Volume 22 Issue 4 April 2022 ISSN 1746-1391

European Journal of Sport Science

European Journal of Sport Science
The Official Journal of the European College of Sport Science

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ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tejs20

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To cite this article: Fabrício Braga, Fernanda Domecg, Marcelo Kalichsztein, Gustavo Nobre, José Kezen, Gabriel Espinosa, Christiane Prado, Marcelo Facio, Gabriel Moraes, Ilan Gottlieb, Ronaldo L. Lima, Alfred Danielian & Michael S. Emery (2022): Abnormal exercise adaptation after varying severities of COVID-19: A controlled cross-sectional analysis of 392 survivors, European Journal of Sport Science, DOI: 10.1080/17461391.2022.2054363

To link to this article: https://doi.org/10.1080/17461391.2022.2054363

EUROPEAN JOURNAL OF SPORT SCIENCE
https://doi.org/10.1080/17461391.2022.2054363

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Abnormal exercise adaptation after varying severities of COVID-19: A controlled cross-sectional analysis of 392 survivors

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ABSTRACT

The multisystem impairment promoted by COVID-19 may be associated with a reduction in exercise capacity. Cardiopulmonary abnormalities can change across the acute disease severity spectrum. We aimed to verify exercise physiology differences between COVID-19 survivors and SARS-CoV-2-naïve controls and how illness severity influences exercise limitation. A single-centre cross-sectional analysis of prospectively collected data from COVID-19 survivors who underwent cardiopulmonary exercise testing (CPET) in their recovery phase (x = 50[36;72] days). Patients with COVID-19 were stratified according to severity as mild [M-Cov (outpatient)] vs severe/critical [SC-Cov(inpatients)] and were compared with SARS-CoV-2-naïve controls (N-Cov). Collected information included demographics, anthropometrics, previous physical exercise, comorbidities, lung function test and CPET parameters. A multivariate logistic regression analysis was performed to identify low aerobic capacity (LAC) predictors post COVID-19. Of the 702 included patients, 310 (44.2%), 305 (43.4%) and 87 (12.4%) were N-Cov, M-Cov and SC-Cov, respectively. LAC was identified in 115 (37.1%), 102 (33.4%), and 66 (75.9%) of N-CoV, M-CoV and SC-CoV, respectively ($p < 0.001$). SC-Cov were older, heavier with higher body fat, more sedentary lifestyle, more hypertension and diabetes, lower forced vital capacity, higher prevalence of early anaerobiosis, ventilatory inefficiency and exercise-induced hypoxia than N-Cov. M-Cov had lower weight, fat mass, and coronary disease prevalence and did not demonstrate more CEPT abnormalities than N-Cov. After adjustment for covariates, SC-Cov was an independent predictor of LAC (OR = 2.7; 95% CI, 1.3-5.6). Almost two months after disease onset, SC-CoV presented several exercise abnormalities of oxygen uptake, ventilatory adaptation and gas exchange, including a high prevalence of LAC.

HIGHLIGHTS:

- Weeks after the acute disease phase, one-third of mild and three-quarters of severe and critical patients with COVID-19 presented a reduced aerobic capacity. Previous studies including SARS-CoV-1 survivors observed much lower values.
- A severe or critical COVID-19 case was an independent predictor for low aerobic capacity.
- In our sample, pre-COVID-19 exercise significantly reduced the odds of post-COVID-19 low aerobic capacity. Even severe or critical patients who exercised regularly had a prevalence of low aerobic capacity 2.5 times lower than those who did not have this routine before sickening.

KEYWORDS
Aerobic fitness; exercise; fatigue; acute disease

1. Introduction

Multisystemic COVID-19 involvement has been described, including pulmonary parenchymal destruction(González et al., 2021), pulmonary hypertension (PH) (Tudoran et al., 2021), right ventricular dysfunction(Paternoster et al., 2021), and myocardial injury (Yancy & Fonarow, 2020) associated with cardiac ventricular arrhythmias(Kochi, Tagliari, Forleo, Fassini, & Tondo, 2020) and left ventricular dysfunction (Szekely et al., 2020). These abnormalities combined with long periods of immobility and potential treatment side effects (e.g. corticosteroids) could markedly decrease exercise capacity in post-COVID-19 patients. Indeed, the lower mobility could increase aerobic deconditioning, causing fatigue and breathlessness, being the sole reason for exercise limitation, not related to

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Supplemental data for this article can be accessed https://doi.org/10.1080/17461391.2022.2054363.

cardiorespiratory organ impairments in COVID-19. E-Figure 1 schematizes the classical model of metabolic-cardiovascular-ventilatory coupling proposed by Wasserman and Whipp (Wasserman & Whipp, 1975) adapted to the potential pathophysiological changes presented in COVID-19.

Data from SARS-CoV-1 demonstrated that resting lung function and subsequent aerobic capacity (AC) could be reduced even one year after acute onset (Carfì, Bernabei, & Landi, 2020; Hui et al., 2005).

The cardiopulmonary exercise test (CPET) is the gold-standard technique to identify hidden physiological mechanisms leading to exercise limitation (Togna et al., 2013) and plays an essential role in the COVID-19 recovery phase.

The aims of the current study are 1) to compare CPET findings between COVID-19 survivors and non-COVID-19 (N-Co) patients evaluated in an outpatient clinical setting and 2) to examine the association between COVID-19 severity and low aerobic capacity (LAC).

2. Methods

2.1. Study design and population

This study is a cross-sectional analysis of prospectively collected data. The COVID-19 group was composed of all consecutive patients with positive reverse-transcription polymerase chain reaction (rt–PCR) for SARS-CoV-2 referred for CPET evaluation at our institution from May 20th, 2020 through March 16th, 2021. Patients were tested at least 28 days after the positive rt–PCR result and after hospital discharge. The exclusion criteria were as follows: 1) age < 18 years old; 2) history of heart failure, valvular or congenital heart disease, hypertrophic cardiomyopathy, chronic renal failure, chronic obstructive or interstitial pulmonary disease, active cancer or implanted pacemaker or cardioverter-defibrillator; 3) professional athletes; 4) inability to complete at least 4 min of exercise; 5) non-cycle ergometer CPET; 6) maximal perceived effort by modified Borg scale lower than 8, and 7) participation in rehabilitation or intensive exercise programme after diagnosis but before CPET. Patients with a respiratory exchange rate (RER) <1.1 were not excluded to identify those with post-COVID-19 ventilatory limitation.

The N-CoV control group was extracted from our CPET database for tests occurring on or after June 1st, 2019, applying the previously mentioned exclusion criteria. To avoid including undiagnosed COVID-19 cases in the control group, only patients evaluated before February 26th, 2020 (date of the index case in Brazil) were included.

This study was approved by the Ethics Committee of the Hospital Federal de Bonsucesso under protocol number 33729120.5.0000.5253. All the procedures in this study were under the 1975 Helsinki Declaration, updated in 2013.

2.2. Measurements

2.2.1. Clinical data

Age, sex, weight, height, percentage body fat and skeletal muscle mass were collected at baseline. Height was measured using a wall-mounted stadiometer. Weight, percentage body fat and skeletal muscle mass were obtained by bioimpedance analysis (Inbody® 770; Inbody Co., LTD, Seoul, Korea) immediately before CPET following technical recommendations previously published (Kyle et al., 2004)

2.2.2. Physical activity level (PAL)

Subjects were asked to self-declare their weekly PAL over the previous 12 months (pre-COVID-19) according to the Saltin–Grimby Scale (Grimby et al., 2015) as sedentary, some physical activity, regular physical activity, and physical activity for training and competition.

2.2.3. Comorbidities

Patients were questioned about the presence of significant comorbidities. Non-exclusive criteria comorbidities included in the analysis were systemic arterial hypertension, diabetes, coronary artery disease [CAD (history of myocardial infarction, coronary stenting, or coronary artery bypass graft)], current or past smoking, dyslipidemia, asthma, cancer, and thyroid disease.

2.2.4. COVID-19 status

The time from COVID-19 symptom onset to CPET performance, acute phase disease severity (DS) and persistence of fatigue and dyspnea after the acute phase were recorded. DS was classified as mild (M-CoV) for those treated in an outpatient setting and severe/critical (SC-CoV) in hospital admission cases. The persistence of symptoms after COVID-19 was rated by the modified British Medical Research Council (mMRC) dyspnea scale, as in previous COVID-19 publications(Huang et al., 2021). The symptomatic patient was defined by an mMRC $\geq$ grade 1. Patients who denied dyspnea or fatigue were deemed asymptomatic even though they complained of other symptoms as chest pain or palpitation. In our clinical experience, those symptoms, when isolated, are very unspecific for long-term symptoms after COVID-19.

2.2.5. Pulmonary function test (PFT)

Before CPET, rest spirometry was performed in all patients following guideline recommendations(Graham et al., 2019) using an automated device (Metalyzer 3B®; Cortex®, Leipzig, Germany). Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) were classified according to Knudson criteria (Morris, 1976). Obstructive ventilation dysfunction (OVD) was determined by an FEV1/FVC≤0.7. The obtained maximal flow-volume loop (MFVL) was used for exercise flow volume analysis to detect exercise expiratory flow limitation (exFVL). Maximal voluntary ventilation (MVV) was estimated by multiplying FEV1 by 40.

2.2.6. Cardiopulmonary exercise test

The subjects performed an exercise test to exhaustion on a magnetic-braked cycle ergometer (Lode Corival®, Groningen, Nederland) using an individualized ramp protocol based on the Wasserman algorithm (Wasserman, Hansen, Sue, & Stringer, 2012). After 2 min of rest, patients were asked to unload pedalling for 3 min before the incremental phase. They were also asked to maintain a fixed cadence between 60 and 80 rpm. The test was interrupted when they could not sustain a minimum cadence of 50 rpm for more than 5 s despite verbal encouragement.

Throughout the exercise, the breath-by-breath tidal volume (VT), breathing frequency (Bf), oxygen uptake (VO2), and carbon dioxide output (VCO2) were measured using a computerized metabolic cart (Metalyzer 3B®; Cortex®, Leipzig, Germany). All data were smoothed by the 15-point moving average method and automatically calculated by analytic software (MetaSoft Studio®; Cortex®, Leipzig, Germany). Oxygen saturation (SpO2) was recorded throughout the exercise using a finger probe Nonin® 3150 WristOx-2 (Nonin Medical Systems, Plymouth, MN, US).

Peak values for physiological variables were defined as the highest 30-s average value (Rozenbaum et al., 2017). The first and second ventilatory thresholds (VT1 and VT2, respectively) were estimated based on standard methodologies previously described (Lucia, Hoyos, & Chicharro, 2000; Wasserman, Stringer, Casaburi, Koike, & Cooper, 1994). The VE/VCO2 slope was calculated by linear regression using the data between rest and VT2. The ΔVO2/workload rate (WR) slope was calculated by linear regression of the ascendent phase of the VO2/WR relationship(Hansen, Casaburi, Cooper, & Wasserman, 1988). The oxygen uptake efficiency slope (OUES) was calculated by linear regression of VO2 and log VE using data from the first minute of incremental exercise to VT2 (Hollenberg & Tager, 2000).

A peak oxygen uptake defined LAC (VO_2) <85% of the predicted values (Wasserman algorithm). A VO2 determined early anaerobiosis (EAn) at the first ventilatory threshold (VT_1) <40% of the maximum predicted value. Ventilatory inefficiency (V_{inf}) was defined by a relationship between minute ventilation and carbon dioxide output (V_E/VCO_2) at VT_1 above the upper limit of the predicted value(Sun, Hansen, Garatachea, Storer, & Wasserman, 2002). According to previously published values, the ventilatory class was defined based on VE/VCO2 slope (Arena & Faghy, 2021). Exercise-induced hypoxia was characterized by a drop in oxygen saturation (SpO_2) >3% between rest and peak exercise(Agostoni & Butler, 1994).

As pulmonary circulation involvement has been described among patients with COVID-19 (Nuche et al., 2020), end-tidal CO_2 pressure (E_TCO_2) was dichotomized into two cutoff points (>34 and >30 mmHg) according to the probability of pulmonary vasculopathy previously described (Yasunobu, Oudiz, Sun, Hansen, & Wasserman, 2005).

Tidal flow volume loops during exercise were measured at rest and every 2 min throughout the exercise. Each measurement collected 45 s of ventilation without subject perception. After 4–6 breaths, an inspiratory capacity manoeuvre was performed as described previously(Guenette, Chin, Cory, Webb, & O'Donnell, 2013).

Dynamic hyperinflation was defined by a decrease of≥10% of inspiratory capacity (IC) and expiratory flow limitation by ≥50% of the tidal volume (V_T) (Radtke et al., 2019; Stubbing, Pengelly, Morse, & Jones, 1980).

2.3. Statistical analysis

Because of the exploratory nature of this study, no sample size calculation was performed, and after applying exclusion criteria, an all-comers design was adopted.

Categorical variables were expressed as counts (%), and continuous variables were expressed as the mean (standard deviation) or median (25^{th}–75^{th} percentiles) as appropriate.

For the comparison between COVID-19 groups, a two-way analysis of variance (ANOVA) or Kruskal–Wallis-Wallis test was used for continuous data, whereas χ^2 or Fisher's exact test was used for categorical data. Post hoc analyses were performed by Bonferroni's or Dunn's test.

For comparing patients with normal and LAC, Student's t-test or the Mann–Whitney U test was used for continuous variables, and χ^2 or Fisher's exact test was used for categorical variables.

To check the independence of the COVID-19 effect on exercise limitation, a multivariate logistic regression model was developed, using LAC as the dependent

variable and age, gender weight, percentage of body fat, skeletal muscle mass, resting heart rate (H_R), rest breathing frequency (B_f), rest SpO_2, past cancer, hypertension, diabetes, coronary artery disease (CAD), physical activity level (PAL), reduced forced vital capacity (FVC), and DS as independent parameters. Variable selection was performed based on clinical relevance and statistical significance on univariate analysis.

The statistical significance level was defined as a p value < 0.05. All analyses were performed using the Statistical Package for the Social Sciences software (IBM SPSS Statistics for Windows, version 22.0, IBM Corp., Armonk, NY).

3. Results

Of the 475 post-COVID-19 patients who underwent CPET, 83 (17.4%) met at least one of the exclusion criteria. Control cases were selected among the 686 patients tested between June 1st, 2019, and February 26th, 2020. Of them, 376 (54.8%) were excluded from the analysis based on exclusion criteria. Ultimately, 702 patients were included: 392 COVID-19 and 310 non-COVID-19 (Figure 1). The median time from symptoms onset and CPET was 50(35;72) and 55(44;75) for N-CoV and SC-CoV, respectively ($p = 0.041$).

3.1. Non-COVID-19, mild COVID-19, and severe/critical COVID-19

Table 1 shows the comparison between groups according to DS. Of the COVID-19 group, 87 (22.1%) were SC-CoV, 51 (58.6%) of them required intensive care treatment, and 16 (18.3%) needed invasive mechanical ventilation (MV). E-figure 2 (Supplemental online material) shows the data distribution (Tukey-style box plots) of the main CPET variable at rest, VT_1 and peak exercise. SC-CoV performed CPET later than M-CoV ($p = 0.041$) and was more symptomatic at that time [79.3% (69/87)] than M-CoV [41.3% (126/305); $p < 0.001$].

3.1.1. Demography, anthropometry

SC-CoV had a higher prevalence of male sex (72.4%) than M-CoV and was older (59.7 ± 12 y), heavier (82.2 ± 16.4 kg) and had a higher percentage of body fat [35.7% (29.4;42.3)] than N-CoV and M-CoV. Compared to N-CoV, M-CoV was lighter (75.5 ± 14.9 kg) and had a lower percentage of body fat (29.7 (24; 35.7)).

3.1.2. Physical activity level

A more overall sedentary lifestyle (59.8%) and a lower frequency (12.6%) of regular physical activity were present in SC-CoV than in the other groups.

3.1.3. Comorbidities

Diabetes (19.5%) and hypertension (43.7%) were more prevalent among the SC-Cov group than others. The frequency of CAD was lower in M-Cov (4.3%) than in N-Cov and SC-Cov.

3.1.4. Lung Function Test

FVC and forced expiratory volume in one second (FEV_1) were markedly reduced in SC-CoV compared to the two

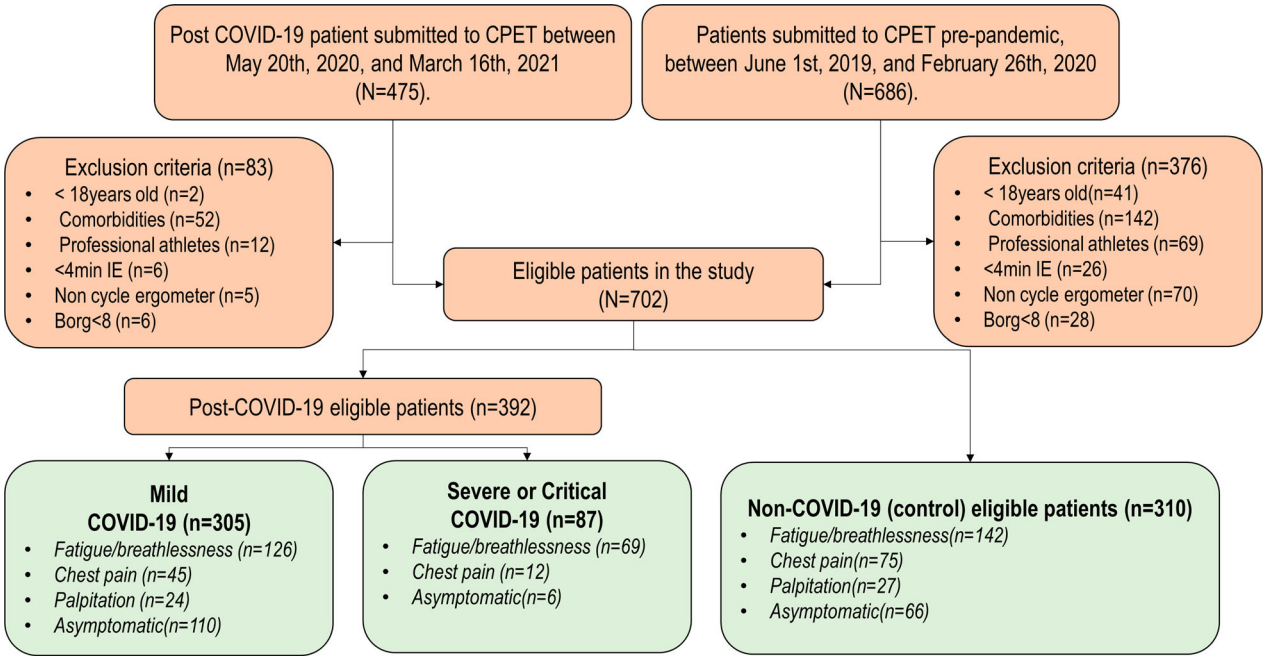

Figure 1. Flowchart of patients who met inclusion/exclusion criteria for the study population, with their referral reasons for CPET.

Table 1. Comparison of clinical, pulmonary function and exercise data between N-Cov, M-Cov and SC-Cov patients.

	All(N = 702)	N-COV (n = 310)	M-COV(n = 305)	SC-COV(n = 87)	*p-value*
Sociodemographic					
Male gender (%)	429(61.1)	197(63.5)	169(55.4)	63(72.4)[b]	*0.008*
Age(years)	52.06 ± 14.32	52.3 ± 14.5	49.7 ± 14	59.7 ± 12[a,b]	*<0.001*
Weight (kg)	78.27 ± 16.95	79.9 ± 18.5	75.5 ± 14.91[a]	82.2 ± 16.4[a,b]	*<0.001*
Height(cm)	170.93 ± 9.89	171.4 ± 9.9	170.5 ± 9.5	170.9 ± 11.1	*0.502*
PBF (% of BW)	30.9(24.4;37.4)	31.1(24.4;37.4)	29.7(24;35.7)[c]	35.7(29.4;42.3)[c,d]	*<0.001*
SMM (kg)	31.4(24.2;36.2)	32.3(24.5;36.9)	29.7(24.6;35.7)	29.6(23.1;35.1)	*0.098*
Time-diagnose (days)			50(35;72)	55(44;75)	*0.041*
Symptomatic* (%)			126(41.3)	69(79.3)	*<0.001*
Physical activity level					*<0.001*
Sedentary	251(35.8)	104(33.5)	95(31.1)	52(59.8)[a,b]	
Some PA	211(30.1)	99(31.9)	89(29.2)	23(26.4)	
Regular PA	195(27.8)	89(28.7)	95(31.1)	11(12.6)[a,b]	
Training and competition	45(6.4)	18(5.8)	26(8.5)	1(1.1)[b]	
Comorbidities					
Hypertension (%)	201(28.6)	86(27.7)	77(25.2)	38(43.7)[a,b]	*0.003*
CAD (%)	63(9)	40(12.9)	13(4.3)[a,b]	10(11.5)	*0.001*
Diabetes (%)	63(9)	25(8.1)	21(6.9)	17(19.5)[a,b]	*0.001*
Smoker (%)	11(1.6)	6(1.9)	5(1.6)	0(0)	*0.434*
Past smoker (%)	87(12.4)	43(13.9)	32(10.5)	12(13.8)	*0.407*
Dyslipidemia (%)	210(29.9)	96(31)	86(28.2)	28(32.2)	*0.668*
Asthma (%)	74(10.5)	25(8.1)	39(12.8)	10(11.5)	*0.155*
Cancer (%)	26(3.7)	14(4.5)	9(3)	3(3.4)	*0.584*
Lung Function Test					
FVC (L)	3.8 ± 1.09	3.9 ± 1.1	3.9 ± 1.1	3.3 ± 1[a,b]	*<0.001*
FEV1(L/s)	3.14 ± 0.88	3.2 ± 0.9	3.2 ± 0.9	2.8 ± 0.8[a,b]	*<0.001*
CPET					
Rest					
VO_2/kg (ml/kg/min)	4.9 ± 1.1	4.8 ± 1.1	5.1 ± 1.1[a]	4.9 ± 1.0	*0.017*
H_R (bpm)	76.52 ± 13.49	75.6 ± 13.6	75.2 ± 12.2	84.7 ± 14.6[a,b]	*<0.001*
SBP (mmHg)	124.95 ± 14.73	126.1 ± 14.9	123.2 ± 14.9[a]	127.2 ± 12.9	*0.017*
DBP (mmHg)	78.89 ± 8.19	79.5 ± 8.3	78.3 ± 8.6	78.9 ± 6.2	*0.194*
SpO_2 (%)	98.34 ± 1.35	98.12 ± 1.2	98.75 ± 1.19[a,b]	97.66 ± 1.6[a,b]	*<0.001*
B_f (irpm)	16.88 ± 4.31	16.7 ± 4.3	16.5 ± 4	18.9 ± 4.9[a,b]	*<0.001*
V_T	0.76(0.61;0.93)	750(620;920)	800(600;900)	760(630;950)	*0.967*
V_E(L)	12.99 ± 3.93	12.8 ± 3.5	12.6 ± 3.8	14.8 ± 4.8[a,b]	*<0.001*
V_E/VCO_2	33.43 ± 5.07	33.4 ± 4.4	32.7 ± 5	36 ± 6.6[a,b]	*<0.001*
VT1					
VO_2/kg (ml/kg/min)	13.52 ± 4.84	13.4 ± 4.5	14.5 ± 5.3[a,b]	10.4 ± 2.9[a,b]	*<0.001*
Workload (W/kg)	0.93 ± 0.47	0.9(0.6;1.2)	0.9(0.7;1.3)[a,b]	0.6(0.4;0.8)[a,b]	*<0.001*
% pVO_2 pred	49(40;59)	48.8(40;59.8)	50.3(41;61.3)	41.1(35.1;51.4)[a,b]	*<0.001*
EA (%)	181(25.8)	77(24.8)	67(22)	37(42.5)[a,b]	*<0.001*
V_E/VCO_2	29.9 ± 4.43	29.7 ± 3.8	29.1 ± 4	33.6 ± 5.8[a,b]	*<0.001*
V_{inf} (%)	28.6%	86(27.7)	69(22.6)	46(52.9)[a,b]	*<0.001*
E_TCO_2 (mmHg)	37.05 ± 4.41	37.4 ± 4	37.5 ± 4.4	34.2 ± 4.9[a,b]	*<0.001*
Peak Exercise					
VO_2/kg (ml/kg/min)	25.1 ± 8.93	25.2 ± 8.8	26.9 ± 9[a,b]	18.7 ± 6.1[a,b]	*<0.001*
RER	1.16 ± 0.08	1.16 ± 0.08	1.15 ± 0.07	1.16 ± 0.09	*0.187*
% pVO_2 pred	0.92 ± 0.23	93.5 ± 24.3	96.1 ± 21.8	76.4 ± 17.3[a,b]	*<0.001*
LAC (%)	40.3%	115(37.1)	102(33.4)	66(75.9)[a,b]	*<0.001*
Workload(W/Kg)	2.19 ± 0.86	2.2 ± 0.8	2.4 ± 0.9[a,b]	1.6 ± 0.6[a,b]	*<0.001*
H_R (bpm)	153.31 ± 22.4	152 ± 23.5	158.1 ± 20.3[a,b]	141.3 ± 20.6[a,b]	*<0.001*
O_2P(ml/bpm)	12.55 ± 4.11	12.9 ± 4	12.7 ± 4.3	10.9 ± 3.4[a,b]	*<0.001*
SBP (mmHg)	187.15 ± 29.61	189.4 ± 31	185.8 ± 28.8	183.9 ± 27.2	*0.181*
DBP (mmHg)	82.11 ± 12.03	82.8 ± 12.4	81.1 ± 12	83.2 ± 10.6	*0.133*
B_f (irpm)	39.08 ± 8.14	39.25 ± 8.2	39.01 ± 8.00	38.74 ± 8.13	*0.885*
V_T	2.18 ± 0.69	2.2 ± 0.7	2.2 ± 0.7	1.9 ± 0.6[a,b]	*0.002*
V_E(L)	84.78 ± 30.67	86.0 ± 30.0	86.5 ± 31.8	74.3 ± 27.1[a,b]	*0.003*
BR (%)	33.0 ± 0.15	32.4 ± 15	33 ± 15.4	32.8 ± 14.4	*0.91*
SpO_2 (%)	98.16 ± 2.17	98.2 ± 1.7	98.5 ± 2.1	96.9 ± 3.3[a,b]	*<0.001*
EIH (%)	19(2.7)	4(1.3)	5(1.6)	10 (11.5)[a,b]	*<0.001*
V_E/VCO_2 slope	30.87 ± 5.64	30.4 ± 4.9	30.1 ± 5.3	35.1 ± 7.1[a,b]	*<0.001*
$\Delta VO_2/\Delta WR$ slope(ml/W)	8.77 ± 1.49	8.9 ± 1.58	8.80 ± 1.39	8.10 ± 1.36[a,b]	*<0.001*
HRR (bpm)	25(19;33)	25(18;33)	27(20;33)	23(15;28)[c,d]	*<0.001*

Data are presented as mean ± SD, median (25th – 75th percentile) or numbers (percentiles). Data from cardiopulmonary exercise tests were obtained on rest, at the first ventilatory threshold and at peak exercise. For categorical data, statistical differences among groups were tested with χ^2 test. For continuous data, statistical differences among groups were tested with analysis of variance or Kruskal-Wallis test based on normal data distribution. Definition of abbreviations: EA: early anaerobiosis; FVC: forced vital capacity; LAC: low aerobic capacity; BR: breathing reserve; % pVO2 pred: percentual of peak predicted oxygen uptake;ΔVO2/ΔWR: oxygen uptake to work rate relationship; BW: body weight; CAD: coronary artery disease; CPET: cardiopulmonary exercise test; DBP: diastolic blood pressure; EIH: exercise-induced hypoxia; ETCO2: end-tidal carbon dioxide pressure; FEV1: forced expiratory volume in 1 s; HR: heart rate; HRR: heart rate recovery in the first minute. M-Cov: mild COVID-19; N-Cov: non-COVID-19; O2P: oxygen pulse; Bf: breathing frequency; OUES: oxygen uptake efficiency slope; OVD: obstructive ventilatory disturbance; PA: physical activity; PBF: percentage of body fat; RER: respiratory exchange rate; SBP: systolic blood pressure; SC-Cov: severe or critical COVID-19; SMM: skeletal muscle mass; SPO2 = arterial oxygen saturation; Time-diagnose: Time since COVID-19 diagnose; VCO2: carbon dioxide output; VE: minute ventilation; Vinf: ventilatory inefficiency; VO2: oxygen uptake; VT: tidal volume, VT1: first ventilatory threshold.

[a]P < .05, comparison with "non-COVID-19" (Bonferroni correction).

[b]P < .05, comparison with "mild- COVID-19" (Bonferroni correction).

[c]P < .05, comparison with "non-COVID-19" (Dunn test).

[d]P < .05, comparison with "mild- COVID-19" (Dunn test).

*breathless or fatigue passed on modified British Medical Research Council

other groups. An FVC below the lower normal limits was present in 9.4, 5.6 and 29.9% of N-CoV, M-CoV and SC-CoV patients respectively ($p < 0.001$). The ratio between forced expiratory volume in one second (FEV_1)/FVC was 82.2 ± 6.1 83.6 ± 5.8 and 84.8 ± 6.8% for N-CoV, M-CoV and SC-CoV respectively ($p < 0.001$). Still, no difference was found for the prevalence of OVD between groups (3.9, 1.6 and 2.3% for N-CoV, M-CoV and SC-CoV respectively [$p = 0.226$])

3.1.5. CPET

At rest, SC-CoV presented a higher heart rate [H_R (84.7 ± 14.6 bpm)], breathing frequency [B_f (18.9 ± 4.9 rpm)], minute ventilation (14.8 ± 4.8 L/min) and a lower S_PO_2 (97.6 ± 1.6%) than N-CoV and M-CoV. In comparison with N-CoV, M-CoV had a higher resting VO_2 (5.1 ± 1.1 ml/kg/min) and S_PO_2 (98.75 ± 1.19%) and lowered systolic blood pressure [SBP (123.2 ± 14.9 mmHg)].

The VT_1 level was reached at lower values of VO_2 in SC-CoV (10.4 ± 2.9 ml/kg/min), workload [0.6 W/kg (0.4;0.8)], oxygen pulse (8.4 ± 2.7 ml/b) and E_TCO_2 (34.2 ± 4.9 mmHg) than the other groups. These patients had a lower VO_2 related to maximal predicted values [41.1% (35.1;51.4)] and a higher prevalence of EAn (42.5%). SC-CoV also shows a higher V_E/VCO_2) than N-CoV and M-CoV, with a much higher frequency of V_{inf} seen among them (52.9%). Moreover, the prevalence of $E_TCO_2 < 34$ (40.2%) and <30 (13.8%) mmHg was much higher in SC-Cov than in N-Cov (9.7 and 2.6%) and M-Cov (11.1 and 2.6%); $p < 0.001$ for both comparisons. Compared to N-CoV, M-CoV had a higher VO_2 (14.5 ± 5.3 ml/kg/min) and workload [0.9 W/kg (0.7; 1.3)] at the VT_1 level.

At peak exercise, SC-CoV showed lower VO_2 (18.7 ± 6.1 ml/kg/min), VO_2 related to maximal predicted values (76.4 ± 17.3%), workload (1.6 ± 0.6 W/kg), H_R (141.3 ± 20.6 bpm), oxygen pulse (10.9 ± 3.4 ml/b), V_E (74.3 ± 27.1 L/min), V_T (1.9 ± 0.6 L), S_PO_2 (96.9 ± 3.3%), $\Delta VO_2/\Delta$ workload rate (8.10 ± 1.36 ml/W) and oxygen uptake efficiency slope [1.7 (1.2; 2.1)], as well as a higher V_E/CO_2 slope (35.1 ± 7.1) than N-CoV and M-CoV. E-figure 3 (Supplemental online material) shows the differences in ventilatory class prevalence. In addition, exercise-induced hypoxia was more prevalent in SC-Cov (11.5%) than in the other groups. No difference was found between groups for dynamic hyperinflation (10.5, 6.9 and 4.8% for N-Cov, M-Cov and SC-Cov respectively [$p = 0.0.91$]) or exercise flow-volume limitation (14.5, 10.8 and 8.0% for N-Cov, M-Cov and SC-Cov respectively [$p = 0.173$]). Interestingly, M-Cov reached a higher VO_2 (26.9 ± 9 ml/kg/min), workload (2.4 ± 0.9 W/kg) and H_R (158.1 ± 20.3 bpm) than N-Cov patients.

H_R recovery at the first-minute post-exercise was lower in SC-Co (23[15;28] bpm) than in the other groups.

3.2. Low aerobic capacity

LAC was observed in 283 patients (40.3%; 95% CI, 36.6-44.1); 115 (37.1; 95% CI, 31.7-42.7), 102 (33.4; 95% CI, 28.2-39.0) and 66 (75.9; 95% CI, 65.5-84.4) for N-CoV, M-CoV and SC-CoV, respectively ($p < 0.001$). Moreover, 36.7% (32/87) of the SC-CoV patients had an aerobic capacity <70% of the predicted values. E-Figure 4 (Supplemental online material) shows the prevalence of each grade of aerobic capacity according to COVID-19 status. The median time from the first symptoms of COVID-19 and CPET were 49 (35;70) and 54.5 (40;75.5) days for COVID-19 with normal and LAC, respectively ($p = 0.059$).

Table 2 shows the characteristics of all participants according to the AC. A higher prevalence of SC-CoV (23.3%) was observed among patients with LAC than those with normal aerobic capacity (5.0%). Moreover, LAC was associated with a higher percentage of body fat; a lower skeletal muscle mass; higher sedentarism; a higher prevalence of hypertension, CAD, diabetes, and cancer; reduced FVC; higher H_R and B_f; and lower S_PO_2. Other CPET differences between patients with normal and LAC are summarized in e-Table-1 (Supplemental online material).

Table 3 shows the multivariate analysis. After adjustment, SC-CoV was 2.76 (95% CI, 1.35-5.66) times as likely to present with LAC as N-CoV. No association was found for M-Cov and LAC (OR = 1.06; 95% CI, 0.68-1.66). There was a progressive negative association between the level of physical activity and the probability of LAC. About sedentarism, the ORs for LAC were 0.37 (95% CI, 0.24-0,60), 0.17 (95% CI, 0.10-0.30) and 0.02 (95% CI, 0.01-0.18) for some physical activity, regular physical activity and physical activity for training and competition, respectively. E-Figure-5 (Supplemental online material) shows the comparison between patients who exercised regularly and those who did not, according to COVID-19 status.

4. Discussion

To our knowledge, this is the most extensive study to examine exercise limitations among COVID-19 survivors and the first to include unselected subjects.

Our data suggest that SC-CoV patients have a worse physiological response to exercise than N-CoV and M-CoV patients. SC-CoV showed not only a higher prevalence of LAC but also an earlier contribution of anaerobic metabolism (lower relative VO_2 at VT1), worse ventilatory adaptation (higher V_E/VCO_2 at VT_1 and slope),

Table 2. Univariate comparison analysis between patients with normal and low aerobic capacity.

Variables	NAC (N = 419)	LAC (N = 283)	*P values*
Demographics and Anthropometrics			
Male gender (%)	245(58.5)	184(65)	*0.081*
Age(years)	51.3 ± 12.7	53.1 ± 16.4	*0.102*
Weight (kg)	77.4 ± 16.4	79.5 ± 17.7	*0.111*
Height(cm)	171.1 ± 9.2	170.7 ± 10.9	*0.552*
PBF (% of BW)	29.1 ± 9.1	34.6 ± 9.3	*<0.001*
SMM (kg)	32.4(24.6;37.1)	29.5(23.3;34.8)	*0.001*
PA level (%)			*<0.001*
Sedentary	84(20)	167(59)	
Some PA	127(30.3)	84(29.7)	
Regular PA	164(39.1)	31(11)	
PA for training and competition	44(10.5)	1(0.4)	
COVID-19			*<0.001*
N-Cov	195(62.9)	115(37.1)	
M-Cov	203(66.6)	102(33.4)	
SC-Cov	21(24.1)	66(75.9)[a,b]	
Comorbidities			
Hypertension (%)	106(25.3)	95(33.6)	*0.017*
CAD (%)	28(6.7)	35(12.4)	*0.010*
Diabetes (%)	22(5.3)	41(14.5)	*<0.001*
Smoker (%)	9(2.1)	2(0.7)	*0.131*
Past smoker (%)	45(10.7)	42(14.8)	*0.106*
Dyslipidemia (%)	114(27.2)	96(33.9)	*0.057*
Asthma (%)	39(9.3)	35(12.4)	*0.195*
Cancer (%)	9(2.1)	17(6)	*0.008*
Thyroid disease (%)	48(11.5)	25(8.8)	*0.264*
Lung Function Test			
FVC (L)	3.98 ± 1.03	3.52 ± 1.12	*<0.001*
FEV1(L/s)	3.28 ± 0.82	2.93 ± 0.92	*<0.001*
OVD (%)	12(2.9)	7(2.5)	*0.754*
Reduced FVC (%)	12(2.9)	60(21.2)	*<0.001*
FEV_1/FVC	82.8 ± 5.8	83.6 ± 6.7	*0.127*
Resting Vital Signs			
H_R (bpm)	73.05 ± 12.42	81.66 ± 13.4	*<0.001*
SBP (mmHg)	124.72 ± 14.76	125.29 ± 14.7	*0.616*
DBP (mmHg)	79.07 ± 7.72	78.61 ± 8.84	*0.471*
SpO2 (%)	98.48 ± 1.26	98.12 ± 1.44	*<0.001*
B_f (irpm)	16.32 ± 3.89	17.72 ± 4.75	*<0.001*

Low aerobic capacity was defined by a peak VO2 lower than 85% of the predicted value based on the Wasserman algorithm. Data are presented as mean ± SD, median (25th – 75th percentile) or numbers (percentiles). For categorical data, the statistical difference among groups was tested with the χ^2 test. For continuous data, statistical differences among groups were tested with t-student or Mann-Whitney-U tests based on normal data distribution. Definition of abbreviations: NAC: normal aerobic capacity; LAC: Low aerobic capacity; N-Cov: non-COVID-19; M-Cov: mild COVID-19; SC-Cov: severe or critical COVID-19; PBF: percentage of body fat; BW: body weight; SMM: skeletal muscle mass; PA: physical activity; CAD: coronary artery disease; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; OVD: obstructive ventilatory disturbance; H_R: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; S_PO_2 = arterial oxygen saturation; B_f: breathing frequency.

and a higher frequency of ventilation-perfusion mismatch and/or pulmonary vasculopathy (lower E_TCO_2 at VT1). Although it is reasonable to infer that COVID-19 itself is responsible for these differences, an older age, worse body morphology (higher weight and percentage body fat) and physical activity profile, and higher prevalence of CAD and diabetes certainly also contributed to an impaired exercise response.

In contrast, M-Cov patients did not demonstrate exercise abnormalities compared to N-Cov. M-Cov showed lower weight and body fat, lower CAD, lower rest SBP and higher S_PO_2, and higher peak VO_2 and WR than N-Cov.

Rinaldo et al. (Francesco Rinaldo et al., 2021) analyzed 75 post-COVID patients (76% initially severe/critical) more than three months after hospital discharge. LAC (pVO_2<85% predicted) was present in 55% and V_{inf} (V_E/VCO_2 slope > 30) in 15%. Skjorten et al(Skjørten et al., 2021) examined 156 SC-Cov patients (median 104 days after hospital discharge). LAC (pVO2/kg < 80%) was present in 47%, and 15% of patients demonstrated V_{inf}. The increased prevalence of SC-CoV in both studies compared to our cohort (22%) is likely reflected in their higher percentage of LAC. However, our SC-CoV group had a more prominent V_{inf} (53%), which may reflect the shorter period between the acute disease and CPET.

Two small invasive CPET (iCPET) studies have been recently published, both seeking the mechanism behind LAC in COVID-19 survivors. Baratto et al. (Baratto et al., 2021) performed iCPET the day before hospital discharge, and LAC was observed in 17/18 patients. Singh et al. (Singh et al., 2022) performed iCPET 11 months after acute COVID-19 in 10 patients (90% M-CoV), all of whom showed LAC. Both authors concluded that the primary mechanism for LAC was a lower arteriovenous oxygen difference rather than primary cardiocirculatory or ventilatory limitation.

Table 3. Multivariate Analysis of Independent Risk Factors for low aerobic capacity.

Variables	β	SE (β)	*p*-value	OR (95%CI)
Age(years)	−0.06	0.01	<0.001	0.943 (0.926-0.961)
Male gender	−2.89	0.40	<0.001	17.857 (8.130-40.000)
Weight (kg)	−0.06	0.01	<0.001	0.941 (0.923-0.959)
PBF (%)	0.14	0.02	<0.001	1.146 (1.101-1.192)
SMM (KG)	0.00	0.00	0.445	
Rest H_R (bpm)	0.03	0.01	0.000	1.035 (1.017-1.053)
Rest B_f(irpm)	0.06	0.03	<0.001	1.062 (1.009-1.119)
Rest S_PO_2	0.00	0.09	0.996	
Past Cancer	1.34	0.60	0.026	3.826 (1.171-12.505)
Hypertension	−0.06	0.26	0.820	
Diabetes	0.84	0.38	0.028	2.322 (1.095-4.923)
CAD	0.93	0.38	0.013	2.546 (1.221-5.311)
PAL			<0.001	
Sedentary (reference)				1
Some physical activity	−0.98	0.24	<0.001	0.376 (0.237-0.596)
Regular physical activity	−1.76	0.29	<0.001	0.173 (0.098-0.303)
Physical activity for training and competition	−3.81	1.08	<0.001	0.022 (0.003-0.184)
Reduced FVC	1.90	0.41	<0.001	6.669 (2.966-14.993)
COVID-19			0.019	
Non-COVID-19 (reference)				1
Mild	0.06	0.23	0.720	
Severe or Critical	1.02	0.37	0.006	2.763 (1.348-5.664)
Constant	1.04	8.79	0.906	

See Tables 1 and 2 legends for expansion of abbreviations.

Additionally, both concluded that ventilatory maladaptation was a reduction in the $PaCO_2$ set point and not an increase in dead space caused by pulmonary parenchymal or vascular involvement. Despite the more precise physiological assessment, iCPET may have been influenced by a potential referral bias as utilized in these studies. In conjunction with the small sample sizes, this potential bias makes extrapolation to a broader, unselected population of COVID-19 patients more difficult.

In Baratto et al., the mean pulmonary arterial pressure (mPAP) and total pulmonary vascular resistance at peak exercise met the criteria of exercise-induced PH (Oliveira et al., 2016), and patients with COVID-19 still reached mPA*P* values close to 30 mmHg in the warmup phase of the CPET. In our study, SC-CoV showed a high prevalence of reduced E_TCO_2 at VT_1. Indeed, shallow values (<30 mmHg) were seen in 13.8% of these patients compared to only 2.6% of N-Cov. This pattern of E_TCO_2 and V_E/VCO_2 are already established noninvasive markers of PH in patients with different forms of lung dysfunction(Armstrong, Thirapatarapong, Dussault, & Bartels, 2013). E_TCO_2 at the VT_1 level <30 mmHg should always raise the possibility of pulmonary vascular involvement (Yasunobu et al., 2005), although other etiologies are also possible.

Moreover, we performed CPET a median of 25 days after hospital discharge. Some of the SC-CoV patients in our study would not have been able to achieve an exhaustive CPET the day before hospital discharge, especially those with essential signs of residual pulmonary vasculopathy or parenchymal disruption. Therefore, we cannot definitively exclude pulmonary vascular limitation secondary to COVID as a cause of excess ventilation among COVID-19 survivors.

Not surprisingly, M-CoV showed fewer signs of exercise limitation than SC-CoV, achieving higher VO_2, weight-adjusted workload values, and H_R at peak exercise than N-CoV. At baseline, they had lower weight, percentage body fat and SBP, and prevalence of CAD. Many authors have reported several underlying conditions increasing the risk of more severe forms of COVID-19. Bennett et al. (Bennett et al., 2021) analyzed almost 20,000 cases of COVID-19, reporting a 30% and 81% increase in the risk of hospitalization for chronic heart disease and morbid obesity, respectively. Less severe obesity has also been associated with a higher risk of hospitalization.

As usual for other infectious diseases during the acute disease phase, even M-CoV patients were recommended to avoid exercise. Therefore, it is reasonable to infer that their AC was even better before the disease. Brawner et al. (Brawner et al., 2021) reported an inverse relationship between exercise and the risk of hospitalization for COVID-19. Thus, in a probable virtuous circle, a better health status could have contributed to a less severe form of COVID-19, and both confer minor exercise limitation after disease.

After adjustments for 14 variables, SC-CoV was an independent predictor of LAC but not M-CoV. Age, male sex, weight, percentage body fat, resting H_R and B_f, cancer, diabetes and CAD history, PAL and a reduced FVC were also associated with LAC. More than three-quarters of SC-Cov had LAC, and 36.8% had an AC lower than 70% predicted. These values are much higher than those observed by Ong et al. (Ong et al., 2004) among SARS-CoV-1 survivors, where 41% demonstrated LAC 3 months after hospital discharge. Hui et al. (Hui et al., 2005) analyzed 97 survivors from SARS-CoV-1 and showed a 16% reduction in AC one year after release. LAC is an important prognostic factor of all-cause mortality, potentially modifiable.

It was not necessarily surprising that the pre-COVID-19 exercise reduced the odds of post-COVID-19 LAC. SC-CoV patients who exercised regularly had a prevalence of LAC 2.5 times lower than those who did not have this routine before sickening. Thus, in addition to reducing the extent of infection, hospitalization and mortality for COVID-19 (Cho et al., 2021), regular exercise may provide a "buffer" to the decrease in fitness impairment after hospitalization.

This research has some limitations that are necessary to highlight. First, all patients came from the same geographic region (Rio de Janeiro). Differences in health policies and facilities, environment, genetics, viral strains, and treatments may influence generalizability to other geographic areas. Second, as patients were hospitalized in different institutions and were referred to CPET days after discharge, collecting extensive in-hospital variables was not feasible and was not analyzed. Third, comorbidities and PAL were self-reported, and although widely used in medical research, it has some limitations. Fourth, the time between symptom onset and CPET was variable, and treatment strategies were not accounted for. Fifth, any matching controller pairing technique was adopted to keep a larger sample size. Sixth, we do not have pre-COVID-19 exercise data on patients. Seventh, the N-CoV group were not inquired by m-MRC, thus we could not compare the persistence of the symptoms between groups. Last, neither invasive nor noninvasive direct cardiac output and pulmonary circulation measures were performed.

5. Interpretation

SC-CoV patients have remarkable exercise physiology differences based on CPET compared with M-CoV and N-CoV patients, and it is an independent predictor of LAC after disease. M-Cov had a healthier baseline profile and did not differ from N-Cov in CPET achievements. Whether COVID-19 survivors were hospitalized, regular baseline exercise was associated with maintaining exercise capacity after disease. Due to the possibility of long-term disability, the CPET is a crucial tool to identify fitness impairment and clarify the underlying mechanisms and guide strategies for performance recovery.

Additional information

The e-Appendix, e-Figures, and e-Tables can be found online Supplemental Materials.

Author contributions

All named authors fulfil each of the four specified criteria for authorship. F.B. and F.D. are guarantors of the paper. We declare that the results of this study are presented clearly, honestly and without fabrication, falsification or any kind of data manipulation. Moreover, we state that the present results do not constitute an endorsement by ACSM.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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