symptoms had reduced HRV compared with controls, indicating dysautonomia. Similarly, Kurtoğlu et al[38] speculated that patients who had recovered from COVID-19 had reduced HRV compared with controls. In contrast to the present study's findings, Ponomarev et al[39] reported that SDNN and rMSSD showed no significant differences before, during, or after COVID-19. Although several studies have demonstrated an association between HRV variation and clinical progression in acute COVID-19[40,41] the prognostic value of reduced HRV and abnormal HRT in patients with PCCs is unclear. Similar to HRV, HRT parameters are closely related to the cardiovascular autonomic system. Although many other reports have shown that abnormal HRT is associated with impaired cardiovascular autonomic system and baroreflex response,[42,43] no data were found regarding the association between HRT parameters and persistent symptoms in patients who had had COVID-19. Moreover, data on the cardiovascular effects of COVID-19 after 6 months were limited. In the present study, TO levels and the rate of abnormal TO were significantly higher in the post–COVID-19 group than in the control group and also positively cor-

related with some HRV parameters that indicate autonomic dysfunction.

Resting electrocardiography showed that those in the post–COVID-19 group had significantly higher heart rates than those in the control group. Stahlberg et al[44] described a subsyndrome in patients with PCCs and persistent palpitation that they called *post-COVID tachycardia syndrome*. This syndrome includes postural orthostatic tachycardia, inappropriate sinus tachycardia, and sinus tachycardia. The authors noted that between one-quarter and half of patients presenting to a multidisciplinary post–COVID-19 referral clinic report tachycardia or palpitations persisting for at least 12 weeks. In the present study, 60.8% of patients had palpitations persisting for more than 24 weeks. These results are consistent with those reported by Stahlberg et al.

To our knowledge, the present study is the first to assess HRV and HRT abnormalities in patients with persistent symptoms after having COVID-19. Reduced HRV and HRT may indicate increased cardiovascular risk among survivors of SARS-CoV-2 infection. Thus, it is important to diagnose and evaluate patients with PCCs with dysautonomia and follow these patients for future cardiovascular events. Heart rate variability and HRT may also present a useful therapeutic target in patients experiencing the long-term effects of COVID-19.

Limitations

The most important limitation of this study is related to its design, as only patients with mild COVID-19 were included. Patients with severe COVID-19 who have used drugs such as steroids, which have potential chronotropic effects, were excluded. The second important limitation is that the present analysis was performed at the time of admission to the cardiology outpatient clinic and at 6 months after acute COVID-19. Closer and longer follow-up is required to identify the full implications of COVID-19. Third, the present study was conducted at a single center with a relatively small sample. Fourth, the generalizability of this study is limited because patients with comorbid diseases, which may have potential chronotropic effects or may cause autonomic dysfunction, were excluded.

Conclusion

In this study, patients who had recovered from COVID-19 had significantly lower HRV parameters and higher TO than controls. Thus, autonomic dysfunction may be a common sequela among these patients. Considering their diagnostic and prognostic importance, HRV and HRT parameters may be useful prognostic markers and therapeutic targets for patients with persistent symptoms after COVID-19.

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