



Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors

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To the Editor:

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and the related coronavirus disease 2019 (COVID-19) hit Europe in February 2020 [1], raising issues on acute phase management and, later on, the management of its long-term sequelae. Cardiopulmonary exercise testing (CPET), which is the gold standard for the evaluation of exercise capacity, is included in the list of examinations of the European Respiratory Society/American Thoracic Society task force for the follow-up of COVID-19 patients [2]. However, it is not performed in every clinical centre, as it requires specific technical skills. The objective of this observational, prospective study was to evaluate the sequelae of COVID-19 by assessing exercise performance during incremental CPET.

COVID-19 patients who recovered from the acute phase were enrolled from the Registry for COVID-19 Emergency (RE.CO.V.ER), funded by the University of Milan, Italy. The study was approved by Milan Area 1 ethics committee (2020/ST/407). Written informed consent was obtained from each participant. Patients admitted between February and April 2020 and followed-up at the post-COVID-19 outpatient service at San Paolo Hospital (Milan, Italy), were invited to undergo CPET (May to August 2020). Inclusion criteria were: 1) age >18 years; and 2) molecular (RT-PCR) diagnosis of SARS-CoV-2 infection [3]. Exclusion criteria were the absence of signed informed consent, an acute respiratory exacerbation in the 4 weeks before enrolment, and the presence of medical conditions contraindicating CPET (acute or unstable cardio-respiratory conditions, osteo-muscular impairment that could compromise exercise performance) [4]. Information on past medical history, smoking status and COVID-19 therapies were collected. Dyspnoea sensation was assessed using the Italian version of the modified Medical Research Council dyspnoea scale (mMRC). SARS-CoV-2-related pneumonia diagnosis was based on specific radiological chest findings (radiographs: multifocal peripheral lung ground glass opacities and/or consolidations, monolateral or bilateral; computed tomography (CT): bilateral lung infiltrates, ground-glass opacities, consolidation, crazy paving pattern, air bronchogram signs and intralobular septal thickening). Patients underwent spirometry and diffusing lung capacity for carbon monoxide (D_{LCO}) test evaluated by the single breath technique. Symptom-limited, incremental, exercise testing was performed on an electronically braked cycle ergometer using the Vmax Spectra Cardiopulmonary Exercise Testing System (SensorMedics, Yorba Linda, CA, USA) [4]. The rate of work rate increment ($W \cdot \text{min}^{-1}$) was identified on an individual basis according to expected exercise tolerance and resting functional data. Measured and computed CPET variables were recorded [5]. Breathing reserve is $(1 - (\text{peak ventilation}/(\text{FEV}_1 \times 35))) \times 100$, where FEV_1 is forced expiratory volume in 1 s. Heart rate reserve (HRR) is $(1 - (\text{peak heart rate}/(220 - \text{age}))) \times 100$.

Chest CT signs were evaluated by a radiologist and a respiratory physician during the follow-up. Two CT scores were used to show the magnitude of the residual involvement: the CT severity score and the visual percentage of residual parenchymal involvement [6, 7].

Differences between patients with a preserved (peak oxygen consumption (V_{O_2}) $\geq 85\%$ predicted [4]) and those with a reduced exercise capacity in terms of resting pulmonary function tests, ventilatory exercise response and imaging were computed. Based on early data on D_{LCO} from COVID-19 patients [8], a sample size of at least 30 patients per group would be sufficient to detect a difference of 10% of predicted



Shareable abstract (@ERSpublications)
CPET reveals only a mild impairment of exercise capacity, with preserved ventilatory and gas exchange response at 3 months follow-up in COVID-19 survivors, due to deconditioning
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D_{LCO} (a minimal clinically relevant difference in respiratory diseases) between them (statistical power of 80%, alpha error of 5%). Student's *t*- or Mann–Whitney 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.

75 (43 males, 57%) patients were recruited. 39 patients had a critical, 18 severe, and 18 mild-moderate disease [9]. Mean±SD time from discharge to outpatient visit was 97±26 days. Seven (9%) patients had a history of asthma, whereas no previous diagnosis of interstitial lung disease or COPD were reported. 26 (34%) had a diagnosis of systemic hypertension, nine (12%) of diabetes, three (4%) of ischaemic heart disease, and three (4%) of arrhythmia. 43 (63%) patients showed a residual parenchymal involvement at CT. Spirometry showed normal mean values: forced vital capacity was 104±17% predicted and FEV₁ 100±16% predicted. However, mean D_{LCO} was 71±14% of predicted with a mean haemoglobin level of 15.0±1.5 g·dL⁻¹. The average peak V'_{O_2} of our population was 20.0 mL·min⁻¹·kg⁻¹ corresponding to a mean±SD 83±15% of the predicted value; the mean±SD slope of the relation between ventilation and carbon dioxide output during exercise (V'_E/V'_{CO_2} slope) was 28.4±3.1, with median (interquartile range) peak exercise value for the alveolar–arterial gradient for oxygen of 26 (18–31) mmHg. 41 (55%) patients showed a peak V'_{O_2} <85% of predicted (table 1). Patients with a reduced exercise capacity did not exhibit a ventilatory limitation by CPET (breathing reserve <15%), whereas 13 patients showed a circulatory limitation (HRR <15%), and 15 a reduced anaerobic threshold (<45%) with or without reduction of HRR.

TABLE 1 Differences between patients with normal and reduced exercise capacity

	Normal exercise capacity (n=34)	Reduced exercise capacity (n=41)	<i>p</i> -value
Male, n (%)	16 (47)	27 (65)	0.101
Age, years	58±10	56±13	0.482
BMI, kg·m ⁻²	29.2±4.0	28.0±5.1	0.309
Smoking status never/current/ex-smoker, n (%)	21/4/9 (62/12/26)	28/10/3 (68/24/8)	0.700
FEV ₁ , % pred	107±19	102±15	0.170
FVC, % pred	103±18	98±13	0.215
D_{LCO} [#] , % pred	74±14	69±13	0.175
K_{CO} , % pred	83±16	85±14	0.630
Alveolar volume, % pred	89±13	83±14	0.063
CT abnormal/total, n (%)	19/30 (63)	24/41 (58)	0.683
CT-SS [†]	16.0±9.2	18.6±10.7	0.616
%V-RPI [‡]	20 (15–45)	17 (15–40)	0.611
mMRC (0/1/2/3/4)	15/13/6/0/0	14/18/9/0/0	0.672
V'_{O_2} peak, % pred	97±9	72±9	<0.001
V'_{O_2} peak absolute, mL·min ⁻¹ ·kg ⁻¹	22.1±5.5	18.3±4.9	<0.001
Work peak, % pred	97±19	76±13	<0.001
Anaerobic threshold, % V'_{O_2} max predicted	62±13	48±9	<0.001
V'_{O_2} /work slope, mL·min ⁻¹ ·W ⁻¹	11.0±1.2	9.9±1.3	<0.001
Respiratory exchange ratio at peak	1.18±0.09	1.22±0.11	0.121
Heart rate reserve, %	10±11	16±12	0.040
Heart rate peak, bpm	145±19	138±22	0.136
Oxygen pulse peak, % pred	110±15	85±19	<0.001
Ventilation peak, min ⁻¹	67±21	58±18	0.068
V'_E/V'_{CO_2} slope, L·L ⁻¹	28.1±3.2	28.7±3.1	0.453
V'_E/V'_{CO_2} slope >30, n (%)	5 (15)	6 (15)	0.993
Alveolar–arterial gradient for O ₂ at peak [‡] , mmHg	26 (19–31)	26 (16–31)	0.719
P_{aCO_2} at peak [‡] , mmHg	35±4	35±4	0.955
Lactate at peak [‡] , mmol·L ⁻¹	7.5±2.7	7.1±2.5	0.464
Borg scale of dyspnoea at peak	4.0±2.3	3.5±2.3	0.373
Borg scale of perceived exertion at peak	5.3±2.0	5.5±2.0	0.638

All quantitative data are presented as mean±SD or median (interquartile range), unless otherwise specified. Values presented in bold type refer to *p*<0.05. Reduced exercise capacity when peak oxygen consumption (V'_{O_2}) <85% predicted. [#]: diffusing capacity of the lung for carbon monoxide (D_{LCO}) available for 32 patients with normal exercise capacity and 37 patients with reduced exercise capacity, respectively; [†]: computed tomography (CT) imaging available for 30 patients with normal exercise capacity and 41 with reduced exercise capacity; [‡]: blood gas analysis data available for 33 patients with normal exercise capacity and 34 with reduced exercise capacity. BMI: body mass index; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; K_{CO} : carbon monoxide transfer coefficient; CT-SS: CT severity score; %V-RPI: visual percentage of residual parenchymal involvement; mMRC: modified Medical Research Council scale for dyspnoea; V'_E : ventilation; V'_{CO_2} : carbon dioxide output; P_{aCO_2} : partial arterial pressure for carbon dioxide.

Patients with a reduced exercise capacity showed an early anaerobic threshold, indicating a higher degree of deconditioning; they reached lower levels of performance and earlier termination, with a lower work, a lower peak oxygen pulse, a higher HRR, and a wider breathing reserve. A reduced slope of oxygen uptake to work rate relationship (V'_{O_2}/WR slope) in the exercise-limited subgroup is consistent with a worse anaerobic efficiency. Deconditioning might be related to a direct effect of the viral load on the muscle tissue, with an impaired O_2 extraction and use [10], as well as to a prolonged hospital stay and post-hospitalisation syndrome. Remarkably, parameters of ventilatory efficiency or gas exchange were still in the limit of normal and we did not find a significant difference between patients with preserved and those with a reduced exercise capacity [11]; neither pulmonary function tests nor CT imaging helped to discriminate patients with a lower peak V'_{O_2} . This is in line with the data reported by GAO *et al.* [12] on 10 COVID-19 survivors 1 month after discharge from rehabilitation. Nevertheless, RAMAN *et al.* [13] reported a reduced exercise capacity in a comparable proportion of moderate-to-severe COVID-19 survivors, although they showed a mild ventilatory inefficiency. No data on D_{LCO} or gas exchange at peak of CPET were reported, but an explanation for this difference in residual ventilatory impairment could rely on the earlier evaluation time from discharge (median 1.6 months). Moreover, ONG *et al.* [14] showed that SARS survivors had only a mild reduction of lung function and exercise capacity at CPET, which could not be accounted for impairment of pulmonary function, with 41% presenting a reduced anaerobic threshold, in agreement with our findings.

In our study, symptoms at rest and at peak were comparable. Nevertheless, 39 (52%) patients reported dyspnoea during their daily activity. Residual dyspnoea is frequently reported by COVID-19 survivors [15, 16]; its origin can depend on multiple factors, and a mildly impaired exercise capacity associated with deconditioning might play a role.

The main limitations of our study are its single-centre nature, which impacts on the generalisability, and the absence of a baseline assessment.

In conclusion, COVID-19 survivors show a mild reduction of their exercise capacity, probably caused by muscle deconditioning. This is the first study on CPET performance, pulmonary function tests and CT imaging, showing no relevant functional sequelae on ventilatory and gas exchange response to exercise. A longer follow-up is needed to evaluate the full spectrum of recovery.

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