Cardiorespiratory Abnormalities in Patients Recovering from Coronavirus Disease 2019

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Background: A large number of patients around the world are recovering from coronavirus disease 2019 (COVID-19); many of them report persistence of symptoms. The aim of this study was to test pulmonary, cardiovascular, and peripheral responses to exercise in patients recovering from COVID-19.

Methods: Patients who recovered from COVID-19 were prospectively evaluated using a combined anatomic and functional assessment. All patients underwent clinical examination, laboratory tests, and combined stress echocardiography and cardiopulmonary exercise testing. Left ventricular volumes, ejection fraction, stroke volume, heart rate, E/e′ ratio, right ventricular function, oxygen consumption (V_{O_2}), lung volumes, ventilatory efficiency, oxygen saturation, and muscle oxygen extraction were measured in all effort stages and compared with values in historical control subjects.

Results: A total of 71 patients were assessed 90.6 ± 26 days after the onset of COVID-19 symptoms. Only 23 (33%) were asymptomatic. The most common symptoms were fatigue (34%), muscle weakness or pain (27%), and dyspnea (22%). V_{O_2} was lower among post-COVID-19 patients compared with control subjects ($P = .03$, group-by-time interaction $P = .007$). Reduction in peak V_{O_2} was due to a combination of chronotropic incompetence (75% of post-COVID-19 patients vs 8% of control subjects, $P < .0001$) and an insufficient increase in stroke volume during exercise ($P = .0007$, group-by-time interaction $P = .03$). Stroke volume limitation was mostly explained by diminished increase in left ventricular end-diastolic volume ($P = .10$, group-by-time interaction $P = .03$) and insufficient increase in ejection fraction ($P = .01$, group-by-time interaction $P = .01$). Post-COVID-19 patients had higher peripheral oxygen extraction ($P = .004$) and did not have significantly different respiratory and gas exchange parameters compared with control subjects.

Conclusions: Patients recovering from COVID-19 have symptoms associated with objective reduction in peak V_{O_2}. The mechanism of this reduction is complex and mainly involves a combination of attenuated heart rate and stroke volume reserve. (J Am Soc Echocardiogr 2021;34:1273-84.)

Keywords: COVID-19, Long COVID, Post-COVID, Cardiopulmonary exercise test, Stress echocardiography

The majority of publications concerning cardiovascular manifestations of coronavirus disease 2019 (COVID-19) deal with the acute infection.[1-3] In contrast, less is known about the long-term cardiovascular consequences of COVID-19. Researchers have described a high incidence of fatigue, dyspnea, muscle pain, chest pain, and neuropsychiatric symptoms among patients recovered from COVID-19.[4-6]

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Other researchers in Germany, China, the United States, and the United Kingdom have described the extent of cardiac injury in recovered patients.[7-11] However, these studies involved only cardiac imaging performed at rest.[7-11] Impaired exercise capacity in patients recovering from COVID-19 may be multifactorial. Apart from ventilatory or gas exchange abnormalities secondary to residual pulmonary disease, attenuated increase in stroke volume (SV) could be the result of left ventricular (LV) dysfunction due to myocarditis or cytokine dysregulation,[12-14] right ventricular (RV) dysfunction induced by pulmonary hypertension, and diastolic dysfunction.[1,15] Other possible causes include chronotropic incompetence and reduced peripheral oxygen extraction due to direct viral damage or deconditioning secondary to muscle disuse. None of these previous studies included any form of objective functional assessment. Given the large number of patients recuperating from COVID-19, functional studies to help delineate the cause of post-COVID-19 symptoms are needed.

Cardiopulmonary exercise testing (CPET) is the gold standard for the assessment of integrative exercise responses involving the pulmonary, cardiovascular, and skeletal muscle systems.[16,17] CPET objectively

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categorizes physical effort during predefined activity levels (rest, anaerobic threshold, and peak exercise), providing factual assessment of pulmonary and cardiac function, as well as estimations of peripheral vascular resistance during all exercise stages. Furthermore, as COVID-19 severe enough to require medical attention manifests with lung injury[18] and often has cardiac complications,[1] we also performed echocardiography at rest. Our CPET protocol also included echocardiography performed during anaerobic threshold and maximal exercise.[19,20] We previously showed that these combined examinations allow accurate discrimination of different causes of effort intolerance, by recognizing ventilatory limitation, abnormal gas exchange, limited SV reserve, chronotropic incompetence, and/or reduced peripheral muscular oxygen extraction.[19,20] Two previous small studies of patients recovered from COVID-19 who underwent CPET showed mostly ventilatory and presumed muscular limitations to exercise.[21,22] A study of pulmonary function and 6-min walking testing in patients recovering from acute COVID-19 showed worse diffusion capacity and lung volumes and shorter walking distances in patients recovering from severe acute disease compared with mild disease.[23] We aimed to test whether pulmonary, cardiovascular, and peripheral responses to exercise in patients recovered from COVID-19 are abnormal and correlate with residual symptoms.

METHODS

Study Protocol

We prospectively evaluated individuals recovering from COVID-19 in a dedicated outpatient clinic. All patients had well-established diagnoses of COVID-19, survived the acute event, and met the World Health Organization criteria for discontinuation of quarantine. The inclusion criteria were all patients with COVID-19 who were evaluated in the emergency department at the Tel Aviv Medical Center, including those requiring hospitalization and those subsequently treated as outpatients, ranging from mild to critical acute disease according to the National Institutes of Health definitions (mild: signs and symptoms not including shortness of breath or dyspnea on exertion, without abnormal imaging findings; moderate: evidence of lower respiratory disease during clinical assessment or imaging, with oxygen saturation ≥ 94% on room air; severe: oxygen saturation < 94% on room air, respiratory rate > 30 breaths/min, partial pressure of oxygen/fraction of inspired oxygen < 300 mm Hg, or lung infiltrates > 50%; critical: acute respiratory distress syndrome, septic shock, and multiorgan involvement). The only exclusion criteria

were inability to provide informed consent and refusal to participate in the study. All patients underwent comprehensive medical assessment with detailed history, physical examination, and blood tests. We specifically inquired about symptoms related to effort intolerance. Dyspnea was defined as the subjective experience of breathing discomfort comprising qualitatively distinct sensations varying in intensity. We also performed a comprehensive cardiopulmonary evaluation that included (1) rest echocardiography, (2) lung spirometry, and (3) combined CPET and exercise echocardiography to objectively discriminate among the mechanisms responsible for different symptoms. The study was approved by the institutional review board (0574-16-TLV). All patients provided informed consent. Patients recovered from COVID-19 were compared with 35 control subjects. The control subjects were selected using a frequency-matching approach from a pool of 76 patients who performed combined CPET and stress echocardiography, using the same protocol, demonstrating normal peak oxygen consumption (VO_2) at our institution. The predefined baseline matching parameters were age (within 5 years), height (within 10 cm), weight (within 10 kg), exact gender, and prevalence of ischemic heart disease, diabetes, and hypertension. The selection process produced groups with comparable determinants of peak VO_2 and balanced comorbidities. The groups were different in size, as there were no set couples of matched patients. Subanalyses included comparing patients recovered from COVID-19 who had persistent symptoms (fatigue, dyspnea, or muscle weakness or pain) with patients who were free of these symptoms and comparing patients recovered from COVID-19 according to their acute disease severity. The CPET and echocardiographic results of patients recovered from COVID-19 were also compared with well-characterized reference values.[16,17,24]

Rest Echocardiography

Echocardiography was performed, as recommended,[24-26] by cardiologists with expertise in echocardiographic acquisition and interpretation and using the same equipment for all patients (CX 50; Philips Medical Systems, Best, the Netherlands).

Exercise Protocol

A symptom-limited graded-ramp bicycle exercise test was performed in the semisupine position on a tilting, dedicated, microprocessor-controlled eddy current brake stress echocardiographic cycle ergometer (Ergoselect 1000 L; CareFusion, Houten, the Netherlands; Supplemental Methods). Forced vital capacity and forced expiratory volume in 1 sec were measured before exercise. Maximal voluntary ventilation was calculated by multiplying forced expiratory volume in 1 sec by 35.[17] We estimated expected peak VO_2 on the basis of age, height, and weight, with an equation pertaining to bicycle testing.[16,17,27] Breath-by-breath minute ventilation (VE), carbon dioxide production (VCO_2), their ratio (VE/VCO_2, representing ventilatory efficiency), and VO_2 were measured using a Medical Graphics metabolic cart (ZAN, nSpire Health, Longmont, CO). The oxygen pulse was calculated as VO_2/heart rate (HR).[28] Anaerobic threshold was determined manually using the modified V-slope method.[17] Arterial blood oxygen saturation was measured using noninvasive pulse oximetry. The intensity of dyspnea or fatigue was assessed using the modified Borg scale. The exercise-effort quality was assessed by respiratory exchange ratio (RER) at peak exercise. A 12-lead electrocardiogram was monitored continuously, and HR and blood pressure were measured at rest and every minute during

exercise. HR reserve was calculated as the change in HR from rest to peak exercise, divided by the difference between age-predicted maximal HR and resting HR. Chronotropic incompetence was defined as failure to achieve ≥80% of HR reserve during exercise.[29] In patients treated with β-blockers, chronotropic incompetence was defined as failure to achieve >62% of HR reserve.[30]

Stress Echocardiographic Testing

Echocardiographic images were obtained concurrently with breath-by-breath gas exchange measurements at rest, immediately after reaching a stable RER of ≥1.00 (anaerobic threshold), and at peak effort by a single cardiologist (Y.S.).[19,20] Data collected at each time period included LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV ejection fraction (LVEF), SV, peak E-wave velocity, e′ in the septal and lateral mitral annulus, tricuspid annular plane systolic excursion (TAPSE), and RV S′. LV diameters and volumes and LVEF were measured as recommended using two-dimensional echocardiography.[25] Forward SV was calculated from LV outflow tract Doppler with subsequent calculation of cardiac output and index.

A-V_{O_2} difference, which represents oxygen extraction by the muscles, was calculated by using the Fick equation at each activity level.[31,32] As there are no reference values for LVEDV, LVESV, and A-V_{O_2} difference in response to exercise, we selected the cutoffs for these parameters on the basis of our previous work and corroborated

the cutoffs in our control cohort.[33] Cutoff values for RV stress echocardiographic parameters were derived from the recommendations of the European Association of Cardiovascular Imaging.[34]

All test results were analyzed by an experienced physician who was unaware of participant group or symptomatology (Y.T.) (Supplemental Methods).

Interobserver and Intraobserver Variability

Interobserver variability for LVEDV and LVESV was determined by a second independent blinded observer who measured these variables in 15 randomly selected patients. Intraobserver variability was determined by having the observer who measured the data in all patients remeasure the echocardiographic variables in 15 patients 1 week later. Interobserver and intraobserver variability was assessed using the intraclass correlation coefficient and the within-subject coefficient of variation (calculated as the ratio of the SD of the measurement difference to the mean value of all measurements). An intraclass correlation coefficient > 0.85 was used as a measure of good variability and positive reproducibility for the measurements.

Statistical Analysis

Descriptive results are expressed as mean ± SD for continuous variables and as percentages for categorical variables. The distributions of continuous variables were tested to ensure that normality assumptions were fulfilled. Group comparisons used analysis of variance, the Wilcoxon test, the Fisher exact test, or the χ^2 test, as appropriate. To compare sample means with known reference values, a one-sample t test was used. For comparison with the control group, or between subgroups, and to avoid bias incurred by multiple comparisons, we used repeated-measures linear-model analysis to define the within-group effect for each parameter over time, the between-group differences over time, and the group-by-time interactions. To analyze independent determinants of exercise tolerance, the primary end point was peak V_{O_2}. Stepwise multivariate linear regression models were constructed (with peak V_{O_2} as the dependent variable
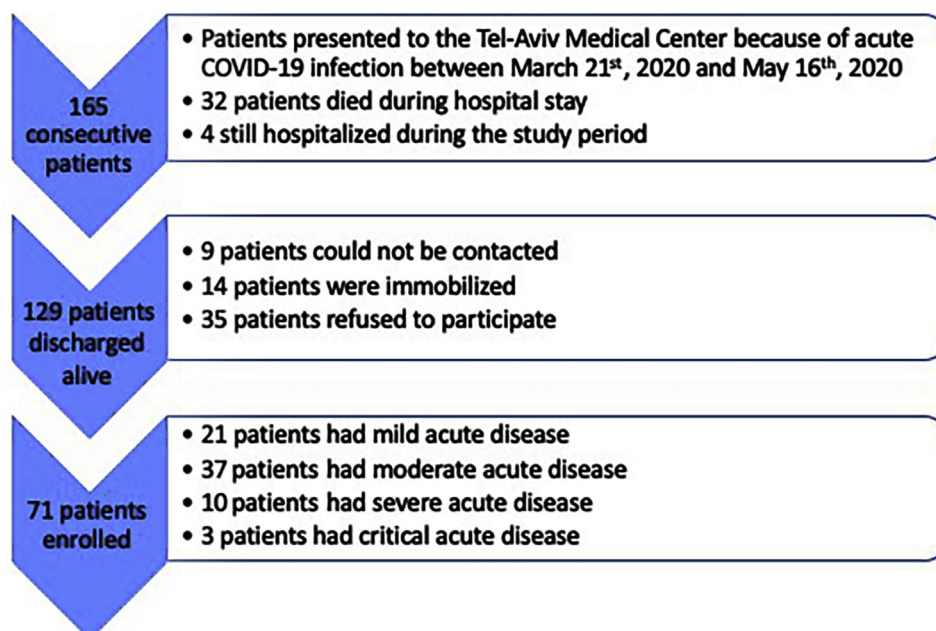

Figure 1 Flowchart of study design.

Table 1 Patient characteristics

Variable	Post-COVID-19 (n = 71)	Control (n = 35)	P
Clinical characteristics			
Age, y	52.6 ± 16	53.6 ± 16	NS
Sex, male	47 (66)	24 (68)	NS
Height, m	1.71 ± 0.1	1.70 ± 0.1	NS
Weight, kg	82 ± 21	79.6 ± 15	NS
Body mass index, kg/m²	27.5 ± 6	27.4 ± 5	NS
Body mass index ≥ 35 kg/m²	4 (5.5)	3 (8.5)	NS
Hypertension	30 (43)	16 (46)	NS
Diabetes	9 (13)	5 (14)	NS
Heart failure	1 (1.5)	0 (0)	NS
Ischemic heart disease	3 (4)	1 (3)	NS
Lung disease, any	11 (15)	2 (6)	.15
Chronic obstructive pulmonary disease	6 (8)	1 (3)	NS
Smoking	8 (11)	1 (3)	.14
Bronchodilator inhalers	8 (11)	1 (3)	.14
β-blockers	8 (11)	5 (15)	NS
Furosemide	0 (0)	1 (3)	NS
Angiotensin-converting enzyme inhibitor	10 (14)	5 (14)	NS
Symptoms and signs			
Fatigue	24 (34)	9 (26)	NS
Muscle weakness/pain	19 (27)	0 (0)	NA
Dyspnea	16 (22)	26 (74)	<.0001
Chest pain	13 (18)	0 (0)	NA
Memory loss	12 (17)	0 (0)	NA
Anxiety	12 (17)	0 (0)	NA
Anosmia	9 (12)	0 (0)	NA
Any symptom	48 (67)	29 (83)	NS
Lung crackles	1 (1)	0 (0)	NA
Leg edema	6 (9)	0 (0)	NA
Laboratory evaluation			
Hemoglobin, g/dL	13.9 ± 1.3	13.9 ± 1.3	NS
White blood cells, $10^3/\mu L$	7.5 ± 1.9	NA	NA
Lymphocytes, $10^3/\mu L$	2.2 ± 0.8	NA	NA
Platelets, $10^3/\mu L$	231 ± 74	NA	NA
Glucose, mg/dL	98 ± 37	NA	NA
Troponin I, ng/L	11.4 ± 20	NA	NA
Brain natriuretic peptide, pg/mL	24.3 ± 19	NA	NA
D-dimer, mg/L	1.3 ± 0.7	NA	NA
C-reactive protein, mg/L	5.1 ± 13	NA	NA

(Continued)

Table 1 (Continued)

Variable	Post-COVID-19 (n = 71)	Control (n = 35)	P
Fibrinogen, mg/dL	318 ± 78	NA	NA
Ferritin, ng/mL	135 ± 167	NA	NA
Blood urea nitrogen, mg/dL	17.9 ± 6	NA	NA
Creatinine, mg/dL	0.9 ± 0.2	1.01 ± 0.2	NS
Bilirubin, mg/dL	0.6 ± 0.4	NA	NA
Aspartate aminotransferase, U/L	29.1 ± 29	NA	NA
Alanine transaminase, U/L	29.3 ± 41	NA	NA
Albumin, g/L	44.7 ± 3	NA	NA
Right ventricle			
Pulmonary acceleration time, msec	117 ± 24	NA	NA
Right atrial pressure, mm Hg	6.0 ± 2	5.1 ± 1	.002
RV end-diastolic area, cm²	19.5 ± 5.5	20.5 ± 6.5	NS
RV end-systolic area, cm²	11.3 ± 3.7	11.3 ± 3.5	NS
RV fractional area change, %	46.7 ± 8	44.3 ± 9	NS
TAPSE, cm	2.3 ± 0.4	NA	NA
RV S′, cm/sec	10.4 ± 2	NA	NA
Respiratory evaluation			
FVC, L	3.9 ± 1.4	3.7 ± 1.2	.06
FVC, % predicted	103.7 ± 31	94.9 ± 15	.06
FEV_1, L	3.2 ± 1.0	3.3 ± 1.1	NS
FEV_1, % predicted	100.8 ± 23	98.8 ± 17.4	NS
$FEV_1 < 70\%$ predicted	3 (4)	0 (0)	NS
FEV_1/FVC ratio	79.6 ± 10	85.5 ± 9	.006
FEV_1/FVC, % predicted	99.0 ± 12	109.5 ± 11.1	.002
CPET parameters			
Anaerobic threshold, L/min	0.97 ± 0.27	1.06 ± 0.44	.32
Anaerobic threshold, mL/min/kg	12.3 ± 3.6	15.4 ± 5.7	.02
Oxygen uptake efficiency slope, mL/min	1,690 ± 787	NA	NA
Oxygen uptake efficiency slope < 85% expected	34 (48)	NA	NA
VE/Vo_2 at anaerobic threshold	24.9 ± 4	27.7 ± 5	.01
Minimal oxygen saturation, %	97.8 ± 1.5	98.1 ± 1.3	NS

(Continued)

Table 1 (*Continued*)

Variable	Post-COVID-19 (n = 71)	Control (n = 35)	P
Breathing reserve < 15	3 (4)	0 (0)	NS
Peak breathing frequency ≥ 50 breaths/min	5 (7)	1 (3)	NS
Abnormal VE/Vco$_2$ at anaerobic threshold	4 (5)	1 (3)	NS
Abnormal oxygen saturation	6 (8)	0 (0)	.09
Chronotropic incompetence	53 (75)	3 (8)	<.0001
Duration of exercise, min	10.2 (8.2–12.3)	8.0 (6.2–17.9)	NS
RER	1.15 ± 0.07	1.16 ± 0.15	.87

Data are expressed as mean ± SD, number (percentage), or median (interquartile range).
FEV$_1$, Forced expiratory volume in 1 sec; *FVC*, forced vital capacity; *NA*, not available.

and the different clinical, CPET, echocardiographic, or combined CPET and exercise echocardiographic variables as independent variables). To correct for possible overfitting of the model considering that there were only 71 subjects, we grouped the variables into clinical, laboratory, LV, RV, respiratory, and peripheral parameters. The first step was to select for each group all the variables with *P* values < .05 in a univariable analysis. In the second step, to detect multicollinearity, we used correlation factor analyses to determine if any pairs of predictor variables were highly correlated (correlation coefficient > 0.7) and therefore likely to result in multicollinearity. In the third step, in each subgroup, the variable with the lowest *P* value was chosen to be included in the analysis. Because of their known associations with peak Vo$_2$, we forced age and gender into all analyses. The final parameters included age, gender, troponin, HR, SV, TAPSE, and A-Vo$_2$ difference. All computations were performed using JMP for Windows version 9.0 (SAS Institute, Cary, NC).

RESULTS

We identified 165 consecutive adult patients who presented to the Tel Aviv Medical Center (between March 21, 2020, and May 16, 2020) for acute COVID-19 (Figure 1). Among these patients, 32 died during the hospitalization and four were still hospitalized. From the remaining 129 patients discharged alive, nine patients could not be contacted, 14 patients were immobilized and debilitated at baseline, and 35 patients refused to attend the post-COVID-19 clinic. All 71 patients who recovered from COVID-19 and were prospectively evaluated between June 15 and August 1, 2020, at our clinic and agreed to participate in the present study represent the study group (mean age, 52.6 ± 16 years [range: 18–80 years]; 47 men [66%]). During the acute phase, 21 patients (30%) had mild disease, 37 (52%) had moderate disease, 10 (14%) had severe disease, and three (4%) had critical disease (two required prolonged mechanical ventilation and one required venoarterial extracorporeal membrane oxygenation). Troponin was elevated in 22 patients (31%) during

the acute infection. In 10 patients, it was >4 times higher than the upper limit of normal, in three patients 3 to 4 times higher, in two patients 2 to 3 times higher, and in the remaining patients only marginally elevated. Troponin remained elevated in only two patients (3%) at the time of follow-up (*P* < .0001). In both patients, troponin was only marginally elevated (less than twice the upper limit of normal). Before acute infection, 50 patients (71%) exercised at least once a week, while 21 (29%) did not perform any type of routine exercise. Patients were assessed a mean of 90.6 ± 26 days after the onset of their first COVID-19 symptoms. At the time of evaluation, none of the patients had fever or any signs or symptoms of acute illness. However, only 23 (33%) were completely free of symptoms, while 48 (67%) had one or more of the following symptoms: fatigue (34%), muscle weakness or pain (27%), dyspnea (22%), chest pain (18%), anxiety (17%), and anosmia (12%). The mean time after acute illness did not differ between patients with and those without symptoms (88.8 ± 20 vs 88.6 ± 24 days, *P* = .98). Symptomatic status was independent of time after acute illness (hazard ratio: 1.00; 95% CI: 0.96–1.04; *P* = .98). Baseline characteristics of the study cohort are presented in Table 1. Baseline characteristics of patients who did not undergo the post-COVID-19 evaluation are shown in Supplemental Table 1. These patients were older and had higher rates of diabetes and heart failure.

The 35 historical control patients were matched for main clinical characteristics and comorbidities (age, gender, weight, height, hypertension, diabetes). Baseline characteristics and echocardiographic and CPET parameters of the study cohort compared with control subjects are shown in Table 1.

Combined CPET and Stress Echocardiography

The results of CPET and stress echocardiography during different stages of exertion of the study cohort compared with control subjects are shown in Table 1, Table 2, and Figure 2. Post-COVID-19 patients reached a lower anaerobic threshold and lower peak Vo$_2$, with lower HR and oxygen pulse, compared with control subjects. They also had lower LVEDV, LVEF, SV, and cardiac output in all stages of exertion. A-Vo$_2$ difference was higher among the post-COVID-19 group. There was no significant difference in breathing rate, tidal volume, or VE/Vco$_2$ ratio. Importantly, 53 post-COVID-19 patients (75%), including eight patients treated with β-blockers, demonstrated obvious chronotropic incompetence, in contrast to three patients (8%) in the control group. RER in patients with and those without chronotropic incompetence was similar (1.16 ± 0.05 vs 1.15 ± 0.06, *P* = .23). The results of combined CPET and stress echocardiography for the study cohort compared with normal reference values are shown in Supplemental Table 2.

Recovery From Severe or Critical versus Mild or Moderate COVID-19

In comparison with patients who had mild or moderate disease during the acute infection, patients with histories of severe or critical acute disease had higher LVEDVs, lower LVEFs, and poorer gas exchange parameters (worse saturation response and higher VE/Vco$_2$ and VE/Vo$_2$ ratios at anaerobic threshold; Supplemental Table 3).

Subgroup Analysis on the Basis of Symptoms

Patients who reported ongoing symptoms were compared with asymptomatic patients (Table 3). Patients who were symptomatic

Table 2 Combined CPET and stress echocardiographic parameters during different stages of exertion compared with historical control subjects

Measurement	Baseline	Anaerobic threshold	Maximal effort	P value, between groups	P value, within groups	P value, group-by-time interaction
Vo₂						
Vo₂, L/min						
COVID-19 recovery	0.4 ± 0.13	0.97 ± 0.27	1.6 ± 0.5	.03	<.0001	.007
Control	0.4 ± 0.1	1.01 ± 0.4	2.24 ± 0.9			
Oxygen pulse, mL/beat						
COVID-19 recovery	5.5 ± 1.7	9.6 ± 2.5	12.4 ± 4.1	.60	<.0001	.03
Control	5.1 ± 1.5	9.3 ± 2.7	14.6 ± 5.3			
HR, beats/min						
COVID-19 recovery	70.1 ± 11	101.8 ± 14	135.9 ± 23	.006	<.0001	.87
Control	78.4 ± 10	112.0 ± 20	150.3 ± 21			
Left ventricle						
LVEDV, mL						
COVID-19 recovery	93.8 ± 23	111.0 ± 27	107.9 ± 26	.10	<.0001	.03
Control	112.7 ± 43	131.5 ± 44	124.1 ± 41			
LVESV, mL						
COVID-19 recovery	35.0 ± 18	36.9 ± 28	31.2 ± 20	.82	.99	.07
Control	38.1 ± 25	30.1 ± 19	31.0 ± 24			
LVEF, %						
COVID-19 recovery	64.7 ± 14	66.9 ± 20	71.8 ± 16	.01	.01	.01
Control	65.3 ± 12	78.2 ± 21	73.4 ± 21			
Hemodynamics						
SV, mL						
COVID-19 recovery	60.6 ± 13	75.6 ± 17	72.9 ± 16	.0007	<.0001	.03
Control	74.4 ± 20	98.4 ± 22	92.9 ± 2			
Cardiac output, L/min						
COVID-19 recovery	4.4 ± 1.0	7.8 ± 1.9	9.8 ± 2.7	<.0001	<.0001	.005
Control	5.8 ± 1.3	11.6 ± 3.9	14.0 ± 4.2			
E-wave velocity, cm/sec						
COVID-19 recovery	62.9 ± 14	80.4 ± 16	90.8 ± 19	.06	<.0001	.0002
Control	59.2 ± 14	97.5 ± 28	121.5 ± 21			
e′ septal, cm/sec						
COVID-19 recovery	7.6 ± 2.4	10.1 ± 2.6	11.8 ± 3.5	.16	<.0001	.01
Control	7.3 ± 3.3	12.2 ± 6.5	12.0 ± 3.5			
E/e′ septal ratio						
COVID-19 recovery	8.7 ± 3.0	8.4 ± 2.4	8.2 ± 2.6	.48	.23	.27
Control	9.3 ± 3.9	8.9 ± 2.7	8.0 ± 2.5			
Ventilation and gas exchange						
Breathing rate, breaths/min						
COVID-19 recovery	20.7 ± 5.3	25.4 ± 5.0	37.1 ± 7.2	.90	<.0001	.90
Control	20.3 ± 3.9	25.4 ± 6.2	36.7 ± 9.2			

(*Continued*)

Table 2 (*Continued*)

Measurement	Baseline	Anaerobic threshold	Maximal effort	P value, between groups	P value, within groups	P value, group-by-time interaction
Tidal volume, L						
COVID-19 recovery	0.65 ± 0.16	1.1 ± 0.3	1.7 ± 0.5	.34	<.0001	.04
Control	0.58 ± 0.08	1.3 ± 0.7	1.9 ± 0.8			
VE/V$_{CO_2}$ ratio						
COVID-19 recovery	30.0 ± 9	27.6 ± 3	29.8 ± 3	.46	.02	.10
Control	28.9 ± 4	29.6 ± 5	30.7 ± 3			
Peripheral extraction						
A-V$_{O_2}$ difference, L/L						
COVID-19 recovery	0.09 ± 0.03	0.13 ± 0.03	0.18 ± 0.05	.004	<.0001	.20
Control	0.08 ± 0.03	0.11 ± 0.03	0.13 ± 0.04			

Data are expressed as mean ± SD.

had smaller left ventricles and higher LVEFs. There was no difference in peak V$_{O_2}$, HR, SV, cardiac output, E/e′ ratio, tidal volume, VE/V$_{CO_2}$ ratio, or A-V$_{O_2}$ difference. Supplemental Figures 1 to 3 depict the differences between patients with specific symptoms and those without these symptoms. Patients with dyspnea (Supplemental Figure 1) had attenuated changes in SV, HR, cardiac output, and lung tidal volume and increased VE/V$_{CO_2}$ ratio (decreased ventilatory efficiency). Patients with fatigue (Supplemental Figure 2) had attenuated changes in HR but otherwise were not different from patients without fatigue in any of the combined CPET and exercise echocardiographic parameters. Patients with muscle weakness or pain (Supplemental Figure 3) did not differ from patients without these symptoms.

Univariate and Multivariate Analyses

Clinical parameters associated with reduced peak V$_{O_2}$ were older age, male sex, lower weight, lower hemoglobin, and higher troponin and creatinine at the time of presentation to the post–acute COVID-19 care clinic. The only rest echocardiographic or respiratory parameters associated with reduced peak V$_{O_2}$ were those related to smaller LV size (LVEDV or LV diameter), larger RV size (RV end-diastolic area), poorer RV function (lower TAPSE), or low lung volume (forced expiratory volume in 1 sec, forced vital capacity). Stepwise multivariable analyses of predictors of peak V$_{O_2}$ are shown in Supplemental Table 4.

Interobserver and Intraobserver Variability

Comparison of inter- and intraobserver variability for LVEDV and LVESV showed good agreement between measurements (Supplemental Table 5).

DISCUSSION

This is the first study to evaluate patients recovered from COVID-19 with combined stress echocardiography and CPET. Assessing patients in separate stages of effort, including anaerobic threshold, is more relevant to everyday activity than peak exercise alone. Our study represents an att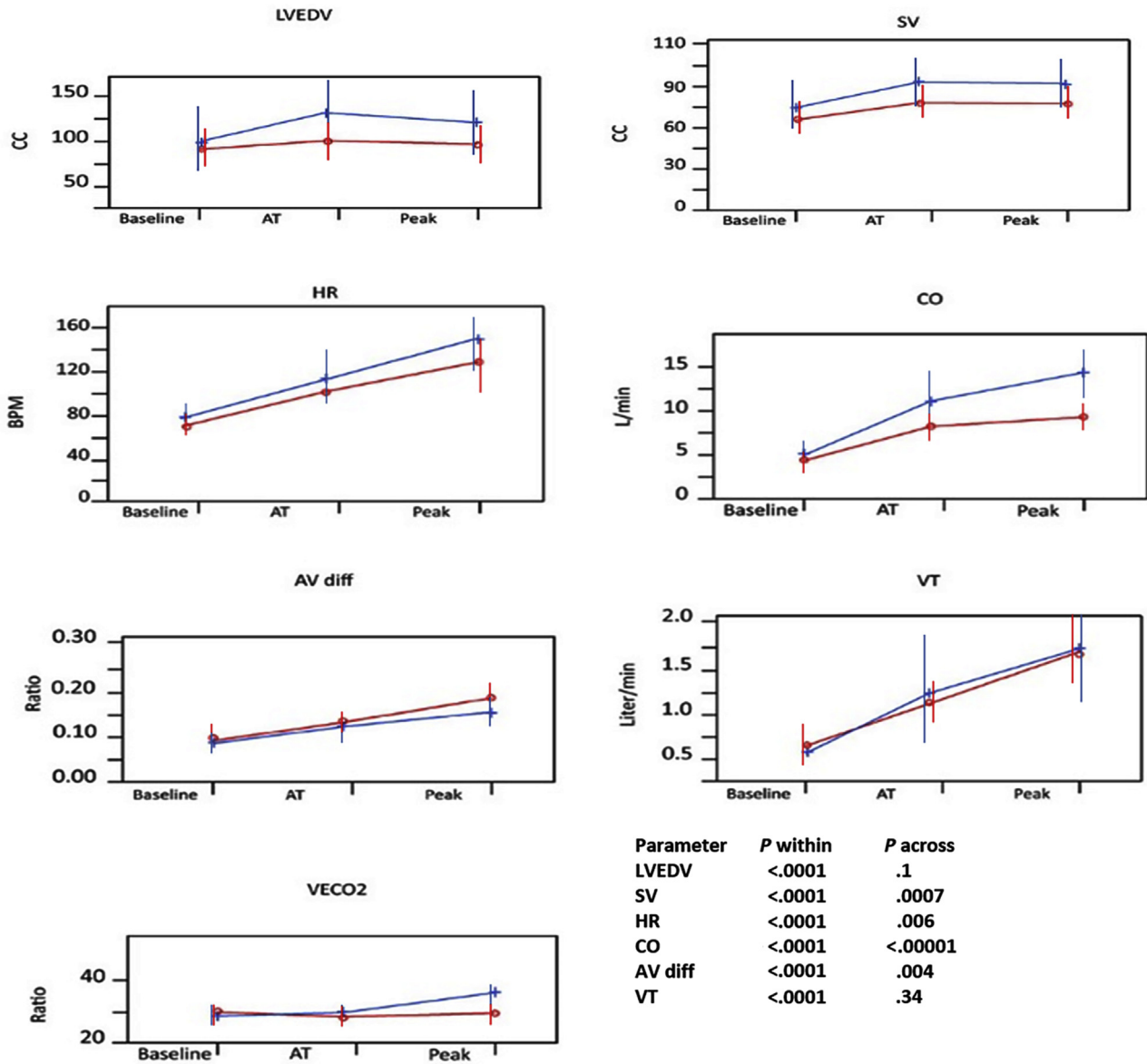empt to objectively explain the functional impairment reported by many patients recovering from COVID-19. Our major findings are as follows: (1) two thirds of the patients reported at least one residual symptom, similar to previous publications[4-6]; (2) abnormally low peak V$_{O_2}$ is common among patients recovering from COVID-19; (3) the mechanism of the reduction is a combination of chronotropic incompetence and attenuated SV reserve and is different according to specific symptoms; (4) severe gas exchange abnormalities and very limited breathing reserve are rather rare causes of effort intolerance; and (5) chronotropic incompetence, limited SV reserve, limited RV systolic reserve, and peripheral factors (low peak A-V$_{O_2}$ difference) each contributes independently to the reduced exercise capacity in patients recovering from COVID-19.

Chronotropic Incompetence

In patients recovering from COVID-19, peak-exercise HR was reduced and contributed to their limited exercise capacity. Interestingly, chronotropic incompetence was equally present in patients recovering from mild or moderate and severe or critical acute disease. Furthermore, chronotropic incompetence was specifically more common among patients reporting dyspnea and/or fatigue compared with patients free of these symptoms and was a strong independent predictor of peak V$_{O_2}$. Moreover, we found that chronotropic incompetence was not the consequence of reduced motivation during CPET (as demonstrated by RER). On the basis of the available data, it is not possible to determine why patients recovering from COVID-19 have chronotropic incompetence, so further research is necessary in this area.

Insufficient Increase in SV

Normally, SV increases during exercise until the anaerobic threshold, secondary to increases in LVEDV and contractility, both resulting from heightened adrenergic tone. Then, SV plateaus because of increased tachycardia and shortened filling time of the left ventricle.[20] Insufficient increase in SV during the initial stages of stress seen in post-COVID-19 patients compared with control subjects may be the result of either insufficient increase in LVEDV or a blunted increase in contractility. Although we cannot determine the exact mechanism responsible for this limitation, several explanations exist: (1) Reduced LV contractile reserve (Video 1; available at

Parameter	P within	P across
LVEDV	<.0001	.1
SV	<.0001	.0007
HR	<.0001	.006
CO	<.0001	<.00001
AV diff	<.0001	.004
VT	<.0001	.34

Figure 2 Baseline, anaerobic threshold (AT), and maximal CPET and stress echocardiography in patients recovering from COVID-19 (*red line*) and historical control subjects (*blue line*) for LVEDV, SV, HR, cardiac output (CO), arteriovenous oxygen (A-V_{O_2}) difference (AV diff), tidal volume (VT), and VE/V_{CO_2} ratio (VECO$_2$).

www.onlinejase.com). Acute COVID-19 can induce endothelialitis,[35] which may cause microvascular dysfunction resulting in LV contractile abnormalities. Microvascular dysfunction usually manifests with reduced maximal V_{O_2}, preserved anaerobic threshold, ST-segment abnormalities, and low peak oxygen pulse with failure of V_{O_2} and oxygen pulse to increase appropriately at the last phase of exercise, associated with decreasing SV and increasing A-V_{O_2} difference.[28] (2) Diastolic dysfunction with poor LV compliance and increased LV filling pressure. In our cohort, only one patient had an increase in E/e' ratio above 14 suggestive of increased LV filling pressure. (3) Reduced RV systolic reserve resulting in poor LV filling (Video 2; available at www.onlinejase.com). This was the case in eight patients in our cohort. RV dysfunction is well described among hospitalized patients with acute COVID-19[1,36] and may persist into recovery. (4) Severe dehydration or bleeding. None of the studied patients

had clinical or laboratory parameters to suggest either factor. (5) Insufficient recruitment of blood from the splanchnic vascular compartment, which has been historically termed "vasoregulatory asthenia"[33,34,37] (Video 3; available at www.onlinejase.com). We cannot exclude this etiology in our cohort. Autonomic dysregulation was not directly assessed in our study, but interestingly it can result in both chronotropic incompetence and abnormal blood flow distribution. It has been described in post-COVID-19 patients and may explain these two main abnormalities.[38-40]

Peripheral Factors

Peak A-V_{O_2} difference is an independent predictor of reduced exercise capacity. Surprisingly, patients recovering from COVID-19 had higher peak A-V_{O_2} difference than control subjects. As patients

Table 3 Combined CPET and stress echocardiographic parameters during different stages of exertion comparing symptomatic and asymptomatic patients who recovered from COVID-19

Measurement	Baseline	Anaerobic threshold	Maximal effort	P value, between groups	P value, within groups	P value, group-by-time interaction
V_{O_2}						
V_{O_2}, L/min						
Asymptomatic	0.38 ± 0.13	0.99 ± 0.26	1.7 ± 0.5	.46	<.0001	.54
Symptomatic	0.40 ± 0.13	0.92 ± 0.22	1.5 ± 0.5			
Oxygen pulse, mL/beat						
Asymptomatic	5.1 ± 1.9	10.0 ± 2.6	12.5 ± 3.5	.76	<.0001	.65
Symptomatic	5.1 ± 1.5	9.2 ± 2.4	12.2 ± 4.5			
HR, beats/min						
Asymptomatic	70.9 ± 11	99.7 ± 12	136.5 ± 19	.77	<.0001	.84
Symptomatic	73.8 ± 13	101.7 ± 14	133.1 ± 22			
Left ventricle						
LVEDV, mL						
Asymptomatic	98.1 ± 26	114.7 ± 29	112.1 ± 28	.05	<.0001	.88
Symptomatic	90.6 ± 23	107.8 ± 27	104.0 ± 26			
LVESV, mL						
Asymptomatic	37.2 ± 23	43.2 ± 29	35.9 ± 25	.03	.001	.68
Symptomatic	32.9 ± 19	33.6 ± 28	28.3 ± 24			
LVEF, %						
Asymptomatic	64.5 ± 15	63.2 ± 20	69.7 ± 17	.008	.0008	.82
Symptomatic	65.8 ± 14	68.5 ± 28	75.2 ± 23			
Hemodynamics						
E-wave velocity, cm/sec						
Asymptomatic	59.6 ± 13	81.0 ± 14	94.3 ± 12	.69	<.0001	.27
Symptomatic	63.6 ± 14	80.6 ± 18	89.3 ± 22			
e′ septal, cm/sec						
Asymptomatic	7.7 ± 2	10.2 ± 2	12.3 ± 4	.27	<.0001	.17
Symptomatic	7.3 ± 2	10.2 ± 3	11.6 ± 3			
E/e′ septal ratio						
Asymptomatic	8.2 ± 3	8.5 ± 2	8.5 ± 3	.33	.56	.37
Symptomatic	9.2 ± 3	8.5 ± 3	8.1 ± 3			
SV, mL						
Asymptomatic	60.1 ± 12	76.5 ± 17	73.9 ± 15	.56	<.0001	.88
Symptomatic	57.7 ± 11	75.5 ± 18	71.7 ± 16			
Cardiac output, L/min						
Asymptomatic	4.4 ± 1.1	7.7 ± 1.7	10.0 ± 2	.88	<.0001	.83
Symptomatic	4.2 ± 0.9	7.8 ± 2.0	9.5 ± 3			
Ventilation and gas exchange						
Breathing rate, breaths/min						
Asymptomatic	20.1 ± 4	24.5 ± 5	35.0 ± 7	.57	<.0001	.33
Symptomatic	20.8 ± 6	25.3 ± 5	37.7 ± 7			

(Continued)

Table 3 (*Continued*)

Measurement	Baseline	Anaerobic threshold	Maximal effort	P value, between groups	P value, within groups	P value, group-by-time interaction
Tidal volume, L						
Asymptomatic	0.64 ± 0.17	1.12 ± 0.3	1.76 ± 0.5	.83	<.0001	.73
Symptomatic	0.66 ± 0.15	1.10 ± 0.3	1.65 ± 0.4			
VE/V$_{CO_2}$ ratio						
Asymptomatic	33.0 ± 4	26.7 ± 2.3	28.9 ± 2.7	.73	<.0001	.07
Symptomatic	28.9 ± 4	28.4 ± 4.2	30.5 ± 4.0			
Peripheral extraction						
A-V$_{O_2}$ difference, L/L						
Asymptomatic	0.09 ± 0.02	0.13 ± 0.03	0.17 ± 0.03	.91	<.0001	.28
Symptomatic	0.09 ± 0.03	0.12 ± 0.02	0.18 ± 0.06			

Data are expressed as mean ± SD.

recovering from COVID-19 had reduced peak V_{O_2} compared with control subjects, the increase in peak A-V_{O_2} difference suggests that patients recovering from COVID-19 attempt to compensate for reduced cardiac output by increasing peripheral muscle oxygen extraction, resulting in increased peak A-V_{O_2} difference, and that reduced peak V_{O_2} is not merely the result of long-lasting deconditioning. This contrasts with the conclusions of a prior study of 10 post-COVID-19 patients with persistent dyspnea who underwent CPET.[22] In that study, eight patients were found to have abnormally low peak V_{O_2} (<85% of predicted), but only one had a cardiac limitation and two had ventilatory limitations. The authors concluded that metabolic limitation and muscular deficiency were the likely etiology in the rest of the patients. We show that a cardiac limitation is more likely than a peripheral muscular limitation.

Ventilatory and Gas Exchange Abnormalities

Acute COVID-19 causes respiratory illness ranging from mild upper respiratory disease to severe pneumonia. Surprisingly, we found that during the recovery phase, baseline respiratory parameters were normal in the majority of patients, and limited breathing reserve was the limiting factor for effort in only three patients (4%). Severe abnormal gas exchange was also rare. Nevertheless, as opposed to hemodynamic parameters, ventilatory and gas exchange abnormalities were more common in patients recovering from severe or critical compared with mild or moderate acute disease. During exercise, elevated breathing rate, increased VE/V$_{CO_2}$, and low oxygen saturation were notable only in patients recovering from severe or critical acute infection, probably reflecting residual pulmonary damage. Similar findings were found in a study of 28 post-COVID-19 patients who underwent CPET, in which eight patients were found to have elevated VE/V$_{CO_2}$, reflecting an exercise ventilatory inefficiency and related to lower HR recovery.[21] In a study of 57 post-COVID-19 patients who underwent pulmonary function and 6-min walk tests, the patients were found to have impaired diffusion capacity and lower lung volumes. Those with histories of severe infection, compared with those with nonsevere infection, had a higher incidence of these abnormalities, as well as shorter 6-min walk distances.[23]

Subgroup Analysis on the Basis of Symptoms

We show how patients with specific symptoms compared with those free of those symptoms. Patients with dyspnea were found to have various cardiac and respiratory abnormalities in response to exercise, while patients presenting with fatigue presented mostly with attenuated HR response. Patients with muscle weakness or pain did not have significantly different CPET parameters compared with those without these symptoms. As a whole, symptomatic patients did not have significant differences in peak V_{O_2} and other CPET parameters compared with asymptomatic patients. This could be explained by the fact that many survivors of COVID-19 continue to report different psychological and emotional difficulties,[41,42] which can also present with physical symptoms, without objective limitations.

Study Limitations

The present analysis was performed at a single point in time, about 3 months following COVID-19 acute infection, and it is unknown whether the abnormalities identified will translate into long-term abnormalities. We report that peak HR is blunted in patients recovered from COVID-19, but we cannot exclude the possibility that the continued effects of β-blockers or mild ventilatory limitations may have influenced the blunted HR response. Nevertheless, the results were unchanged when adjustments were performed for long-term β-blocker use, and very low breathing reserve was a very rare cause of effort limitation in our cohort. Our imaging protocol was performed in the semisupine position, which generates a somewhat different hemodynamic response than the more commonly used treadmill exercise. SV and cardiac output measurements may have been underestimated or overestimated because of the technical challenge of acquiring echocardiographic images during exercise. However, this technique has been used successfully and validated against radionuclide angiography and Fick SV with reported excellent day-to-day reproducibility and intraobserver and interobserver variability.[31] A-V_{O_2} difference was not independently measured but was calculated using the Fick equation as V_{O_2}/cardiac output.[31,32] The number of patients who had severe or critical acute disease was small, resulting in a lack of power to detect clinically significant differences in peak V_{O_2} compared with patients with mild or moderate acute disease. It is possible that a larger cohort of such patients

would yield a stronger association between acute disease severity and different exercise abnormalities. Selection bias was inherent to this study. First, we included only patients who required emergency department evaluation during acute COVID-19. Second, 20% of patients died during their acute illness. Last, among patients who were discharged alive, a considerable number of patients could not perform CPET because of immobilization or did not agree to participate. We present a cohort of limited size. As matching our cohort to historical data may introduce potential unknown confounders, the differences in CPET and stress echocardiographic parameters between patients recovering from COVID-19 and the control group should be interpreted cautiously.

CONCLUSION

Most patients recovering from COVID-19 report ongoing symptoms and exhibit significant objective reduction in effort capacity. The mechanism of this reduction is complex and mainly involves a combination of attenuated HR and SV reserve.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2021.08.022.

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SUPPLEMENTAL METHODS

Rest Echocardiography

Measurements of mitral inflow included the peak early filling (E-wave) and late diastolic filling (A-wave) velocities and E/A ratio. Early diastolic mitral septal and lateral annular velocities (e′) were measured in the apical four-chamber view.[1] Left atrial volume was calculated using the biplane area-length method at end-systole. From four-chamber views encompassing the entire right ventricle, end-systolic and end-diastolic RV areas and the tricuspid annulus were measured. Apart from qualitative grading, RV function was evaluated by TAPSE, systolic tricuspid lateral annular velocity (RV S′), and fractional area change.[2,3] Hemodynamic right-sided assessment included measurements of the pulmonic flow acceleration time, to assess pulmonary vascular resistance and assessment of right atrial pressure using the inferior vena cava method.[4]

Exercise Protocol

A symptom-limited graded-ramp bicycle exercise test was performed in the semisupine position on a tilting dedicated microprocessor-controlled eddy current brake stress echocardiographic cycle ergometer (Ergoselect 1000 L). Forced vital capacity and forced expiratory volume in 1 sec were measured before exercise. Maximal voluntary ventilation was calculated by multiplying forced expiratory volume in 1 sec by 35.[5] We estimated expected peak V_{O_2} on the basis of age, height, and weight.[5,6] We then calculated the workload necessary to reach the patient's estimated peak V_{O_2} in 8 to 12 min. The protocol included 3 min of unloaded pedaling, symptom-limited ramp-graded exercise, and 2 min of recovery. Breath-by-breath VE, V_{CO_2}, their ratio (VE/V_{CO_2}), and V_{O_2} were measured using a Medical Graphics metabolic cart (ZAN). Calibration was done before each test. Peak V_{O_2} was the highest averaged 30-sec V_{O_2} during exercise and was expressed as absolute peak V_{O_2} and the ratio of measured peak V_{O_2} to expected V_{O_2} by age, sex, and height.[5,6] The oxygen pulse was calculated as V_{O_2}/HR. VE/V_{CO_2} at anaerobic threshold was defined as the lowest immediately after anaerobic threshold and before the onset of ventilatory compensation for exercise-induced lactic acidosis and was expressed as absolute nadir VE/V_{CO_2}. Anaerobic threshold was determined manually using the modified V-slope method.[5] V_{CO_2} was plotted against V_{O_2}. A line parallel to the line of identity was drawn through V_{CO_2} versus V_{O_2} points during the incremental phase of the exercise test. The point at which V_{CO_2} departed from the line (began to increase more rapidly than V_{O_2}) was taken as the V-slope anaerobic threshold. Arterial blood oxygen saturation was measured using noninvasive pulse oximetry. Quality of exercise effort was assessed by respiratory RER (ratio of V_{CO_2} to V_{O_2}) at peak exercise. A 12-lead electrocardiogram was monitored continuously, and HR and blood pressure were measured at rest and every minute during exercise. β-Blockers were left unchanged.

Exercise Echocardiographic Testing

Echocardiographic images were obtained concurrently with breath-by-breath gas exchange measurements, at rest, immediately after reaching a stable RER of ≥1.00 (anaerobic threshold) and at peak effort by a single cardiologist (Y.S.).[7,8] Data collected at each time period included LVEDV, LVESV, LVEF, SV, peak E velocity, e′ in the septal and lateral mitral annulus, TAPSE, and RV S′. LVEDV, LVESV, and LVEF were calculated on the basis of the Simpson apical four-chamber view.[7,8] Adequate images for evaluation of LV volumes were defined as a well-aligned left ventricle without apical foreshortening and with the ventricular endocardial contours well visualized for tracing. LV SV was calculated by multiplying LV outflow tract area at rest by the LV outflow tract velocity-time integral measured using pulsed-wave Doppler during each activity levels. E/e′ ratio was calculated at all effort stages to assess LV filling pressure. During sinus tachycardia, whenever merging of mitral E and A velocities or e′ and a′ occurred, whether to a single waveform (complete merging), or whether E and A waves could still be identified (incomplete merging), peak E-wave velocity, e′, and E/e′ ratio were measured using the methods of Nagueh et al.[9] and Sohn et al.[10] A-V_{O_2} difference was calculated by using the Fick equation as V_{O_2}/echocardiography-calculated cardiac output, at each activity level.[11,12] All exercise echocardiograms were analyzed by an experienced physician trained in quantitative analyses who was unaware of participant group or condition (Y.T.).

SUPPLEMENTAL RESULTS

Comparison with Reference Values

ΔLVEDV, ΔLVEF, and ΔSV were attenuated in 49%, 30%, and 30% of patients recovering from COVID-19, compared with normal values.[5,6,13] The insufficient increase in HR and SV resulted in a cardiac output response to exercise that was lower than normal in 69% of the post-COVID-19 patients. The attenuated cardiac output response resulted in abnormal peak V_{O_2} in 59% of patients recovering from COVID-19 compared with normal reference values expected for age and sex (Supplemental Table 2).

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Supplemental Table 1 Characteristics of patients who were not assessed at the post-acute COVID-19 clinic

Variable	Study group (n = 71)	Patients who were not assessed at the post–acute COVID-19 clinic (n = 58)	P
Clinical characteristics			
Age, y	52.6 ± 16	63.5 ± 19	.02
Sex, male	47 (66)	32 (55)	.20
Height, m	1.71 ± 0.1	1.67 ± 0.1	.04
Weight, kg	82 ± 21	73.9 ± 15	.03
Hypertension	30 (43)	33 (57)	.11
Diabetes	9 (13)	21 (36)	.002
Heart failure	1 (1.5)	6 (10)	.04
Ischemic heart disease	3 (4)	6 (14)	.17
Lung disease	11 (15)	12 (21)	.49
Smoking	8 (11)	11 (19)	.31
β-blockers	8 (11)	14 (24)	.32
Furosemide	0 (0)	5 (9)	.01
Angiotensin-converting enzyme inhibitor	10 (14)	10 (17)	.86

Data are expressed as mean ± SD or as number (percentage).

Supplemental Table 2 Combined CPET and stress echocardiographic parameters during different stages of exertion compared with normal values

Measurement	Baseline	AT	Maximal effort	P for trend	Threshold	Deviating n (%)
V_{O_2}						
V_{O_2}, L/min	0.4 ± 0.13	0.97 ± 0.27	1.6 ± 0.5	<.0001	Peak < 85% expected	42 (59)
V_{O_2}/kg, mL/min/kg	5.0 ± 1.7	12.3 ± 3.6	21.1 ± 6.1	<.0001	Peak < 85% expected	49 (69)
V_{O_2}/BMI, mL/min/(kg/m^2)	15.9 ± 4.8	35.8 ± 8.7	60.1 ± 17.2	<.0001	Peak < 85% expected	50 (70)
Oxygen pulse, mL/beat	5.5 ± 1.7	9.6 ± 2.5	12.4 ± 4.1	<.0001	Peak < 85% expected	13 (18)
HR, beats/min	70.1 ± 11	101.8 ± 14	135.9 ± 23	<.0001	<85% expected	53 (75)
Left ventricle						
LVEDV, mL	93.8 ± 23	111.0 ± 27	107.9 ± 26	<.0001	Maximum < 110 mL	35 (49)
LVESV, mL	35.0 ± 18	36.9 ± 28	31.2 ± 20	<.0001	Maximum < 20 mL	16 (23)
LVEF, %	64.7 ± 14	66.9 ± 20	71.8 ± 16	.001	Peak < 63%	21 (30)
Right ventricle						
RV S′, cm/sec	10.4 ± 2.0	12.8 ± 2.7	14.1 ± 3.2	<.0001	Peak < 10.5 cm/sec	8 (11)
TAPSE, cm	2.3 ± 0.4	2.5 ± 0.4	2.6 ± 0.4	<.0001	Peak < 1.9 cm	2 (3)
Hemodynamics						
E-wave velocity, cm/sec	62.9 ± 14	80.4 ± 16	90.8 ± 19	<.0001	0.91–1.1	0 (0)
e′ septal, cm/sec	7.6 ± 2.4	10.1 ± 2.6	11.8 ± 3.5	<.0001	12.4–14.1	37 (52)
e′ lateral, cm/sec	9.2 ± 2.9	12.3 ± 3.0	13.9 ± 3.7	<.0001	16.1–18.1	53 (75)
E/e′ septal ratio	8.7 ± 3.0	8.4 ± 2.4	8.2 ± 2.6	.31	≥15	3 (4)
E/e′ lateral ratio	7.3 ± 2.5	6.9 ± 1.9	6.8 ± 1.9	.65	≥14	0 (0)
E/e′ average ratio	7.9 ± 2.6	7.5 ± 1.9	7.4 ± 1.9	.16	≥14	1 (1.5)
SV, mL	60.6 ± 13	75.6 ± 17	72.9 ± 16	<.0001	ΔSV < 20%	21 (30)
Cardiac output, L/min	4.4 ± 1.0	7.8 ± 1.9	9.8 ± 2.7	<.0001	Peak < 12.1 L/min	49 (69)
Ventilation						
Breathing rate, breaths/min	20.7 ± 5.3	25.4 ± 5.0	37.1 ± 7.2	<.0001	Peak > 50	5 (7)
Tidal volume, L	0.65 ± 0.16	1.1 ± 0.3	1.7 ± 0.5	<.0001	Peak < 85% expected	26 (37)
Breathing reserve, %	75.6 ± 7	63.4 ± 10	35.3 ± 13	<.0001	Peak < 15%	3 (4)
Gas exchange						
Oxygen saturation, %	97.8 ± 1.5	97.7 ± 1.8	97.6 ± 2.0	.58	<95%	6 (8)
V_E/V_{CO_2} ratio	30.0 ± 9	27.6 ± 3	29.8 ± 3	.03	AT > 34	4 (6)
V_E/V_{O_2} ratio	26.5 ± 8	24.9 ± 4	34.5 ± 5	<.0001	AT > 34	2 (3)
Peripheral extraction						
A-V_{O_2} difference, L/L	0.09 ± 0.03	0.13 ± 0.03	0.18 ± 0.05	<.0001	Peak < 0.1	2 (3)

Data are expressed as mean ± SD.
AT, Anaerobic threshold; *BMI*, body mass index.

Supplemental Table 3 Combined CPET and stress echocardiographic parameters during different stages of exertion according to acute disease severity

Measurement	Baseline	Anaerobic threshold	Maximal effort	P value, between groups	P value, within groups	P value, group-by-time interaction
V_{O_2}						
V_{O_2}, L/min						
Mild/moderate disease	0.40 ± 0.13	0.98 ± 0.3	1.7 ± 0.5	.32	<.0001	.35
Severe/critical disease	0.42 ± 0.15	0.89 ± 0.2	1.5 ± 0.5			
V_{O_2}/kg, mL/min/kg						
Mild/moderate disease	5.0 ± 1.8	12.6 ± 3.7	21.7 ± 6.2	.28	<.0001	.26
Severe/critical disease	5.1 ± 1.3	11.0 ± 2.8	18.3 ± 4.9			
V_{O_2}/BMI, mL/min/(kg/m^2)						
Mild/moderate disease	16.6 ± 4.9	37.4 ± 8.1	63.9 ± 15.3	.02	<.0001	.12
Severe/critical disease	13.9 ± 3.9	30.7 ± 9.0	49.0 ± 17.9			
Oxygen pulse, mL/beat						
Mild/moderate disease	5.5 ± 1.6	9.7 ± 2.6	12.6 ± 4.3	.63	<.0001	.82
Severe/critical disease	5.5 ± 1.8	9.3 ± 2.3	11.6 ± 3.2			
HR, beats/min						
Mild/moderate disease	72.8 ± 13	103.0 ± 13	137.3 ± 24	.17	<.0001	.54
Severe/critical disease	76.0 ± 11	95.5 ± 14	129.3 ± 16			
Left ventricle						
LVEDV, mL						
Mild/moderate disease	92.0 ± 20	108.4 ± 24	104.5 ± 24	.04	<.0001	.33
Severe/critical disease	102.4 ± 34	128.9 ± 32	126.4 ± 32			
LVESV, mL						
Mild/moderate disease	33.2 ± 18	34.0 ± 15	29.6 ± 13	.12	.0002	.65
Severe/critical disease	43.4 ± 25	55.9 ± 29	46.0 ± 24			
LVEF, %						
Mild/moderate disease	65.5 ± 14	68.8 ± 19	73.2 ± 16	.07	.001	.79
Severe/critical disease	59.3 ± 12	57.7 ± 18	64.6 ± 14			
Right ventricle						
RV S′, cm/sec						
Mild/moderate disease	10.5 ± 2	12.9 ± 3	14.3 ± 3	.27	<.0001	.20
Severe/critical disease	10.2 ± 2	12.3 ± 2	13.3 ± 2			
TAPSE, cm						
Mild/moderate disease	2.3 ± 0.4	2.5 ± 0.4	2.7 ± 0.4	.22	<.0001	.94
Severe/critical disease	2.2 ± 0.4	2.4 ± 0.3	2.5 ± 0.3			
Hemodynamics						
E-wave velocity, cm/sec						
Mild/moderate disease	63.7 ± 14	79.7 ± 16	91.6 ± 20	.47	<.0001	.07
Severe/critical disease	59.2 ± 11	73.4 ± 17	86.3 ± 13			
e′ septal, cm/sec						
Mild/moderate disease	7.7 ± 2	10.3 ± 3	11.9 ± 4	.65	<.0001	.68
Severe/critical disease	6.5 ± 2	9.5 ± 2	11.4 ± 3			
e′ lateral, cm/sec						

(Continued)

Supplemental Table 3 (*Continued*)

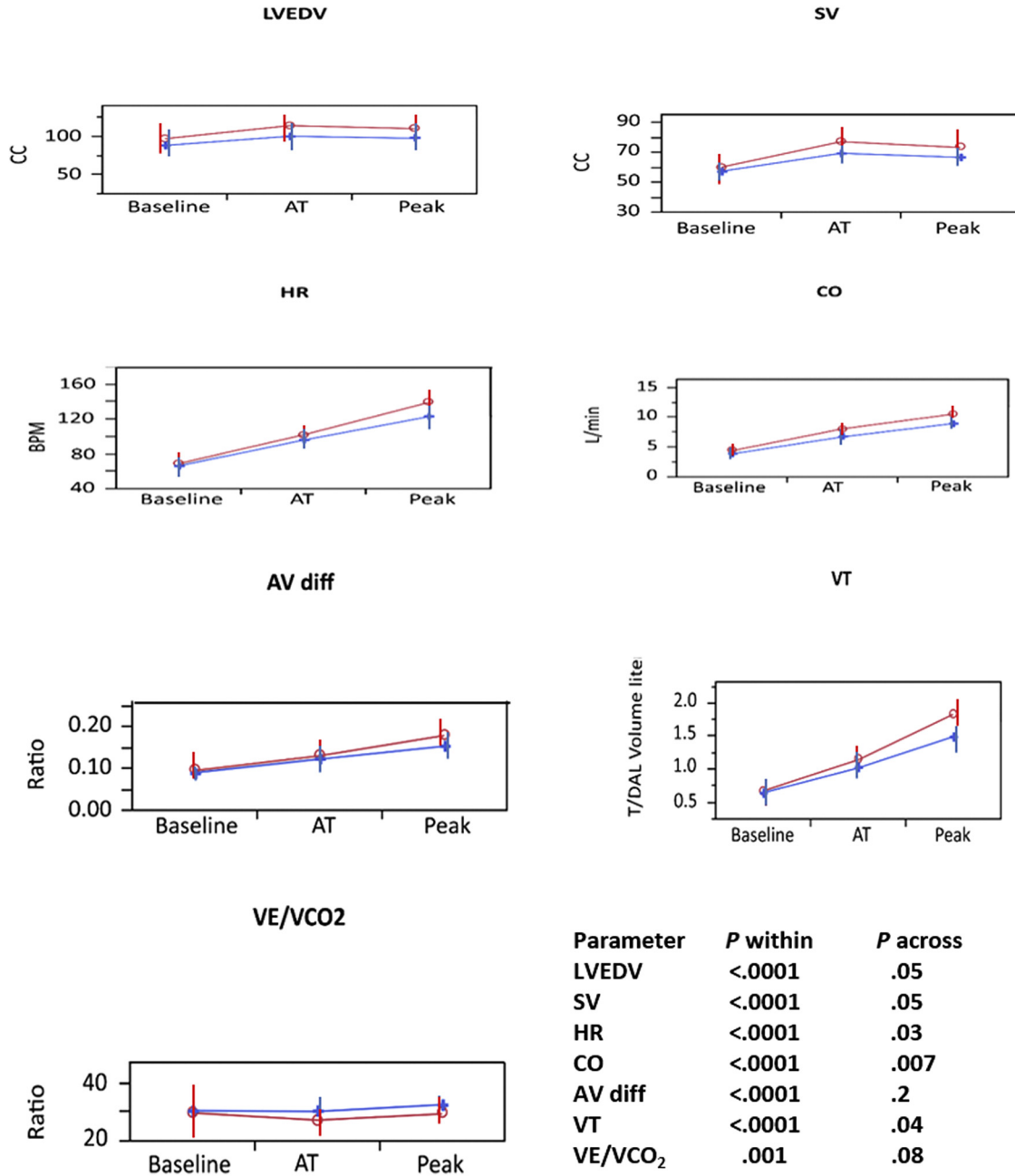| Measurement	Baseline	Anaerobic threshold	Maximal effort	P value, between groups	P value, within groups	P value, group-by-time interaction
Mild/moderate disease	9.4 ± 3	12.5 ± 3	14.3 ± 4	.04	<.0001	.41
Severe/critical disease	7.9 ± 2	11.4 ± 2	12.0 ± 2			
E/e′ septal ratio						
Mild/moderate disease	8.7 ± 3	8.4 ± 2	8.2 ± 3	.64	.47	.67
Severe/critical disease	8.9 ± 4	8.9 ± 2	8.0 ± 2			
E/e′ lateral ratio						
Mild/moderate disease	7.2 ± 2	6.8 ± 2	6.7 ± 2	.77	.98	.50
Severe/critical disease	7.5 ± 2	7.5 ± 2	7.4 ± 2			
E/e′ average ratio						
Mild/moderate disease	7.9 ± 2	7.4 ± 2	7.3 ± 2	.92	.58	.49
Severe/critical disease	8.2 ± 3	8.1 ± 2	7.6 ± 2			
SV, mL						
Mild/moderate disease	58.7 ± 11	75.0 ± 18	72.0 ± 17	.48	<.0001	.54
Severe/critical disease	59.1 ± 11	78.1 ± 15	77.5 ± 13			
Cardiac output, L/min						
Mild/moderate disease	4.2 ± 1.0	7.8 ± 1.9	9.8 ± 2.7	.86	<.0001	.63
Severe/critical disease	4.5 ± 1.1	7.6 ± 1.9	10.1 ± 2.5			
Ventilation						
Breathing rate, breaths/min						
Mild/moderate disease	20.0 ± 5	25.5 ± 4	36.3 ± 7	.03	<.0001	.04
Severe/critical disease	24.0 ± 6	24.5 ± 7	41.7 ± 5			
Tidal volume, L						
Mild/moderate disease	0.65 ± 0.16	1.1 ± 0.3	1.7 ± 0.5	.95	<.0001	.63
Severe/critical disease	0.64 ± 0.16	1.15 ± 0.4	1.6 ± 0.4			
Breathing reserve, %						
Mild/moderate disease	75.8 ± 7	63.8 ± 11	36.4 ± 11	.12	<.0001	.008
Severe/critical disease	74.2 ± 4	62.3 ± 10	30.8 ± 12			
Gas exchange						
Oxygen saturation, %						
Mild/moderate disease	98.0 ± 1	97.8 ± 2	97.8 ± 2	.04	.27	.30
Severe/critical disease	97.0 ± 2	97.1 ± 2	96.4 ± 3			
VE/V_{CO_2} ratio						
Mild/moderate disease	29.7 ± 9	27.3 ± 3	29.0 ± 3	.04	<.0001	.05
Severe/critical disease	31.2 ± 3	29.6 ± 4	33.2 ± 4			
VE/V_{O_2} ratio						
Mild/moderate disease	26.1 ± 5	24.5 ± 4	33.3 ± 5	.01	<.0001	.04
Severe/critical disease	28.0 ± 3	26.9 ± 4	39.8 ± 5			
Peripheral extraction						
$A\text{-}V_{O_2}$ difference, L/L						
Mild/moderate disease	0.09 ± 0.03	0.13 ± 0.03	0.18 ± 0.05	.19	<.0001	.39
Severe/critical disease	0.09 ± 0.03	0.12 ± 0.03	0.16 ± 0.05			

Data are expressed as mean ± SD.
BMI, Body mass index.

**Supplemental Table 4** Multivariable analysis: prediction of peak V_{O_2}

Variable	Rest	Peak exercise
	Coefficient $\pm$ SE	Coefficient $\pm$ SE
Age	-0.01 ± 0.02 ($P = .0003$)	NS
Gender, male	0.22 ± 0.15 ($P = .008$)	0.08 ± 0.05 ($P = .02$)
Troponin I	NS	NS
SV	0.02 ± 0.01 ($P = .0003$)	0.02 ± 0.001 ($P < .0001$)
TAPSE	0.27 ± 0.2 ($P = .02$)	0.12 ± 0.03 ($P = .03$)
HR	-0.01 ± 0.02 ($P = .0009$)	0.01 ± 0.001 ($P < .0001$)
A-V_{O_2} difference	6.6 ± 3.1 ($P = .009$)	7.0 ± 1.2 ($P = .0005$)
P	$<.0001$	$<.0001$
R^2	0.67	0.91

Supplemental Table 5 Inter- and intraobserver agreement

	Mean difference, mL	Intraclass correlation coefficient	Within-subject coefficient of variation, %
Intraobserver agreement			
LVEDV	0.8	0.93 ($P = .65$)	1.8
LVESV	1.5	0.89 ($P = .82$)	6.2
Interobserver agreement			
LVEDV	0.7	0.89 ($P = .81$)	2.5
LVESV	1.0	0.85 ($P = .83$)	7.5

Parameter	P within	P across
LVEDV	<.0001	.05
SV	<.0001	.05
HR	<.0001	.03
CO	<.0001	.007
AV diff	<.0001	.2
VT	<.0001	.04
VE/VCO$_2$	.001	.08

Supplemental Figure 1 Baseline, anaerobic threshold (AT), and maximal CPET and stress echocardiography in patients recovering from COVID-19 with dyspnea (*blue line*) or without dyspnea (*red line*) for LVEDV, SV, HR, cardiac output (CO), A-V$_{O_2}$ difference (AV diff), tidal volume (VT), and VE/V$_{CO_2}$ ratio. Note that patients with dyspnea had lower LVEDV, SV, HR, cardiac output, and VT and marginally higher VE/V$_{CO_2}$ ratio.
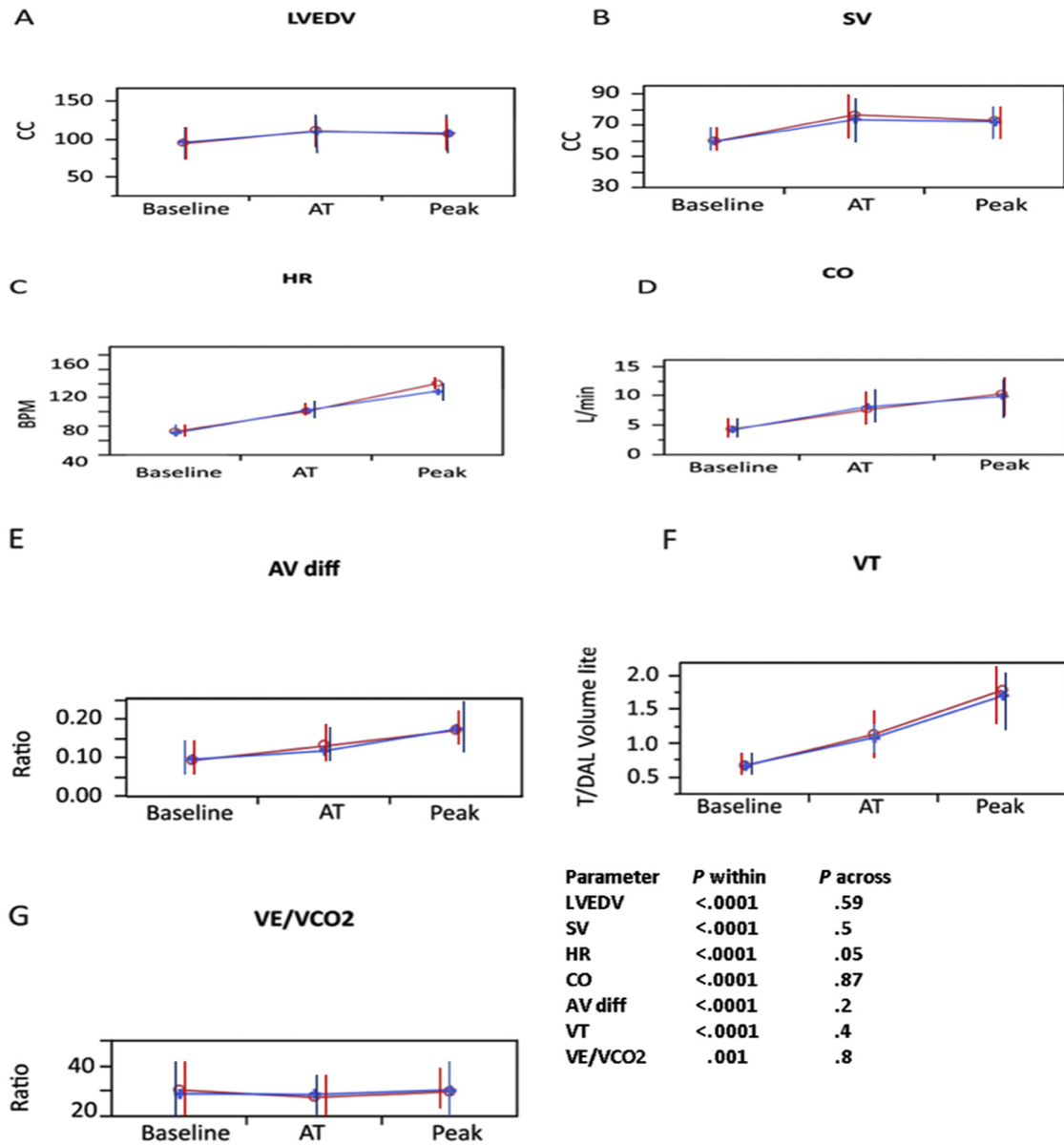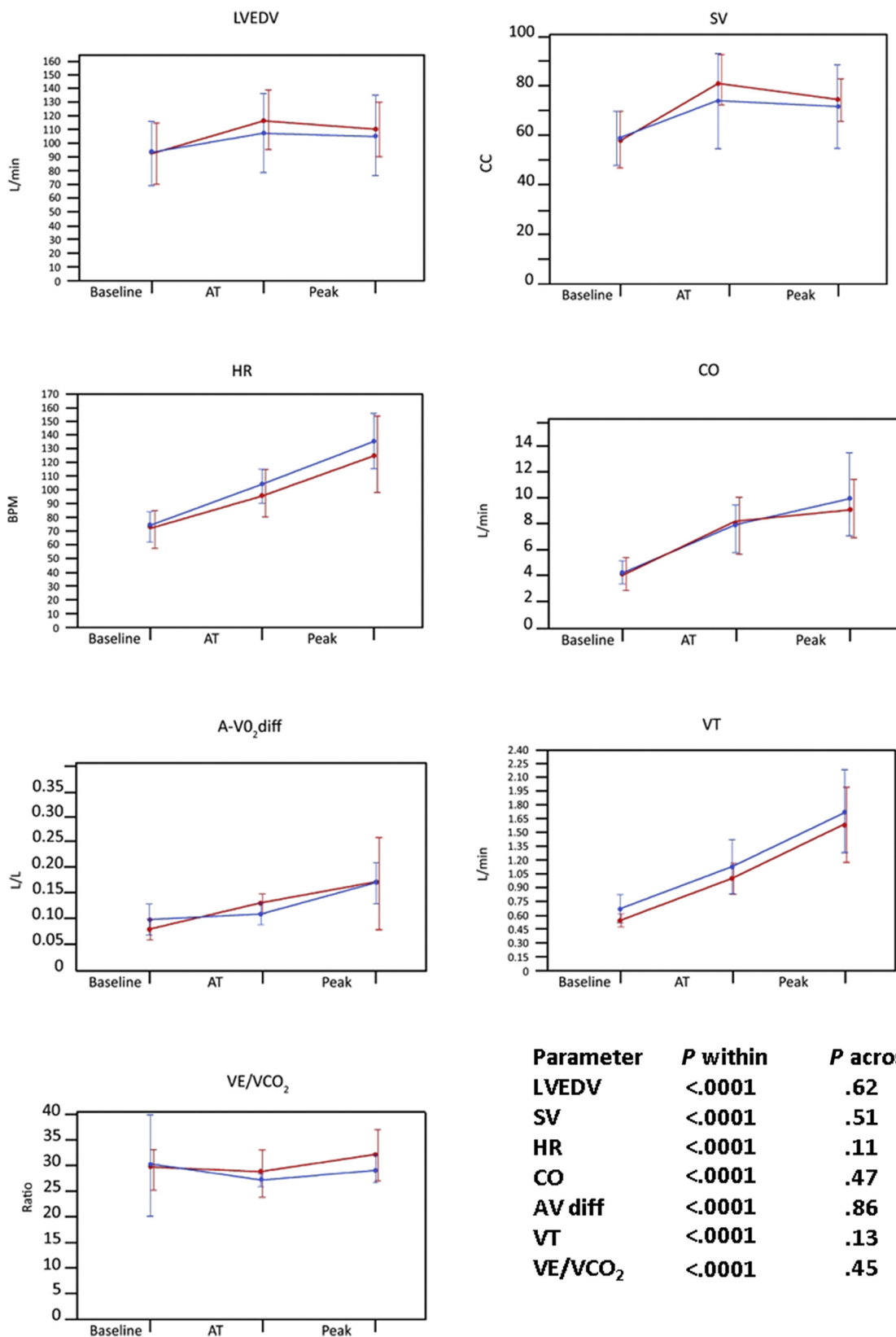
Supplemental Figure 2 Baseline, anaerobic threshold (AT), and maximal CPET and stress echocardiography in patients recovering from COVID-19 with fatigue (*blue line*) or without fatigue (*red line*) for (**A**) LVEDV, (**B**) SV, (**C**) HR, (**D**) cardiac output (CO), (**E**) A-Vo$_2$-difference (AV diff), (**F**) tidal volume (VT), and (**G**) VE/Vco$_2$ ratio. Note that patients with fatigue had lower HR, but otherwise there were no significant differences in all other parameters compared with patients without fatigue.

Parameter	P within	P across
LVEDV	<.0001	.59
SV	<.0001	.5
HR	<.0001	.05
CO	<.0001	.87
AV diff	<.0001	.2
VT	<.0001	.4
VE/VCO2	.001	.8

Parameter	*P* within	*P* across
LVEDV	<.0001	.62
SV	<.0001	.51
HR	<.0001	.11
CO	<.0001	.47
AV diff	<.0001	.86
VT	<.0001	.13
VE/VCO₂	<.0001	.45

Supplemental Figure 3 Baseline, anaerobic threshold (AT), and maximal CPET and stress echocardiography in patients recovering from COVID-19 with muscle weakness or pain (*blue line*) and without muscle weakness or pain (*red line*) for LVEDV, SV, HR, cardiac output (CO), A-Vo₂ difference (AV diff), tidal volume (VT), and VE/Vco₂ ratio. Note that patients with muscle weakness or pain did not have significantly different CPET parameters compared with patients without muscle weakness or pain.