Exercise intolerance in post-coronavirus disease 2019 survivors after hospitalisation

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Shareable abstract (@ERSpublications)
Post-COVID-19 survivors may have exercise intolerance; in this study, this was related to high V_D/V_T at exercise and decreased FVC % pred, suggesting that pulmonary microcirculatory injury and ventilatory impairment influence aerobic capacity https://bit.ly/41AYvwl

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Abstract

Rationale Post-coronavirus disease 2019 (COVID-19) survivors frequently have dyspnoea that can lead to exercise intolerance and lower quality of life. Despite recent advances, the pathophysiological mechanisms of exercise intolerance in the post-COVID-19 patients remain incompletely characterised. The objectives of the present study were to clarify the mechanisms of exercise intolerance in post-COVID-19 survivors after hospitalisation.

Methods This prospective study evaluated consecutive patients previously hospitalised due to moderate-to-severe/critical COVID-19. Within mean±SD 90±10 days of onset of acute COVID-19 symptoms, patients underwent a comprehensive cardiopulmonary assessment, including cardiopulmonary exercise testing with earlobe arterialised capillary blood gas analysis.

Measurements and main results 87 patients were evaluated; mean±SD peak oxygen consumption was 19.5±5.0 mL·kg^{-1}·min^{-1}, and the tertiles were ⩽17.0, 17.1–22.2 and ⩾22.3 mL·kg^{-1}·min^{-1}. Hospitalisation severity was similar among the three groups; however, at the follow-up visit, patients with peak oxygen consumption ⩽17.0 mL·kg^{-1}·min^{-1} reported a greater sensation of dyspnoea, along with indices of impaired pulmonary function, and abnormal ventilatory, gas-exchange and metabolic responses during exercise compared to patients with peak oxygen consumption >17 mL·kg^{-1}·min^{-1}. By multivariate logistic regression analysis (receiver operating characteristic curve analysis) adjusted for age, sex and prior pulmonary embolism, a peak dead space fraction of tidal volume ⩾29 and a resting forced vital capacity ⩽80% predicted were independent predictors of reduced peak oxygen consumption.

Conclusions Exercise intolerance in the post-COVID-19 survivors was related to a high dead space fraction of tidal volume at peak exercise and a decreased resting forced vital capacity, suggesting that both pulmonary microcirculation injury and ventilatory impairment could influence aerobic capacity in this patient population.

Introduction

In March 2020, coronavirus disease 2019 (COVID-19) was characterised by the World Health Organization as a pandemic infection and has been considered an international public health emergency for the past 2 years. A few months after the pandemic's start, Brazil had the second highest number of

confirmed COVID-19 cases worldwide. In April 2021, Brazil had become the epicentre of the COVID-19 pandemic, with >4000 deaths per day [1].

COVID-19 infection may be asymptomatic in the acute phase, but clinical presentation might also range from mild respiratory symptoms to severe respiratory failure with associated acute respiratory distress syndrome (ARDS). Additionally, clinical presentation might include extrapulmonary symptoms [2]. After hospitalisation, patients may remain symptomatic and this could be related to cardiac/lung sequalae and/or post-COVID-19 syndrome [3].

The post-COVID-19 syndrome is defined by the presence of persistent symptoms 12 weeks after the onset of COVID-19, and is not attributable to other known causes [3]. Among the most frequent signs and symptoms reported in post-COVID-19 syndrome are fatigue, muscle weakness, dyspnoea, hypoxaemia, depression, anxiety and sleep and cognitive disorders, along with exercise intolerance [3–5], the last of which might lead to a significant decrease in functional capacity and quality of life. Different hypotheses for mechanisms of exercise intolerance after COVID-19 infection have been explored so far, and physical deconditioning has been described as one of the most likely driving forces of symptoms [6, 7], despite the complexity of COVID-19 and the potential for multiorgan involvement.

In this context, recent findings suggest that exercise limitation in post-COVID-19 survivors in more severe patients may be related to 1) central cardiocirculatory disorder due to chronic myocardial inflammation and/or pulmonary microvascular injury [8]; 2) ventilatory inefficiency [9, 10] due to increased dead space (V_D) as a fraction of tidal volume (V_T), possibly related to endothelial and/or microvascular dysfunction [11]; 3) reduced peripheral muscle oxygen extraction [11, 12]. In patients with mild post-COVID-19 syndrome, dysfunctional breathing was a relevant mechanism of exercise intolerance [12]. Nevertheless, despite these recent advances, the pathophysiological mechanisms of exercise intolerance in post-COVID-19 survivors remain incompletely characterised. In the current study, we aimed to clarify the mechanisms of exercise intolerance associated with reduced aerobic capacity after moderate-to-severe/critical COVID-19 hospitalisation.

Materials and methods

Study design and participants

The current study is part of an observational prospective Brazilian initiative to evaluate clinical symptoms and respiratory, radiological and metabolomic function in patients who were hospitalised due to COVID-19 (FENIX Study; Brazilian Clinical Trials Registry ReBEC identifier RBR-8j9kqy).

The current report presents data from consecutive adult patients from the post-COVID-19 outpatient clinic of the Federal University of São Paulo. All included patients had the first medical visit after hospital discharge between August 2020 and May 2021 and had the following characteristics at the time of COVID-19 hospitalisation (inclusion criteria): 1) confirmed diagnosis of COVID-19 by reverse transcription PCR; 2) received supplemental oxygen (O_2) support; and 3) had acute lung parenchymal involvement confirmed by chest computed tomography (CT) scan.

Patients were invited to participate in the study in their first clinical outpatient evaluation after hospital discharge. Those patients who fulfilled the study inclusion criteria and signed an informed consent form had their clinical information recorded, and within 90±10 days after the onset of COVID-19 acute symptoms, performed a comprehensive cardiopulmonary assessment, including a cardiopulmonary exercise testing (CPET) with earlobe arterialised capillary blood gas analysis. All other tests, pulmonary lung function, echocardiogram and high-resolution chest CT (HRCT), were performed within 10 days of CPET (figure 1).

Patients in palliative cancer care, with psychiatric disturbances, musculoskeletal impairment to perform the exercise and uncontrolled known cardiovascular, endocrine–metabolic or renal diseases were excluded from the study. Patients who could not complete the study follow-up visit were also excluded (supplementary figure E1).

The methodological description of pulmonary function tests and modified Medical Council Research (mMRC) dyspnoea scale are described in the supplementary material [13–15].

CPET

Patients performed symptom-limited, ramp-incremental cycle ergometer CPET using a computer-based exercise system with breath-by-breath analysis of metabolic, ventilatory and cardiovascular variables (ULTIMA CardioO_2; Med Graphics, Saint Paul, MN, USA). The work rate was individually selected to provide an incremental phase of 7–12 min (5–20 W·min^{-1}) and started after a 2-min unloading warm-up

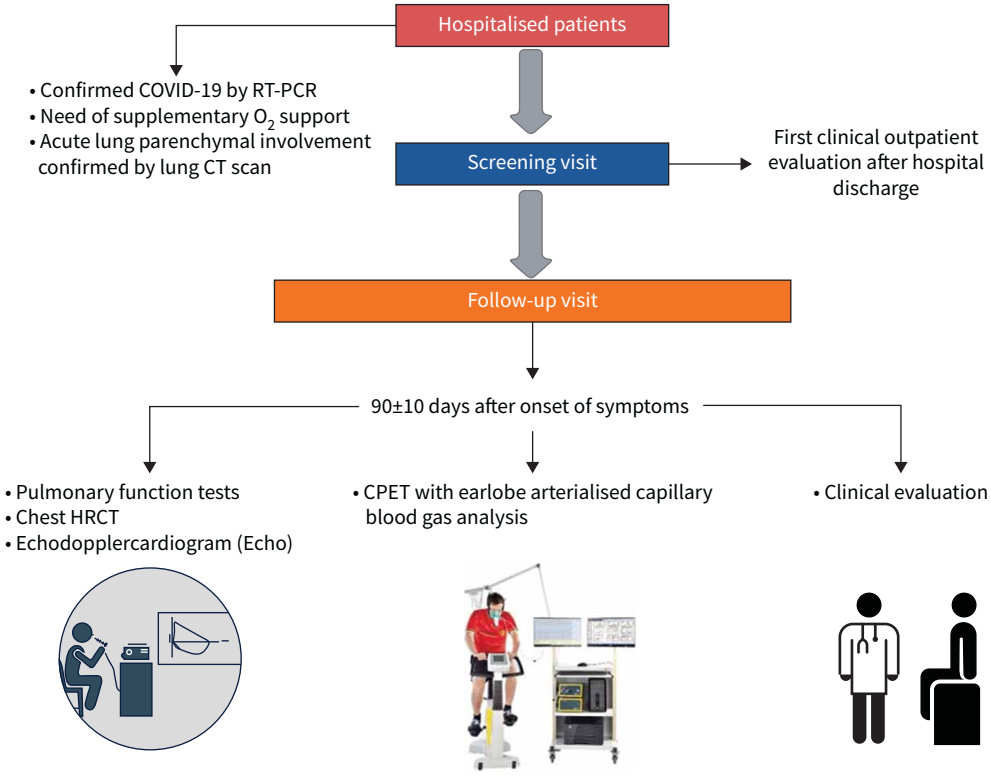

FIGURE 1 Study protocol and patient inclusion. COVID-19: coronavirus disease 2019; RT: reverse transcription; CT: computed tomography; HRCT: high-resolution CT; CPET: cardiopulmonary exercise testing.

period. The measures obtained was described elsewhere [16] and are included in the supplementary material. Earlobe arterialised capillary blood gas samples (Heparinated 200-I microtubes; Radiometer, Copenhagen, Denmark), were drawn at rest and at peak exercise after applying vasodilator capsaicin cream (Moment 0.075%; Apsen Pharmaceutical, São Paulo, Brazil). The blood analyses were performed immediately (ABL800; Radiometer, Brønshøj, Denmark) to obtain lactate and gas exchange variables (arterial oxygen partial pressure, arterial carbon dioxide partial pressure (P_{aCO_2}) and arterial oxygen saturation). Measures of alveolar–arterial O_2 gradient, arterial end-expiratory carbon dioxide gradient (P_{aETCO_2}) and V_D/V_T (Enghoff modification of the Bohr equation) were then calculated [16].

Data analysis

In the study design, there were not enough studies for sample calculation; for this sample, the confidence interval was used for a population proportion (95% CI) considering a third of the patients with reduced peak oxygen uptake (V'_{O_2peak}). Descriptive statistics are present as mean±SD, median and interquartile range of frequencies. Patients were categorised according to V'_{O_2peak} tertiles: $\leqslant$17.0 mL·kg^{-1}·min^{-1}, 17.1–22.2 mL·kg^{-1}·min^{-1} or $\geqslant$22.3 mL·kg^{-1}·min^{-1}. Comparisons between more than two groups were performed with one-way ANOVA with Bonferroni or Kruskal–Wallis *post hoc* analysis, according to the data distribution. Correlation analyses were performed using Pearson's or Spearman's coefficients to identify variables significantly associated with V'_{O_2peak} mL·kg^{-1}·min^{-1}. Receiver operating characteristic (ROC) curves were drawn for variables that had a high correlation with V'_{O_2peak} while accounting for the presence or absence of a V'_{O_2peak} $\leqslant$17.0 mL·kg^{-1}·min^{-1}. The thresholds for each ROC curve were obtained from the points with the greatest sum of sensitivity and specificity. After dichotomising the variables of interest according to ROC thresholds, univariate logistic regression was performed to explore potential V'_{O_2peak} $\leqslant$17.0 mL·kg^{-1}·min^{-1} predictors. Noncollinear variables (r$\geqslant$0.6) from the univariate analysis from different pathophysiological domains (*i.e.* symptoms, lung function, ventilatory, gas-exchange or metabolic responses to exercise) were included in multivariate logistic regression models adjusted for age, sex and prior pulmonary embolism to estimate the probability of having a V'_{O_2peak} $\leqslant$17.0 mL·kg^{-1}·min^{-1}, a second model was analysed with adjustment for age, sex and the presence of any comorbidity (supplementary table E4). The accepted statistical significance value was <0.050. Graphs were created with GraphPad

Prism (version 9.3.0 for Windows; GraphPad Software), and statistical analyses were performed using SPSS for Windows (version 21.0; IBM, Armonk, NY, USA).

Results

96 patients were eligible to participate in this study. Nine patients were excluded. Patient exclusion occurred due to acute arthritis (n=1), severe thrombocytopenia (n=1), acute deep vein thrombosis (n=1), uncontrolled systemic arterial hypertension (n=1), acute metabolic acidosis (n=1) and inability to perform the study follow-up visit (n=4). Therefore, the study sample was composed of 87 patients.

Of the 87 included patients, 54% were admitted to the intensive care unit (ICU) and 49% had ⩾50% ground-glass opacities on chest CT scan. The mean age was 53±13 years; 62% were male; and 63% had two or more comorbidities (table 1). Systemic hypertension, previous smoking history and obesity were the most common comorbidities among the patients studied (supplementary table E1). Detailed information regarding patients' comorbidities, medications of continuous use and COVID-19-related acute symptoms are provided in the supplementary table E1).

The mean V'_{O_2peak} for the entire study sample was 19.5±5.0 mL·kg^{-1}·min^{-1}, corresponding to 93±21% of predicted V'_{O_2} (30% had V'_{O_2peak} ⩽80% pred). V'_{O_2peak} tertiles were ⩽17.0, 17.1–22.2 and ⩾22.3 mL·kg^{-1}·min^{-1}. Patients with V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1} had similar hospitalisation severity as patients with V'_{O_2peak} 17.1–22.2 and ⩾22.3 mL·kg^{-1}·min^{-1}, including days in ICU, need for mechanical ventilation and radiological severity on chest CT at admission. However, at the study follow-up visit

TABLE 1 Baseline characteristics of coronavirus disease 2019 patients

Patients	87
Male	54 (62)
Age, years	53±13
BMI, kg·m^{-2}	30±4
Comorbidities	
No comorbidity	6 (7)
1 comorbidity	25 (29)
⩾2 comorbidities	55 (63)
Hospitalisation	
Hospital days	15±10
Patients in ICU	52 (54)
Days in ICU	12±10
Oxygen supplementation device	
Nasal cannula or mask	42 (48)
NIV or HFNC	25 (29)
Mechanical ventilation	21 (24)
Chest HRCT at admission	
Ground glass opacities ⩾50%	43 (49.5)
Laboratory results at hospital admission	
S_{pO_2}, %	87±7
Lymphocytes, cells·µL^{-1}	1071±638
CRP, mg·L^{-1}	128±74
D-dimer, µg·mL^{-1}	2.5±3.5
P_{aO_2}, mmHg	57±11
P_{aCO_2}, mmHg	32±5
S_{aO_2}, %	89±5
Drug therapy during hospitalisation	
Corticosteroids	78 (90)
Prophylactic anticoagulation	83 (95)
Therapeutic anticoagulation	21 (24)
Cardiovascular complications	
Pulmonary embolism	12 (14)
Myocarditis/cardiomyopathy	8 (9)

Data are presented as n, n (%) or mean±SD. BMI: body mass index; ICU: intensive care unit; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; HRCT: high-resolution computed tomography; S_{pO_2}: pulse oxygen saturation; CRP: C-reactive protein; P_{aO_2}: arterial oxygen partial pressure; P_{aCO_2}: arterial carbon dioxide partial pressure; S_{aO_2}: arterial oxygen saturation.

(90±10 days after the onset of COVID-19), patients with V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1} reported a greater sensation of dyspnoea (mMRC ⩾1) compared to the other two groups (table 2). Additionally, patients with V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1} had lower forced vital capacity (FVC), total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (D_{LCO}) and residual volume compared to the other groups (table 2). The persistence of lung parenchymal involvement on HRCT and cardiac function by echocardiogram at the follow-up visit was similar between groups (table 2).

CPET findings are presented in table 3. Patients with V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1} achieved lower peak work rate (WR), peak heart rate and lower $\Delta V'_{O_2}/\Delta$WR. At the anaerobic threshold, patients with V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1} had higher minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) and lower P_{ETCO_2} and no difference on V'_{O_2} (table 3). Additionally, patients with V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1} had higher $\Delta V'_E/\Delta V'_{CO_2}$ at respiratory compensation point (RCP), peak respiratory rate/V_T, peak V_D/V_T, peak P_{aETCO_2} and associated with a lower peak arterial oxygen content (C_{aO_2}) and higher level of lactate/WR and a greater sensation of dyspnoea and fatigue in proportion to WR compared to patients with V'_{O_2peak} 17.1–22.2 and ⩾22.3 mL·kg^{-1}·min^{-1} (figure 2).

TABLE 2 Coronavirus disease 2019 patients' characteristics during hospitalisation and lung function tests, chest computed tomography and echocardiogram according to peak oxygen uptake (V'_{O_2peak}) tertiles

	Total	V'_{O_2peak}			p-value[#]
		⩽17.0 mL·kg^{-1} min^{-1}	17.1–22.2 mL·kg^{-1} min^{-1}	⩾22.3 mL·kg^{-1} min^{-1}	
Patients	87	29	29	29	
Male	55 (63)	11 (37)[+]	17 (59)[§]	27 (93)	<0.001
Age, years	53±13	60±11[+,f]	52±13	46±10	<0.001
BMI, kg·m^{-2}	29.8±4	29.6±4	30.3±5	29.6±3	0.786
Severity during hospitalisation					
Days in ICU	12±10	15±14	13±13	11±8	0.583
Mechanical ventilation	21 (24)	6 (21)	7 (24)	8 (28)	0.660
Chest HRCT: GGO ⩾50%	43 (49.5)	17 (59)	14 (48)	12 (41)	0.400
Pulmonary embolism	12 (14)	5 (17)	3 (10)	4 (15)	0.755
Follow-up visit[¶]					
Symptoms[¶]					
mMRC ⩾1	60 (69)	27 (93)[+]	21 (72)[§]	12 (41)	<0.001
Fatigue/myalgia	45 (52)	17 (59)	16 (55)	12 (41)	0.389
Memory loss	26 (30)	12 (41)	10 (34)	4 (14)	0.058
No symptoms	17 (20)	1 (3)[+]	4 (14)[§]	12 (41)	0.001
Lung function[¶]					
FVC, % pred	88±13	81±12[f]	91±14	90±13	0.024
FEV_1, % pred	90±13	85±12	92±13	92±14	0.127
FEV_1/FVC	0.82±0.50	0.83±0.60	0.81±0.40	0.83±0.40	0.241
D_{LCO}, % pred	80±23	66±25[f]	86±21	84±19	0.021
D_{LCO}/V_A, % pred	101±22	91±27	102±21	108±18	0.077
TLC, % pred	84±14	81±17	88±12	83±12	0.247
RV, % pred	97±26	102±37	105±22[§]	87±19	0.045
MIP, % pred	105±23	96±29	110±21	109±21	0.174
MEP, % pred	97±25	87±23	99±28	108±22	0.059
Echocardiogram[¶]					
Left ventricular ejection fraction, %	65±7	63±8	65±7	66±5	0.508
TRV, m·s^{-1}	2.3±0.2	2.3±0.3	2.5±0.1	2.1±0.3	0.417
sPAP, mmHg	27±8	29±6	31±3	20±8	0.083
Chest HRCT[¶]					
Near-normal ⩽10%	68 (76)	19 (66)	28 (96)	21 (72)	0.833
Abnormalities ⩾25%	14 (16)	4 (14)	7 (24)	3 (10)	0.565

Data are presented as n, n (%) or mean±SD. BMI: body mass index; ICU: intensive care unit; HRCT: high-resolution computed tomography; GGO: ground-glass opacities; mMRC: modified Medical Research Council dyspnoea scale; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume; TLC: total lung capacity; RV: residual volume; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; TRV: tricuspid valve regurgitation; sPAP: systolic pulmonary artery pressure. [#]: from ANOVA or Kruskal–Wallis and difference between groups by V'_{O_2peak} (mL·kg^{-1}·min^{-1}); [¶]: 90±10 days after hospitalisation, total of patients who underwent spirometry (n=78), lung volumes (n=64), D_{LCO} and muscle strength (n=54), echocardiogram (n=74), chest HRCT (n=87). Other symptoms: cough (16%), headache (14%), depressed mood (13%), insomnia (13%), chest pain (10%); [+]: ⩽17.0 *versus* ⩾22.3 mL·kg^{-1}·min^{-1}; [§]: 17.1–22.2 *versus* ⩾22.3 mL·kg^{-1}·min^{-1}; [f]: ⩽17.0 *versus* 17.1–22.2 mL·kg^{-1}·min^{-1}.

TABLE 3 Cardiopulmonary exercise testing (CPET) responses and blood gas analysis of coronavirus disease 2019 patients at rest and at peak exercise according to peak oxygen uptake (V'_{O_2peak}; mL·kg^{-1}·min^{-1}) tertiles

	Total	V'_{O_2peak}			p-value[#]
		⩽17.0 mL·kg^{-1} min^{-1}	17.1–22.2 mL·kg^{-1} min^{-1}	⩾22.3 mL·kg^{-1} min^{-1}	
Patients	87	29	29	29	
CPET responses					
V'_{O_2peak}, % pred	93±21	80±18[¶,+]	96±18	103±19	<0.001
Peak WR, W	108±46	68±22[¶,+]	104±34[§]	152±33	<0.001
Peak RER	1.10±0.12	1.10±0.11	1.08±0.14	1.12±0.11	0.374
Peak HR, % pred	87±12	79±12[¶,+]	90±10	93±9	<0.001
V'_{O_2AT}, % pred	56±15	52±16	60±16	55±14	0.196
$\Delta V'_{O_2}/\Delta$WR, mL·min^{-1}·W^{-1}	11±2	11±1[¶]	12±2	12±2	0.014
V'_{O_2peak}/HR, % pred	108±24	105 ±26	107±26	111±21	0.620
Peak V'_E/MVV	0.53±0.14	0.48±0.15[¶]	0.54±0.14	0.58±0.10	0.028
Peak V_T, L	1.54±0.49	1.18±0.35[¶,+]	1.55±0.42[§]	1.89±0.44	<0.001
Peak RR/V_T	26±14	33±20[¶]	24±9	23±9	0.017
V'_E/V'_{CO_2AT}	33±6	36±6[¶]	33±6[§]	29±4	<0.001
Peak V'_E/V'_{CO_2}	38±8	41±9[¶]	38±8	35±5	0.012
P_{ETCO_2}AT, mmHg	38±5	36±4[¶]	38±6[§]	41±4	<0.001
Peak P_{ETCO_2}mmHg	33±5	31±5[¶]	33±6	34±4	0.039
Rest S_{pO_2}, %	97±1	96±2	97±1	97±1	0.205
Peak S_{pO_2}, %	95±3	95±4	95±3	95±3	0.900
Blood gas analysis					
Rest V_D/V_T	0.40±0.09	0.45±0.09[¶]	0.38±0.09	0.38±0.07	0.035
Peak V_D/V_T	0.26±0.12	0.34±0.12[¶,+]	0.25±0.12	0.21±0.10	<0.001
Rest P_{A-aO_2}, mmHg	12 (10–14)	14 (11–18)[¶]	13 (10–16)	9 (6–12)	0.025
Peak P_{A-aO_2}, mmHg	26 (19–34)	31 (22–36)	24 (16–31)	24 (18–31)	0.498
Rest C_{aO_2}, mL·dL^{-1}	19.5±2	18.6±3[¶]	19.7±2	20.2±2	0.042
Peak C_{aO_2}, mL·dL^{-1}	21.7±3	20.5±3[¶]	21.7±2	22.6±3	0.034
Rest P_{aO_2}, mmHg	79±8	79±9	78±9	80±7	0.849
Peak P_{aO_2}, mmHg	80±12	77±14	82±10	81±13	0.569
Rest P_{aCO_2}, mmHg	35±4	35±3	34±4[§]	37±4	0.035
Peak P_{aCO_2}, mmHg	33±4	33±4	32±4	34±3	0.188
Hb, mg·dL^{-1}	14.9±2.0	14.2±2.0	15.2±1.0	15.3±2.0	0.053

Data are presented as n, mean±SD or median (interquartile range). WR: work rate; RER: respiratory exchange ratio; HR: heart rate; AT: anaerobic threshold; V'_E: minute ventilation; MVV: maximal voluntary ventilation; V_T: tidal volume; RR: respiratory rate; V'_{CO_2}: carbon dioxide production; P_{ETCO_2}: end-tidal carbon dioxide pressure; S_{pO_2}: pulse oxygen saturation; V_D: dead space volume; P_{A-aO_2}: alveolar–arterial oxygen tension difference; C_{aO_2}: arterial oxygen content; P_{aO_2}: arterial oxygen partial pressure; P_{aCO_2}: arterial carbon dioxide partial pressure; Hb: haemoglobin. [#]: p-values from ANOVA or Kruskal–Wallis and difference between groups by $V'_{O_2peak;}$ [¶]: ⩽17.0 and ⩾22.3 mL·kg^{-1}·min^{-1}; [+]: ⩽17 and 17.1–22.2 mL·kg^{-1}·min^{-1}; [§]: 17.1–22.2 and⩾22.3 mL·kg^{-1}·min^{-1}.

There was a positive correlation between V'_{O_2peak} and FVC, D_{LCO}, V'_E/maximal voluntary ventilation (MVV) and peak C_{aO_2}. There was a negative correlation between V'_{O_2peak}, several comorbidities, dyspnoea (mMRC), $\Delta V'_E/\Delta V'_{CO_2RCP}$, peak respiratory rate/$V_T$, peak V_D/V_T, peak P_{aETCO_2} and peak lactate/WR. No correlation was found between V'_{O_2peak} and days of hospitalisation or days in ICU (supplementary table E2).

The ROC curve analyses to identify the presence of a V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1} showed a statistically significant area under the curve for symptoms (mMRC), FVC, D_{LCO}, peak respiratory rate/V_T, peak V'_E/MVV, peak V_D/V_T, $\Delta V'_E/\Delta V'_{CO_2RCP}$, P_{aETCO_2}, peak WR, peak C_{aO_2}, peak lactate and peak lactate/WR (supplementary table E3).

The univariate logistic regression analysis to predict a V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1}, including relevant variables from different pathophysiological domains (*i.e.* symptoms, lung function, ventilatory, gas-exchange or metabolic responses to exercise) is presented in table 4. Among noncollinear variables, the multivariate logistic regression model adjusted for age, sex and presence of pulmonary embolism identified that a FVC ⩽80% pred and a peak V_D/V_T ⩾29 were independent predictors of a V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1} (table 4). A second multivariate logistic regression model was performed, with adjustment for age, sex and the presence of any comorbidity and FVC % pred and V_D/V_T remained as predictors of V'_{O_2peak} (supplementary table E4). Of note, V_D/V_T had a negative correlation with D_{LCO} % pred (r=0.64, p<0.01); a positive

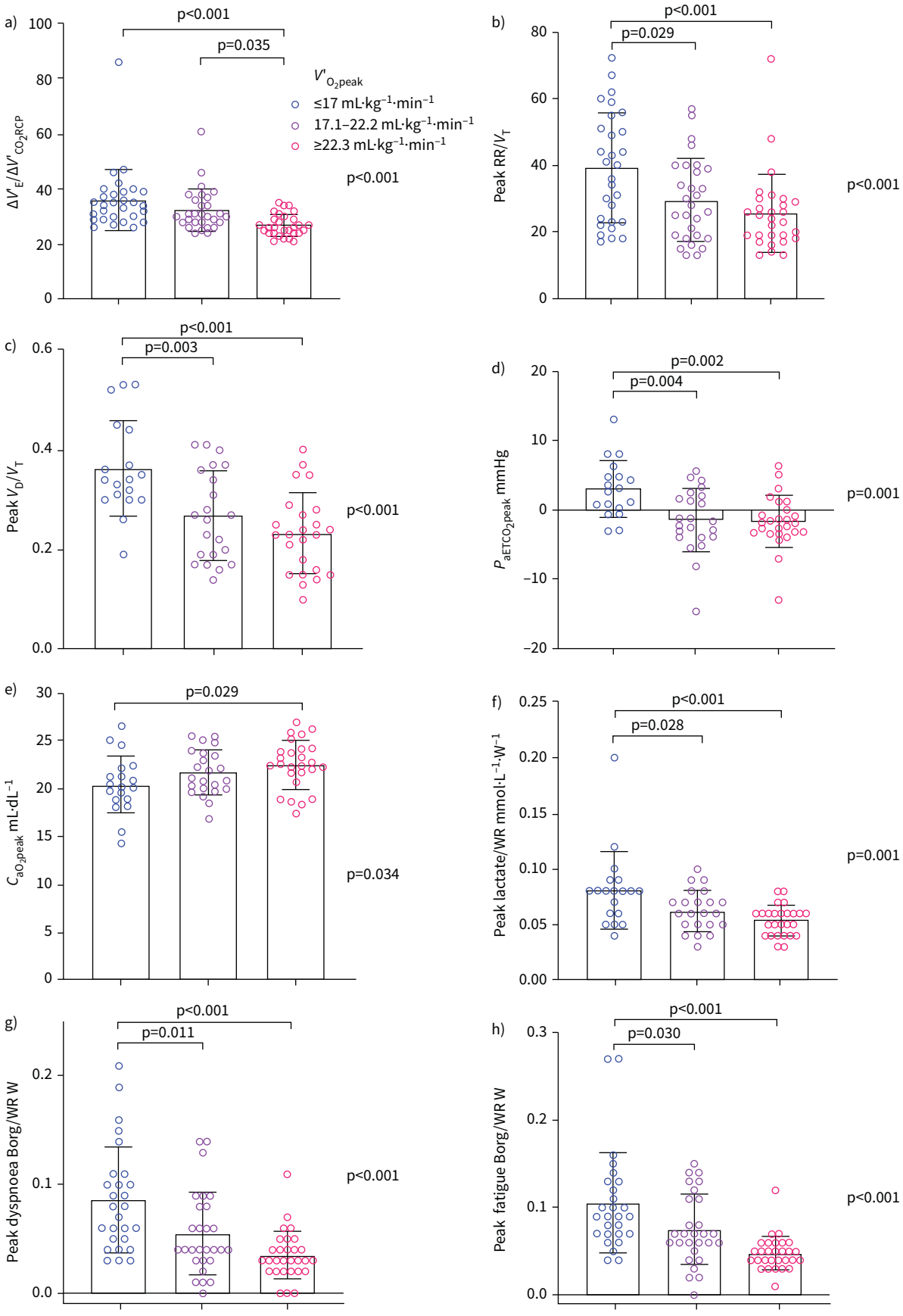
a)
p<0.001
p=0.035
$\Delta V'_E/\Delta V'_{CO_2RCP}$
V'_{O_2peak}
≤17 mL·kg^{-1}·min^{-1}
17.1–22.2 mL·kg^{-1}·min^{-1}
≥22.3 mL·kg^{-1}·min^{-1}
p<0.001
b)
p<0.001
p=0.029
Peak RR/V_T
p<0.001
c)
p<0.001
p=0.003
Peak V_D/V_T
p<0.001
d)
p=0.002
p=0.004
P_{aETCO_2peak} mmHg
p=0.001
e)
p=0.029
C_{aO_2peak} mL·dL^{-1}
p=0.034
f)
p<0.001
p=0.028
Peak lactate/WR mmol·L^{-1}·W^{-1}
p=0.001
g)
p<0.001
p=0.011
Peak dyspnoea Borg/WR W
p<0.001
h)
p<0.001
p=0.030
Peak fatigue Borg/WR W
p<0.001

FIGURE 2 Comparison of peak oxygen uptake (V'_{O_2peak}) (mL·kg^{-1}·min^{-1}) in cardiopulmonary exercise testing responses after 3 months of symptoms in survivors of coronavirus disease 2019. a) Ventilatory equivalents for carbon dioxide at respiratory compensation point (RCP); b) respiratory rate (RR) of tidal volume (V_T) at peak exercise; c) dead space volume (V_D) fraction of V_T at peak exercise; d) arterial to end-tidal carbon dioxide difference at peak exercise (P_{aETCO_2peak}); e) relationship of V'_{O_2} and arterial oxygen content at peak exercise (C_{aO_2peak}); f) lactate by work rate (WR) at peak exercise; g) dyspnoea Borg scale by WR at peak exercise; h) fatigue Borg scale by WR at peak exercise. V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production. p-values calculated by ANOVA or Kruskal–Wallis.

correlation with peak V_D (r=0.62, p<0.001); and a positive correlation with P_{aETCO_2} (r=0.88, p<0.001). Interestingly, FVC and V_D/V_T were not significantly correlated (r=0.14, p=0.292).

Discussion

The present observational study showed that exercise intolerance in post-COVID-19 survivors with a relatively short hospital stay (15±10 days) was related to high V_D/V_T at peak exercise and low FVC % pred after 90±10 days of acute infection. This finding suggests that both pulmonary microcirculation injury and pulmonary ventilatory impairment might play a role in influencing aerobic capacity in the post-COVID-19 survivors.

V_D/V_T is related to the physiological dead space ratio, divided into anatomical dead space (*i.e.* airways that do not participate in gas exchange), and alveolar dead space. A high V_D/V_T results from areas of normal ventilation and low perfusion that contribute to ventilation–perfusion (V'/Q') mismatch. A low V_D/V_T results from areas of low ventilation and normal perfusion. Both high and low V_D/V_T can be present in the same disease [17]. It is important to note that V_D/V_T is expected to reach a level <0.20 after the anaerobic threshold in physiological conditions due to the increased perfusion of areas of the lungs with high V'/Q' ratios at rest and a relatively greater increase in V_T tidal volume than anatomical dead space, the abnormal response is dependent on severity of pulmonary lesions [16]. In our sample, V_D/V_T decreased during exercise in all three groups, but peak V_D/V_T progressively increased from the subgroup V'_{O_2peak} >22.2 mL·kg^{-1}·min^{-1} to the subgroup V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1}. Additionally, despite reducing during exercise, V_D/V_T did not reach physiological values in all three groups. A high V_D/V_T might be related to ventilatory inefficiency (high V'_E/V'_{CO_2}), and dyspnoea sensation, being associated or not with enhanced chemosensitivity and a decreased carbon dioxide set point [17].

TABLE 4 Univariate and multivariate logistic analysis adjusted for sex, age and prior pulmonary embolism for peak oxygen uptake (V'_{O_2peak}) ⩽17.0 mL·kg^{-1}·min^{-1} according to persistence of symptoms, lung function and cardiopulmonary exercise testing (CPET) variables

	Univariate		Multivariate	
	p-values	OR (95% CI)	p-values	OR (95% CI)
Symptoms				
mMRC ⩾1	0.015	3.90 (1.30–11.64)		
Lung function				
FVC ⩽80% pred	<0.001	9.49 (2.96–30.39)	0.004	17.32 (2.53–118.32)
D_{LCO} ⩽65% pred	0.002	9.60 (2.37–38.86)		
CPET				
Ventilatory responses				
Peak V'_E/MVV ⩾49	0.005	0.25 (0.10–0.66)		
Peak RR/V_T ⩾40	<0.001	5.83 (2.10–16.14)		
Gas-exchange responses				
$\Delta V'_E/\Delta V'_{CO_2}$RCP ⩾32	0.001	4.87 (1.83–12.95)		
Peak V_D/V_T ⩾29	<0.001	20.30 (4.08 –100.98)	0.004	26.57 (2.84–248.61)
Peak P_{aETCO_2} ⩾2.65	0.001	7.50 (2.20–25.57)		
Metabolic responses				
$\Delta V'_{O_2}$/ΔWR ⩽11.5 mL·min^{-1}·W^{-1}	0.012	4.10 (1.36–12.32)		
Lactate/WR ⩾0.075 mmol·L^{-1}·W^{-1}	<0.001	10.28 (3.01–35.13)		

Multivariate logistic analysis, with R^2=0.46. Cut-off point of the variables defined by receiver operating characteristic curve. mMRC: modified Medical Research Council; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V'_E: minute ventilation; MVV: maximal voluntary ventilation; RR: respiratory rate; V_T: tidal volume; V'_{CO_2}: carbon dioxide production; RCP: respiratory compensation point; V_D: dead space volume; P_{aETCO_2}: arterial end-expiratory carbon dioxide gradient; WR: work rate.

Our results show that a high V_D/V_T at peak exercise (⩾0.29) is an independent predictor of a V'_{O_2peak} ⩽17.0 mL·min·kg^{-1} (table 4). In addition to the high V_D/V_T, a high peak exercise P_{aETCO_2} (figure 2) might corroborate the presence of V'/Q' inequality in the studied population. Some studies in post-COVID-19 patients showed an increase in V_D/V_T; however, they did not link its association to patients' exercise intolerance [11, 18]. Baratto *et al.* [11] showed that exercise hyperventilation after COVID-19 acute infection was related to enhanced chemoreflex sensitivity rather than increased V_D/V_T. Conversely, others have demonstrated that a reduced V'_{O_2peak} was associated with a mild increase of V'_E/V'_{CO_2} and have suggested that the observed hyperventilation could be related to increased chemoreflex sensitivity secondary to deconditioning, dysfunctional breathing or even dysautonomia [6, 9, 19, 20]. Acute COVID-19 lung lesions have been related to diffuse alveolar damage, interstitial fibrosis and endothelial vascular injuries, which result in areas of shunt (low V'/Q') and/or dead space (high V'/Q'). Along the lines, studies comparing ARDS in COVID-19 *versus* non-COVID-19 patients showed that COVID-19 ARDS patients have a higher dead space ventilation compared to non-COVID-19-ARDS, despite a similar pulmonary compliance [21]. The aforementioned lung insults can potentially cause transitory or persistent lung sequelae [22–24]. In our study, V_D/V_T had a negative correlation with low D_{LCO}, a positive correlation with V_D and a positive correlation with P_{aETCO_2}. Similar findings have been shown for cardiocirculatory diseases such as left heart failure and pulmonary arterial hypertension [25–28]. It is important to note that a low D_{LCO} was found in the long term after severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and SARS-CoV-2 patients, even in those with normal lung parenchyma on HRCT [2, 29–33]. Furthermore, during acute COVID-19 infection, dual-energy thoracic CT studies showed the presence of pulmonary perfusion heterogeneity along with pulmonary ischaemic areas in the absence of visible pulmonary arterial thrombosis and in areas not related to ground-glass opacities or any parenchymal lesions, which may reflect the presence of microvascular injury [34]. Based on this and our study findings, we speculate that chronic lung microvascular injury might be a pathophysiological mechanism leading to high V_D/V_T during exercise in post-COVID-19 patients. This hypothesis is supported by the multivariate regression (table 4), where history of pulmonary embolism was not a determining factor for the increased V_D/V_T. The same occurs when the regression is adjusted for the presence of any comorbidity (supplementary table E4), suggesting that V_D/V_T might be elevated due to microcirculation injury. Of note, this microvascular involvement had no repercussions on the findings of resting echocardiogram in our patients.

FVC % pred was also identified as an independent predictor of a V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1}; however, FVC and V_D/V_T were not significantly correlated. A low FVC has been reported in post-COVID-19 patients as far as 1 year after the acute infection, and similar results have been demonstrated in SARS-CoV-1 survivors [29, 33]. Considering that a low FVC might be related to the ARDS severity, it might indicate the development of restrictive ventilatory impairment secondary to lung interstitial sequelae [35]. This is in line with a tachypnoea pattern, proven by high respiratory rate/V_T. Nonetheless, we did not identify significant differences in TLC and acute parenchymal lung involvement on HRCT according to V'_{O_2peak} severity (table 2).

In addition to a potential interstitial lung disease development impacting FVC, we should also consider pulmonary neuromuscular dysfunction as a possible cause of reduced FVC. Inspiratory muscle weakness and decreases in peripheral muscle strength have been described in post-COVID-19 patients, and were associated with reduced aerobic capacity [35–37]. However, our results did not identify a significant difference in maximal inspiratory pressure according to V'_{O_2peak} severity (table 2).

Interestingly, lactate/WR was higher according to V'_{O_2} tertiles (figure 2), despite the similar anaerobic threshold (table 3). This finding has been demonstrated previously in patients with oxidative myopathy [38]. It suggests that the mechanisms of lactate clearance fail to keep pace with lactate production in post-COVID-19 patients, and/or there is an impairment in O_2 utilisation at higher levels of exercise [39]. In our study, the elevated lactate/WR observed in patients with V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1} might be a consequence of a mildly reduced O_2 delivery (low C_{aO_2}) and/or an imbalance in O_2 muscle utilisation due to a decrease in oxidative fibres secondary to prolonged hospitalisation, neuromuscular drug toxicity, direct viral mitochondrial injury by immediate viral effect and/or systemic inflammation [3, 40]. As a result, the aforementioned mechanisms will stimulate a rapid respiratory rate and increase the neural perception of dyspnoea, but further studies are required to investigate this hypothesis in post-COVID-19 patients.

Our study has some limitations that should be considered. We did not include a healthy-control group; nonetheless, patients with V'_{O_2peak} >22.2 mL·kg^{-1}·min^{-1} had a more preserved aerobic capacity and therefore could be considered from an exercise physiology perspective as a control for the subgroup with V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1}. Despite not having a healthy-control group, our exercise findings are similar to Skjørten *et al.* [6]. Along these lines, it is important to note that all patients included in the subgroup

V'_{O_2peak} 22.2 mL·kg^{-1}·min^{-1} had a V'_{O_2peak} >80% pred, and that most patients with a V'_{O_2} ⩽80% pred were included in the subgroup V'_{O_2peak} ⩽17.0 mL·kg^{-1}·min^{-1}. In physiological terms, the V'_{O_2} in absolute value decreases with ageing, and more so in females than males. In our study, age was different across V'_{O_2peak} subgroups. It is known that age and sex might influence some ventilatory responses due to lower V_{Tpeak} and less efficient ventilation during exercise (without abnormally high V_D/V_T), probably related to increased airway resistance and mechanical constraint with a reduced compliance of the lungs. This phenomenon is more pronounced in older females but, in general, with little impact on exercise capacity. Of note, sex *per se* does not affect gas exchange, but ageing could indeed change the P_{aCO_2} equilibrium [41, 42]. Considering this and aiming to minimise the possible effects of age and sex on exercise physiological responses and in the study findings, the multivariate model was adjusted for age and sex. We did not perform exercise haemodynamics, single-photon emission lung CT or dual-energy CT thoracic angiography, and therefore we can only speculate on the association between high V_D/V_T during exercise and the hypothesis of pulmonary microvascular dysfunction. Additionally, we did not perform comprehensive muscle-related studies, and therefore we are not able to undoubtedly confirm muscle weakness as a potential cause for a reduced V'_{O_2peak}. Finally, the control of breathing during exercise is complex, multifactorial and not completely understood. The current study could not explain or phenotype the pathophysiological mechanisms of exercise intolerance in post-COVID-19 patients.

In summary, the current study demonstrates that a high V_D/V_T at peak exercise and a low resting FVC are associated with a reduced V'_{O_2peak} in moderate-to-severe/critical post-COVID-19 patients. The high peak exercise V_D/V_T might suggest the role of pulmonary microvascular dysfunction on dyspnoea and exercise intolerance in the post-COVID-19 survivors. The low FVC suggests that pulmonary ventilatory dysfunction might be an additional factor influencing aerobic capacity in this patient population. Further studies are needed to confirm whether post-COVID-19 survivors will develop pulmonary vascular disease and/or clinically relevant interstitial pulmonary disease in the long term.

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