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Post-COVID-19 Exercise Stress Test

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Abstract

Objectives: Atypical chest pain, fatigue, and palpitations can be seen in post-coronavirus disease-2019 (COVID-19) period. With the hypothesis of explaining these complaints, we evaluated the exercise stress test (EST) parameters in COVID-19 patients with mild disease.

Materials and Methods: Between the ages of 30-50 years, who had mild COVID-19 in the last 3-9 months, were taken as the COVID-19 group [n=80, male/female (M/F): 40/40]. A total of 160 patients were included, of which age and gender matched 80 patients (M/F: 40/40) without COVID-19 were the control group. During the EST, baseline heart rate HR1(beats/min), baseline systolic, diastolic blood pressure (mmHg) (SBP_1, DBP_1), maximum blood pressures (SBP_{max}, DBP_{max}), and blood pressure changes (ΔSBP, ΔDBP) were recorded. As EST parameters, Duke score, exercise time (min), ST change (mm), exercise capacity (METs), maximum reached HR (% beats/min), distance walked (m), maximum oxygen consumption amount ($VO2_{max}$ mL/kg/min), rate pressure product (RPP mmHg/min/1000), and heart HR recovery 1 (HRR_1 beats/min) was used.

Results: In the COVID-19 group, baseline HR_1, SBP_1, DBP_1, SBP_{max}, DBP_{max}, ΔSBP, ΔDBP, $VO2_{max}$, and RPP were higher, while distance walked and HRR_1 were less. There was no difference between the two groups in terms of Duke score, exercise duration, ST change and exercise capacity.

Conclusion: The fact that the exercise capacities in the COVID-19 group were similar to those in the control group, but there was a difference in the changes in heart rate and blood pressure, RPP, HRR1 suggested that the autonomic system might be affected.

Keywords: Post-COVID-19, exercise stress test, heart rate, blood pressure, heart rate recovery

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Introduction

Atypical chest pain, fatigue, and palpitations can be found in patients who have had coronavirus disease-2019 (COVID-19)[1]. These complaints resemble those in patients with suspected coronary artery disease. Exercise stress testing (EST) is mainly used to estimate the probability of coronary artery disease in the presence of chest pain and to determine exercise capacity or to monitor for palpitations upon exertion[2].

Exercise is associated with an increase in sympathetic tone and skeletal blood flow, but a corresponding decrease in peripheral resistance is found. With exercise, an increase in systolic blood pressure up to a maximum of 230 mm high is expected, while diastolic blood pressure increases or decreases by 10 mm high. When activated, the sympathetic nervous system simulates an increase in energy expenditure and controls cardiovascular responses during exercise. Additionally, norepinephrine and epinephrine have effects on metabolism and hormone secretion, which are important during exercise[3,4]. Changes in the autonomic system during exercise are regulated by neural mechanisms, including central brain command, exercise pressure reflex, a negative feedback mechanism originating from the carotid sinus and aortic arch, cardiopulmonary baroreceptors, and arterial baroreflex, all working together[5].

It has been shown that coronaviruses can travel in a retrograde manner from mechanoreceptors and chemoreceptors in the lungs and lower airways to the autonomic center in the brainstem via synaptic connections, potentially contributing to respiratory failure[6].

Post COVID-19 syndrome has been defined relatively recently and includes a wide spectrum of signs and symptoms. Symptoms, including functional limitations, orthostatic and exercise intolerance, may persist for more than several months in more than 50% of patients[7]. In this study, EST parameters in COVID-19 patients with mild disease were evaluated according to the hypothesis that the described complaints can be explained.

Materials and Methods

Inclusion Criteria

In the study, those who presented to the hospital with at least one of the above-described complaints, did not have a known systemic disease and cardiac family history, did not smoke, did not drink alcohol, did not take any medication, were aged 30-50 years, and had mild COVID-19 in the last 3-9 months, were taken as a COVID-19 group [(n=80, M/F)=40/40]. Including a control group (n=80, M/FM=40/40) without COVID-19, 160 subjects were recruited.

These subjects who had similar mean ages, body mass index (BMI), and ideal physical activities for the last six months were included in both groups. The ideal physical activity was classified as greater than or equal to 150 min of moderate-intensity, ≥75 min of vigorous physical activity per week, or greater than or equal to 150 min of moderate-to-vigorous physical activity per week[8].

Exclusion Criteria from the Study

Patients with known systemic disease, hospitalized for inpatient treatment, suspicious findings on chest X-ray, laboratory values out of normal limits, smoking, taking alcohol or any medication, not undertaking an ideal physical activity, and who were not in the same age group were excluded from the study.

During the disease in the COVID-19 group, chest computed tomography (CT) scans were normal, and laboratory values were within the definition of the mild disease group[9]. During the study, no cardiac and pulmonary pathologies were detectable based on echocardiography, electrocardiography (ECG), troponin, and chest X-ray in both groups. Echocardiography (GE Vivid n70, Horten, Norway) was performed using a standard 2D probe. Image interpretation was based on the right and left cardiac chamber structure, size and function and evaluated in accordance with current European Association of Cardiovascular Imaging guidelines[10].

Systolic and diastolic functions were normal.Laboratory data were within normal limits. .

Laboratory Parameters

In the COVID-19 group during illness and in the control group during the study, glucose, hemoglobin, creatinine, leukocyte, lymphocyte, sedimentation, dimer, fibrinogen, ferritin, C-reactive protein (CRP), and troponin levels were recorded.

COVID-19 had not been categorised as a variant of concern or a variant under investigation. The study duration was 6 months.

Ethical approval was obtained from the Ankara Keçiören Training and Research Hospital was received before starting the study (23.9.2020/2172). After receiving informed consent forms from the participants, a treadmill EST was applied according to the protocol described below.

Treadmill Exercise Stress Test

Tests were performed according to the Bruce protocol using the full vision 3017-TMX425 device. An estimated peak heart rate was 220-patient age. Even if 85% of the estimated maximum heart rate was reached, exercise was continued until symptoms appeared. The patient's symptoms, exercise workload in metabolic equivalents (Mets) were recorded during each phase and recovery phase. Heart rate was measured at each minute of exercise, at maximum exercise, and at 1-5 min (in 1 min increment) while standing after the start of the recovery period. Criteria for completion were fatigue, chest pain, severe palpitations, and/or an increase in heart rate above the maximum predicted for patient age. After peak exercise, participants walked during a two-minute cool-down period. At the end of exercise, heart rate recovery (HRR) was defined as maximum heart rate minus heart rate within the specified period, which represented the decrease in heart rate.

Exercise testing was performed, analyzed, and reported using a computerized database and a standard protocol. In this study, all tests were terminated due to fatigue.

During the exercise test, baseline resting heart rate (HR_1 ,expressed as beats/min), systolic and diastolic baseline blood pressure [SBP_1 and DBP_1(mmHg) respectively], maximum blood pressures [SBP_{max} and DBP_{max}(mmHg) respectively], and blood pressure changes (ΔSBP, ΔDBP) were recorded.

Exercise Stress Test Parameters

Duke score: [exercise time (min)-5ST change (mm)-4^{th} angina index], exercise time (min), ST change (mm), exercise capacity or workload (Mets), maximum reached the heart rate (MrHR) expressed as (% beats/min), distance walked (m), maximum oxygen consumption amount (VO_{2max}) expressed as mL/kg/min=15 x (HR_{max}/HR_{rest}), double product or rate pressure product (RPP) expressed as mmHg/min/1000=max HR x max SBP/1000, and HRR_1 expressed as beat/min=heart rate decreasing in 1 min (normal: >12) during the recovery period were used.

Statistical Analysis

Data analysis was performed using the IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). Whether the distributions of continuous variables were normal or not was determined by Kolmogorov-Smirnov test. Categorical data were given as number (n) and percentage (%), while quantitative data were given as mean ± standard deviation and median (25^{th}-75^{th}) percentile. Pearson's chi-square test was used for the analysis of categorical data unless otherwise stated. A Student's t-test was used when the mean differences between groups were compared, and the Mann-Whitney U test was used to compare continuous variables for which otherwise parametric test assumptions were not met.

The effects of independent variables that may affect the ETS parameters that differ between the COVID-19 and control groups were examined using the "Linear regression and General Linear Model Analysis methods". The ETS parameters are defined as the dependent variables. Independent variables for which we observed

significant effects in different groups were determined. The direction and magnitude of the relationship between each independent variable and the dependent variable within groups were determined by B (Constant), and beta (coefficient of variation). The degree of influence of the independent variable within the group was determined by F (analysis of variance value) and R^2 (Partial Eta Sq) values. P-values were considered significant at the 0.05 level.

Results

Baseline Characteristics

The COVID-19 group was not hospitalized, had the disease of a median of six months [interquartile range (IQR): 5-7 months] before the study period started, and recovery from illness was a median of 13.5 (IQR: 12-14) days. Equally, in both groups, one-half of the patients (n=80) had atypical chest pain, one-quarter (n=40) had fatigue, and one-quarter (n=40) had palpitations. The main characteristics of the groups are shown in Table 1.

Between the two groups, mean baseline HR_1 was higher in the COVID-19 group. Differences between baseline SBP_1, DBP_1 and SBP_{max}, DBP_{max} in the COVID-19 and control groups, respectively, were found. The amount of blood pressure change (Δ) was higher in the COVID-19 group.

No differences between the two groups in terms of Duke score, exercise duration, ST change, and exercise capacity were found.

Differences between the groups in terms of MrHR, distance walked, VO_{2max}, RPP, and HRR_1 were found as shown in Table 2.

Gender Differences

In men (COVID-19 versus control), differences, such as ΔSBP (mmHg): (35.3±12 versus 28±15.8; p=0.022), DBP_{max} (mmHg: 80.7±9.8 versus 73.2±8; p=0.000), ΔDBP [mmHg: 4 (1-6.7) versus 0 (-3-5); p=0.004], no difference in terms of EST parameters were observed.

In women, differences were determined as HR_1 (beats/min) 85.9±11.6 versus 79.4±10.1 p=0.009, SBP_{max} (mmHg): 147 (142.7-154) versus 141 (135.5-151); p=0.018, DBP_1 (mmHg): 77.3±5.8 versus 72.6±7.9; p=0.003, DBP_{max} (mmHg): 78.4±6.6 versus 72.1±7.8;

Table 1. Comparison of baseline characteristics in coronavirus disease-2019 (COVID-19) and control groups

Variables	COVID-19 group (n=80)*	Control group (n=80)	p-value
Age (years) median (IQR)	37,5 (34-40)	35 (32-41)	0.502†
Female/male (n,%)	40/40 (50%)	40/40 (50%)	1‡
BMI (kg/m²)	27 (25.6-28.6)	26.5 (24.6-28.8)	0.152†
Glucose (mg/dL)	88.5 (83-95)	86.5 (83-94)	0.623†
Hemoglobin (gm/dL)	12.6 (11.7-13.5)	13.05 (11.7-13.5)	0.597†
Creatinine (gm/dL)	0.84 (0.68-0.87)	0.82 (0.71-0.88)	0.882†
Leukocytes (μL)	9.4 (8.5-9.8)	5.6 (4.8-6.3)	0.000†
Lymphocyte (μL)	1.2 (0.8-1.3)	1.3 (1.2-1.4)	0.000†
Sedimentation (mm/h)	16 (13.2-24)	5.3 (4.5-6.3)	0.000†
D-dimer (ng/mL)	321 (256-420)	180 (140-217)	0.000†
Fibrinogen (mg/dL)	323.5 (250-387)	230 (210-286)	0.000†
Ferritin (ng/mL)	269.5 (212-335)	123.5 (110-132)	0.000†
CRP (mg/L)	12.4 (9.5-13.5)	5.4 (3.4-6.5)	0.000†
hsTroponin (ng/mL)	7.6 (5.8-9.4)	3.2 (2.3-5.3)	0.000†

**COVID group blood was taken during the infection,*
BMI: Body mass index, IOR: Interquartile range, †Mann-Whitney U test, ‡Chi-square test, CRP: C-reactive protein

p=0.000, MrHR (% beats/min): 89.5 (86.2-92) versus 87 (85-90); p=0.009, exercise capacity (Mets): 13.5 (10.2-13.5) versus 13.2 (10.2-13.5); p=0.307, distance walked (m): 694±130 versus 817±166; p=0.000, RPP (mmHg/min/1000): 17.800 (14.525-20.625) versus 12.400 (11.340-18.300); p=0.01, HRR_1 (beats/min): 25.8±5.29 versus 28.9±5.19; p=0.009.

Regression and General Linear Model Analyses

In the regression and general linear model analyses, troponin in men and sedimentation in women was shown to have negative effects on walking distance in the COVID-19 group, while initial SBP had a positive effect in women in the control group.

It was determined that troponin in the COVID-19 group and especially creatinine in the control group, had a negative effect on HRR_1.

CRP and maximum SBP were found to have a negative effect on HR_{max} in women with COVID-19.

The independent variables that had a significant effect on the EST parameters and their explanation rates on the dependent variable are given in Table 3. In both groups, chest pain, positivity test, and insufficient test efforts were not detected during EST.

Ventricular extrasystole [8 (10%) versus 6 (7.5)] and atrial extrasystole [10 (12.5%) versus 8 (10%)] were detected in both the COVID-19 and control groups. Exercise test positivity was not detected, so we could not make the decision of coronary angiography.

Discussion

In this study, in patients aged 30-50 years with no known systemic disease and who had recovered from a mild COVID-19 infection, the mean HR at the beginning

Table 2. Comparison of heart rate, blood pressure, exercise stress testing parameters of COVID-19 and control groups

Heart rate-blood pressure parameters	COVID-19 group (n=80)	Control group (n=80)	p-value
HR_1 (beat/min)	86.3±12	82.4±11.7	**0.04***
SBP_1 (mmHg)	120 (114-125)	117 (110-124)	**0.045†**
SBP_{max}	150 (145-154)	145 (138-152)	**0.008†**
ΔSBP	33.5±11.9	28.2±14.6	**0.013†**
DBP_1 (mmHg)	77.5 (72-80)	73 (68-80)	**0.003†**
DBP_{max}	79.5±8.4	73.2±8	**0.000***
ΔDBP	2 (-1-6)	0 (-3-5)	**0.019†**
EST parameters			
Duke score	7.6 (6.4-8.7)	8.1 (6.5-8.8)	0.527†
Exercise time(min)	9.1±1.5	9.1±1.7	0.816*
ST change (mm)	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.336†
Exercise capacity (METs)	10.2 (10.2-13.5)	13.5 (10.2-13.5)	0.171†
Mr. heart rate (%)	89.2±3.5	87.8±3.2	**0.012***
Distance walked (m)	672±148	731±192	**0.031***
$VO2_{max}$ (mL/kg/min)	36 (35.7-47.3)	35.7 (35.7-47.3)	**0.013†**
RPP (mmHg/min/1000)	18.250 (14.570-21.225)	15.800 (11.550-19.500)	**0.027†**
HRR (beat/min)	27.3±5.5	29.5±6.3	**0.024***

**Mean ± standard deviation *Student's t-test (Std), †Mann-Whitney U test, Δ: Change*
†median (interquartile range)
HR_1: Initial heart rate, max: Maximum, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, METs: Metabolic equivalents, MrHR: Maximum reached heart rate, Mr: Maximum reached $VO2_{max}$: Maximum oxygen consumption, RPP: Rate pressure product HRR1: Heart rate recovery, COVID-19: Coronavirus disease-2019

of the exercise test, the MrHR, the SBP/DBP and their changes upon effort, VO_{2max}, and RPP were higher than in the control group.

No differences between the two groups in terms of exercise duration, exercise capacity, and ST change were detected. The distance walked and the amount of HRR_1 were found to be less in the COVID-19 group. When compared with the control group, women in the COVID-19 group had greater MrHR, greater RPP, less distance walked, and less HRR_1. It was determined that women had more effective changes in EST parameters.

The fact that the lung CTs during the disease and radiographs during the study were normal in the COVID-19 group, thus caused us to move away from lung damage. When the absence of EST-positive patients due to ECG changes but with normal troponin values, absence of chest pain during exertion, and similar exercise durations are considered together, coronary and myocardial involvement that could explain the aforementioned complaints was not considered.

In the Bruce[11] protocol, exercise duration was associated with ventricular function. In these studies, the frequency of coronary disease decreased as the exercise duration increased in the ECG-positive test group[12]. In our study, the duration of exercise was found to be the same in both groups regardless of gender. The fact that the exercise capacity in the COVID-19 group was similar to that of the control group and that the heart rate increased with exercise are good indicators of cardiovascular disease[13-15]. However, the differences in heart rate and blood pressure changes suggest that there may be autonomic system involvement. An HRR_1 over 25 in the COVID-19 group may indicate that no significant autonomic imbalance exists; however, a lower HRR_1 decrease compared to the control group may indicate that this group does not have a good cardiovascular prognosis[16,17].

Table 3. Effects of independent variables on EST parameters

EST parameters	Group	n	Independent variables*	B†	95 CI%		Beta†	p-value	$R^{2‡}$
Distance walked (m)	**COVID-19, M**	40	Troponin	-21.79	-43.692	0.092	-0.303	**0.05**	0.186
	COVID-19, F	40	Sedimentation	-8.003	-15.081	-0.925	-0.390	**0.029**	0.228
			Ddimer	-0.495	-1.011	0.021	-0.347	**0.05**	0.175
	Control, F	40	Ddimer	-0.799	-1.568	-0.031	-0.430	**0.042**	0.175
			SBP_1	9.741	3.277	16.205	0.551	**0.005**	0.319
HRR1 (beat/min)	**COVID-19**	80	Troponin	-0.649	-1.151	-0.147	-0.304	**0.012**	0.100
	Control	80	Sedimentation	-0.696	-1.420	0.028	-0.249	**0.05**	0.058
			Creatinine	-14.42	-27.185	-1.669	-0.272	**0.027**	0.079
			HR_1	-0.131	-0.264	0.002	-0.243	**0.05**	0.061
MrHR (% beat/min)	**COVID-19, F**	40	CRP	-0.854	-1.535	-0.173	-0.597	**0.017**	0.264
			SBP_{max}	-0.199	-0.405	0.008	-0.456	**0.058**	0.233
	Control, F	40	Age	-0.223	-0.451	0.005	-0.358	**0.05**	0.164
			Fibrinogen	-0.018	-0.032	-0.003	-0.439	**0.017**	0.241
			SBP_{max}	0.122	-0.004	0.248	0.380	**0.05**	0.162
$VO2_{max}$ (mL/kg/min)	**COVID-19, M**	40	SBP_{max}	0.474	0.065	0.883	0.698	**0.026**	0.224
			DBP_{max}	0.559	-5.912	2.345	2.345	**0.046**	0.176
			HR_1	-0.289	-0.548	-0.036	-0.484	**0.021**	0.228
	Control, F	40	CRP	-1.54	-3.038	-0.051	-0.477	**0.043**	0.181

**CRP: C-reactive protein, SBP1: Baseline systolic blood pressure, HR1: Baseline heart rate, DBP1: Baseline diastolic blood pressure, SKB_{max}, DKB_{max}: Maximum systolic, diastolic blood pressure, COVID-19: Coronavirus disease-2019, M: Male, F: Female, MrHR: Maximum reached heart rate, CI: Confidence interval, †Linear regression, B: Constant, Beta: Coefficient of variation between dependent variable and independent variable, ‡General linear model, R^2 partial eta squared: Independent variable (within group) variance explanation rate (0.162:16.2%)*

COVID-19 can cause prolonged fatigue[1,18]. The decrease in the response of the heart muscle, which sometimes occurs after prolonged fatigue, may be manifested by a decrease in blood volume and accumulation of blood in the legs even after the situation returns to normal conditions. This phenomenon is called deconditioning[19]. Additionally, gender differences in the adaptation of innate and immune responses that influence the immunological response to pathogens can be found[20].

HRR_1 is defined as a reduction in heart rate, usually 1 min after cessation of exercise, and is an important indicator of all-cause mortality. HRR_1 is thought to indicate a reactivation of the parasympathetic nervous system with a reduction in the action of the sympathetic nervous system and possibly reduced circulating catecholamines[21]. It has been suggested that women have more parasympathetic impulses, less systolic volume, and lower cardiorespiratory condition than men. In one study, HRR was faster in women after exercise than in men. (4±1.1 beats per min, $p<0.001$)[22]. In our study, a decrease in heart rate was found in the normal range (>12) but less (25.8±5.29 versus 28.9±5.19; $p=0.009$) in women in the COVID-19 than in the control group.

RPP is the product of SBP and HR and is an indicator of myocardial oxygen consumption. SBP and HR have also been shown to be predictors of in-hospital mortality and long-term mortality[23,24]. HR and SBP are indicators of autonomic nervous system (ONS) functioning. An increase in RPP during stress indicates that ONS functions as normal buffering and good coronary perfusion[25]. However, conflicting studies on the efficacy of RPP[26,27]. Gender-related differences in RPP between the ages 35 and 54 were found to be low[28]. In our study, RPP was found to be higher in women with corona compared with the control group, and no change was found in men (18.690±4606 versus 17.963±4584; $p=0.481$).

The autonomic nervous system regulates functions that we do unconsciously control, such as HR, BP, sweating, and body temperature. COVID-19 may also increase sympathetic activity through changes in blood gases, angiotensin-converting enzyme imbalance, immune/inflammatory factors, or emotional distress apart from the contribution of comorbid diseases[29]. The potential immune/inflammatory effects of a sympathetic/parasympathetic imbalance may also play a role in the pathophysiology of COVID-19[30].

It has been found that prolonged or chronic COVID-19 affects women more than men, particularly in autonomic cardiovascular areas, such as orthostatic intolerance and inappropriate tachycardia. Most females have up to one-third less skeletal muscle mass than males and therefore have a less powerful "muscle pump" when standing have smaller hearts and are more prone to pelvic venous pooling[31,32]. Autoimmunity disorders, which are more common in women, may affect post-COVID-19 autonomic dysfunction and gender preference[33]. These probable reasons and increased sympathetic activity may partly explain the low distance traveled in women, high RPP, and low HRR.

Linear correlations were found between some parameters of heart rate variability (HRV) and laboratory indices in COVID-19 patients. It has been reported that in severe patients without improvement in HRV parameters, a longer time is needed to clear the virus and recovery[34]. In our study, the effects of troponin, sedimentation, and CRP on some parameters of the EST were found in some subgroups, as shown in Table 3.

Ten minutes after standing up, an increase in heart rate of more than 30 beats per minute for more than three months without orthostatic hypotension is defined as another sign of autonomic dysfunction under the name of long COVID-19 postural orthostatic tachycardia in those who have had COVID-19[35].

One year post-COVID, a study conducted in 22 patients with complaints similar to our study concluded that cardiac functions were not affected and complaints could not be attributed to underlying COVID-19 related cardiac disease[36].

In our study, it is possible that the higher blood pressure and heart HR values upon exertion in the COVID-19 group

were due to more increased sympathetic tone and less decrease in peripheral resistance. An abnormal elevation in blood BP during EST and recovery has been shown to be associated with an increased risk of developing hypertension in both men and women[37]. The reason for the relationship between hypertension and COVID-19 is still unclear[38].

Study Limitations

It is difficult to say whether the pre-test exercise capacities would be similar even if the participants' age ranges, BMI values, and weekly effort levels are the same. Chest radiographs were evaluated as normal. The sensitivity of chest radiographs in the diagnosis of COVID-19 (>11 days) has been reported as 79%[39].

Conclusion

As a result, after an average of six months, the effort capacity of those who had mild COVID-19 was similar to that of the control group. However, it was thought that the effect of exertion on HR and BP might be greater, and therefore, the autonomic system might be affected for a long time recovering from COVID-19. More comprehensive studies are needed for the reproducibility and clear analysis of the results.

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Ethics

Ethics Committee Approval: Ethical approval was received before starting the study from the Ankara Keçiören Training and Research Hospital Ministry of Health (approval no: 23.09.2020/2172, date: 11.06.2020).

Informed Consent: Informed consent form was obtained from the patients.

Peer-review: Externally peer-reviewed.

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