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Short communication

Severity does not impact on exercise capacity in COVID-19 survivors

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ABSTRACT

Background: current data on the impact of acute illness severity on exercise capacity and ventilatory efficiency of COVID-19 survivors, evaluated at cardiopulmonary exercise test (CPET), are limited.

Methods: in this post-hoc analysis of our previous observational, prospective, cohort study on mechanisms of exercise intolerance in COVID-19 survivors, we aimed at evaluating the impact of acute COVID-19 severity on exercise capacity, pulmonary function testing (PFT) and chest computed tomography (CT) outcomes.

Results: we enrolled 75 patients (18 with mild-to-moderate disease, 18 with severe disease, and 39 with critical disease). Mean (standard deviation – SD) follow-up time was 97 (26) days. Groups showed a similar PFT and CT residual involvement, featuring a mildly reduced exercise capacity with comparable mean (SD) values of peak oxygen consumption as percentage of predicted (83 (17) vs 82 (16) vs 84 (15), $p = 0.895$) among groups, as well as the median (interquartile range – IQR) alveolar-arterial gradient for O_2 in mmHg at exercise peak (20 (15–28) vs 27 (18–31) vs 26 (21-21), $p = 0.154$), which was in the limit of normal. In addition, these patients featured a preserved mean ventilatory efficiency evaluated through the slope of the relation between ventilation and carbon dioxide output during exercise (27.1 (2.6) vs 29.8 (3.9) vs 28.3 (2.6), $p = 0.028$), without a clinically relevant difference.

Conclusions: Disease severity does not impact on exercise capacity in COVID-19 survivors at 3 months after discharge, including a ventilatory response still in the limit of normal.

1. Introduction

The heterogeneity of COVID-19 clinical manifestations became evident since its appearance in December 2019 [1]. However, the impact of the severity of the acute phase of the disease on potential long-term sequelae is still unclear, particularly regarding exercise response [2]. The aim of our study was therefore to compare cardiopulmonary exercise testing (CPET) outcomes in patients with different acute disease severity, in the mid-term after COVID-19 resolution.

2. Methods

The present study is a post-hoc analysis of the data collected in our cohort observational prospective study aimed at evaluating the mechanisms of residual reduced exercise capacity in COVID-19 survivors (Milan Area 1 Ethics Committee - 2020/ST/407) [3]. Consecutive patients admitted during the first wave of COVID-19 [4], between February–April 2020, at the Respiratory Unit at San Paolo Hospital (Milan, Italy), who attended post-COVID-19 respiratory clinic were invited to undergo CPET in May–August 2020. Inclusion criteria were: 1) age >18 years, 2) previous molecular diagnosis of SARS-CoV-2 infection. Exclusion criteria were the absence of a signed informed consent, acute respiratory exacerbation in the previous 4 weeks and the presence of medical conditions contraindicating CPET.

Clinical data of the patients were reviewed during the clinical visit. Severity of the disease was defined on WHO guidance [5]: 1) mild

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(symptomatic patients with no evidence of pneumonia); 2) moderate (pneumonia and an oxygen saturation measured by pulse oximetry, SpO_2, >90% in room air); 3) severe (pneumonia and SpO2 <90% in room air); 4) critical (Acute Respiratory Distress Syndrome, ARDS, with an arterial oxygen partial pressure to fractional inspired oxygen - P/F ratio - <300 mmHg during the application of Continuous Positive Airway Pressure, CPAP, with at least 5 cmH_2O of Positive End-Expiratory Pressure, PEEP, in case of bilateral pneumonia). Dyspnoea was quantified according to the Italian version of the modified Medical Research Council dyspnoea during daily living scale (mMRC). All patients underwent spirometry and single breath diffusing lung capacity for carbon monoxide test (DLCO). The prescription of chest computed tomography (CT) was based on clinical judgment. When available, follow-up chest CT was evaluated by a radiologist and a respiratory physician. Two CT scores were used to estimate the magnitude of the residual involvement: the CT severity score (CT-SS) and the visual percentage of residual parenchymal involvement (%VRPI) [6,7].

Symptom-limited, incremental, exercise testing was performed a week from the clinical visit (Vmax Spectra Cardiopulmonary Exercise Testing System, SensorMedics, Yorba Linda, USA) using individualized ramp protocols on an electronically braked cycle ergometer. Gas exchange variables were acquired breath-by-breath; measured and computed variables were collected [8,9]. We obtained an arterial blood sample for blood gas analysis (BGA) and lactates at the peak of the exercise [10]. A reduced exercise capacity was defined by a peak oxygen consumption (VO_2) <85% predicted. Ventilatory inefficiency was defined by a slope of the relation between ventilation and carbon dioxide output during exercise (VE/VCO_2 slope) > 30 L/L.

Quantitative data are described with means and standard deviations (SD) or median and interquartile ranges (IQR) according to their distribution, and qualitative data with absolute frequencies and percentages. Anova and Kruskal Wallis tests were computed to assess statistical differences for normal or non-normal quantitative variables, respectively. Qualitative data were analysed with Pearson's chi-squared test. A p-value <0.05 was considered statistically significant. Statistical tests were performed using the Statistical Package for Social Sciences (SPSS, Chicago IL, USA), version 23.0.

3. Results

We enrolled 75 patients, of whom 18 with mild-to-moderate disease, 18 with a severe disease, and 39 with a critical disease (Table 1). Mean time (SD) between hospital discharge and PFT/CPET was 97 (26) days. Patients with critical disease were older than those with mild-moderate disease. No significant differences were observed in terms of pulmonary function tests (PFT), though with some residual impairment, and mMRC score across the different severity groups. A higher share of critical vs mild-moderate illness patients presented abnormal CT findings at follow-up, although the magnitude of parenchymal involvement in these patients was not different compared to the other two groups. We did not find any statistical difference among groups in the distribution of comorbidities, with systemic hypertension and asthma being the most common cardio-respiratory chronic conditions (data not shown). No differences emerged in terms of peak exercise capacity, peak blood gas parameters or cardiovascular response to exercise. The number of patients presenting reduced exercise capacity was comparable among groups (p = 0.790), as those presenting a residual ventilatory inefficiency (p = 0.718). One patient in the critical group presented hyperventilation, with no evidence of DLCO and CT residual involvement, as in the emerging entity of Long COVID. Nevertheless, patients with severe disease showed a significantly higher mean value of VE/VCO_2 slope in comparison with those with a mild-moderate disease (p-value = 0.028).

Table 1
Lung function, CT and CPET parameters according to disease severity.

	All patients (n = 75)	Mild-moderate disease (n = 18)	Severe disease (n = 18)	Critical disease (n = 39)	p-value* Anova or Kruskal-Wallis
Male/Female n (percentage)	43/32 (57/43)	9/9 (50/50)	7/11 (39/61)	27/12 (69/31)	0.076
Age years	57 (12)	50 (9) †	58 (13)	59 (11) †	**0.042**
BMI kg/m^2	28.6 (4.7)	26.7 (5.3)	28.2 (4.4)	29.6 (4.2)	0.097
Smoking status never/current/ex-smoker (%)	48/8/19 (64/10/26)	14/2/2 (78/11/11)	12/0/6 (66/0/44)	22/5/12 (56/13/31)	0.272
mMRC at the time of CPET (0/1/2/3/4)	32/35/8/0/0	5/9/4/0/0	7/9/2/0/0	17/13/9/0/0	0.559
Mean follow-up time days	97 (26)	95 (29)	97 (29)	98 (26)	0.932
FEV1 % predicted	104 (17)	104 (13)	104 (19)	105 (18)	0.989
FVC %predicted	100 (16)	101 (14)	101 (16)	100 (16)	0.923
DLCO° % predicted	71 (14)	72 (13)	67 (12)	73 (15)	0.378
KCO° % predicted	84 (15)	82 (15)	81 (15)	86 (14)	0.469
Alveolar Volume° % predicted	86(14)	89 (17)	85 (14)	84 (13)	0.505
CT abnormal/total n (%)	43/68 (63)	5/16 (31) †	9/18 (53)	29/38 (76) †	**0.006**
CT- SS#	17 (10)	16.2 (8.4)	13.9 (11.2)	18.7 (10)	0.437
%V-RPI#∞	15 (20–35)	15 (12–30)	15 (7–27)	20 (15–40)	0.342
VO_2 peak % predicted	83 (15)	83 (17)	82 (16)	84 (15)	0.895
VO_2 peak absolute ml/min/kg	20.0 (5.5)	22.1 (6.3)	18.4 (5.0)	19.8 (5.1)	0.127
VO_2 peak <85% predicted n (%)	41 (54)	11 (61)	9 (50)	21 (51)	0.790
Work peak % predicted	85 (19)	84 (14)	88 (29)	85 (15)	0.832
Anaerobic Threshold % VO_2 max predicted	54 (13)	52 (14)	56 (15)	55 (12)	0.550
VO_2/work slope ml/min/W	10.4 (1.4)	10.3 (1.1)	10.3 (1.9)	10.4 (1.2)	0.955
Respiratory Exchange Ratio peak	1.21 (0.10)	1.22 (0.09)	1.18 (0.11)	1.21 (0.10)	0.594
Heart rate reserve %	13 (11)	12 (13)	16 (13)	12 (10)	0.495
Oxygen pulse peak %pred	96 (21)	94 (31)	100 (22)	96 (14)	0.679
Breathing reserve %	44 (13)	48 (13)	45 (14)	42 (13)	0.217
VE/VCO_2 slope L/L	28.4 (3.1)	27.1 (2.6) ‡	29.8 (3.9) ‡	28.3 (2.6)	**0.028**
VE/VCO_2 slope >30 n (%)	11 (14)	1 (5)	5 (27)	5 (13)	0.718
Alveolar-arterial gradient for O_2§∞ mmHg	26 (18–31)	20 (15–28)	27 (18–31)	26 (21–31)	0.154
	94 (11)	99 (10)	95(11)	96 (10)	0.205

(continued on next page)

Table 1 (*continued*)

	All patients (n = 75)	Mild-moderate disease (n = 18)	Severe disease (n = 18)	Critical disease (n = 39)	p-value* Anova or Kruskal-Wallis
PaO_2 peak§ mmHg					
$PaCO_2$ peak§ mmHg	35 (4)	36 (4)	34 (5)	35 (4)	0.491
Physiologic dead space fraction peak %	19 (8)	18 (7)	20 (7)	20 (9)	0.559
Lactate peak§ mmol/L	7.5 (2.7)	8.2 (2.8)	6.6 (2.4)	7.2 (2.6)	0.267
BORG scale of dyspnoea peak	4.0 (2.3)	3.5 (2.4)	3.9 (2.0)	3.7	0.870
BORG scale of perceived exertion peak	5.3 (2.0)	5.4 (2.0)	5.3 (2.2)	5.5	0.946

All quantitative data mean (SD), unless otherwise specified; ∞ median (IQR); in bold: $p < 0.05$; * p-value refers to mild/moderate, severe and critical disease; †p < 0.05 between mild-moderate and critical; ‡p < 0.05 between mild-moderate and severe; ° technically acceptable DLCO exam available respectively for 16 mild-moderate, 16 severe and 36 critical patients; #CT imaging available for 16 mild-moderate, 17 severe and 36 critical patients; § BGA data available for 17 mild-moderate, 15 severe and 37 critical patients; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; KCO: carbon monoxide transfer coefficient; CT-SS: CT severity score; %V-RPI: visual percentage of residual parenchymal involvement; mMRC: modified medical research council scale for dyspnea; VO_2: oxygen consumption; VCO_2: carbon dioxide output; VE: ventilation; $PaCO_2$: partial arterial pressure for carbon dioxide; PaO_2: partial arterial pressure for carbon dioxide.

4. Discussion

In this post-hoc analysis, a ventilatory and gas exchange response profile in the limit of normal was confirmed irrespective of the severity of the acute disease, with comparable reduced exercise capacity and some impairment at resting examinations [3,11]. This is in line with a phenotypical heterogeneity of the acute disease, due to a different degree of adaptation to the stress of the inflammation affecting cardio-respiratory efficiency [12], which can possibly be restored after recovery. Our data expand the finding of Dorelli et al. [13] who did not find differences in the share of patients presenting residual ventilatory inefficiency at CPET 5 months from the discharge, based on ICU vs medical ward stay. Similarly, Liu et al. showed that severity of the acute disease did not emerge as an independent risk factor for the development of pulmonary fibrosis and the related increase in VE/VCO_2 slope at CPET at 7 months follow-up [14].

Of note, Ong et al. [15] also outlined similar results from SARS survivors at 3 months from hospital discharge, with no significant difference in peak VO_2 nor PFT between those who required intensive care and mechanical ventilation and those who did not. Our patients reported lower than expected levels of dyspnoea and fatigue, in keeping with deconditioning as the main mechanism of exercise intolerance in post-COVID [3] with a slightly anticipated termination and possibly an altered perception of dyspnoea [12]. Lastly, we interpreted the difference in VE/VCO_2 slope between mild-moderate and severe patients as not clinically relevant, considering all mean values below the upper normal limits. The main limits of the present study are the monocentric nature, the post-hoc analysis nature affecting the absence of a formal sample size calculation and the numerosity of each group, beyond a certain degree of variability in the time of functional assessment among individual patients.

5. Conclusions

Disease severity does not impact on exercise capacity in COVID-19 survivors at 3 months after discharge, including a ventilatory response still in the limit of normal. However, further studies are needed to clarify the role of residual impairment on a longer term.

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CRediT authorship contribution statement

Rocco Francesco Rinaldo: Conceptualization, Data curation, Formal analysis, Project administration, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Michele Mondoni:** Conceptualization, Data curation, Project administration, Investigation, Writing – review & editing. **Elena Maria Parazzini:** Conceptualization, Investigation, Writing – review & editing. **Andrea Baccelli:** Conceptualization, Data curation, Investigation, Writing – review & editing. **Federica Pitari:** Data curation, Investigation, Writing – review & editing. **Elena Brambilla:** Data curation, Investigation, Writing – review & editing. **Simone Luraschi:** Data curation, Investigation, Writing – review & editing. **Maurizio Balbi:** Data curation, Investigation, Methodology, Writing – review & editing. **Marco Guazzi:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Fabiano Di Marco:** Conceptualization, Methodology, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Stefano Centanni:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

Conflict of interest: Dr. Rinaldo has nothing to disclose. Conflict of interest: Dr. Mondoni has nothing to disclose. Conflict of interest: Dr. Parazzini has nothing to disclose. Conflict of interest: Dr Baccelli has nothing to disclose. Conflict of interest: Dr. Pitari has nothing to disclose. Conflict of interest: Dr. Brambilla has nothing to disclose. Conflict of interest: Dr. Luraschi has nothing to disclose. Conflict of interest: Dr. Balbi has nothing to disclose. Conflict of interest: Prof. Guazzi has nothing to disclose. Conflict of interest: Prof. Di Marco has nothing to disclose. Conflict of interest: Prof. Centanni has nothing to disclose.

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