EUROPEAN RESPIRATORY *journal*

Early View

Research letter

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

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SARS-CoV2 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 test (CPET), which is the gold standard for the evaluation of exercise capacity, is included in the list of examinations of the European Respiratory Society (ERS)/American Thoracic Society (ATS) task force for the follow-up of COVID-19 patients [2]. However, it is not performed in every clinical center, requiring specific technical skills. The objective of this observational, prospective study was to evaluate the sequelae of COVID-19 assessing the exercise performance during incremental CPET.

COVID-19 patients who recovered from the acute phase were enrolled from the Registry for COVID-19 Emergency (RE.COV.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 by each participant. Patients admitted between February and April 2020 and followed-up at a post-COVID-19 outpatient service in Milan, Italy, were invited to undergo CPET (May-August 2020). Inclusion criteria were: 1) age >18 years, 2) molecular (Reverse Transcription – Polymerase Chain Reaction) diagnosis of SARS-CoV-2 infection [3]. Exclusion criteria were the absence of a signed informed consent, an acute respiratory exacerbation in the 4 weeks before the enrollment, and the presence of medical conditions contraindicating CPET (acute or unstable cardio-respiratory conditions, osteo-muscular impairment which could compromise the exercise performance) [4]. Information on past medical history, smoking status, and COVID-19 therapies were collected. Dyspnea sensation was assessed using the Italian version of the modified Medical Research Council dyspnea scale (mMRC). SARS-CoV-2-related pneumonia diagnosis was based on specific radiological chest findings (x-rays: 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 test (DLCO) 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, USA) [4]. The rate of work rate increment (W/min) 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 (BR) is (1 -(peak ventilation/(FEV$_1$x35)))x100, where FEV$_1$ is forced expiratory volume in 1 s. Heart rate reserve (HRR) is (1-(peak heart rate/(220-age)))x100.

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 (CT-SS) and the visual percentage of residual parenchymal involvement (%VRPI) [6,7].

Differences between patients with a preserved (peak oxygen consumption - VO$_2$ - ≥85% predicted [4]) and those with a reduced exercise capacity in terms of resting PFT, ventilatory exercise response and imaging were computed. Based on early data on DLCO 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 DLCO (a minimally clinical relevant difference in respiratory diseases) between them (statistical power of 80%, alpha error of 5%). Student's t- or Mann-Whitney test were computed to assess statistical differences for normal or non-normal quantitative variables, respectively. Qualitative data were analyzed with Pearson's chi-squared test. A p-value <0.05 was considered statistically significant.

Seventy-five (43, 57% males) patients were recruited. Thirty-nine 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 chronic obstructive pulmonary disease were reported. Twenty-six (34%) had a diagnosis of systemic hypertension, 9 (12%) of diabetes, 3 (4%) of ischemic heart disease, and 3 (4%) of arrythmia. Forty-three (63%) patients showed a residual parenchymal involvement at CT. Spirometry showed normal values: mean (SD) forced vital capacity was 104 (17) % of predicted and FEV$_1$ 100 (16) %. However,

mean (SD) DLCO was 71 (14) % of predicted with a mean (SD) hemoglobin level of 15.0 (1.5) g/dL. The average peak VO_2 of our population was 20.0 ml/min/kg corresponding to a mean (SD) 83 (15)% of the predicted; the mean (SD) slope of the relation between ventilation and carbon dioxide output during exercise (VE/VCO_2 slope) slope was 28.4 (3.1) with mean peak exercise value for the alveolar gradient for oxygen (O_2 A-a gradient) of 26 (18-31) mmHg. Forty-one (55%) patients showed a peak VO_2 <85% of the predicted (Table 1). Patients with a reduced exercise capacity did not exhibit a ventilatory limitation by CPET (BR <15%), whereas 13 patients showed a circulatory limitation (HRR <15%), and 15 a reduced anaerobic threshold (<45%) with or without consumption of HRR.

Patients with a reduced exercise capacity showed an early anaerobic threshold (AT), 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 (VO_2/WR slope) in 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-hospitalization 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 PFTs nor CT imaging did help discriminate patients with a lower peak VO_2. This is in line with the data reported by Gao *et al.* on 10 COVID-19 survivors 1 month after discharge from rehabilitation [12]. Nevertheless, Raman *et al.* 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 DLCO 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) [13]. Moreover, Ong *et al.* showed that SARS survivors had only a mild reduction of lung function and exercise capacity at CPET - that could not be accounted for impairment of pulmonary function - with 41% presenting a reduced AT [14], in agreement with our findings.

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

The main limitations of our study are its mono-center nature which impact on the generalizability and a missing 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, PFTs, 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.

Table 1. Differences between patients with normal and reduced exercise capacity.

	Normal exercise capacity (n= 34)	Reduced exercise capacity (n= 41)	p-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
FEV1 %predicted	107 (19)	102 (15)	0.170
FVC %predicted	103 (18)	98 (13)	0.215
DLCO %predicted°	74 (14)	69 (13)	0.175
KCO %predicted	83 (16)	85 (14)	0.630
Alveolar Volume % predicted	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
VO$_2$ peak %predicted	97 (9)	72 (9)	**<0.001**
VO$_2$ peak absolute, ml/min/kg	22.1 (5.5)	18.3 (4.9)	**<0.001**
Work peak %predicted	97 (19)	76 (13)	**<0.001**
Anaerobic threshold %VO$_2$ max predicted	62 (13)	48 (9)	**<0.001**
VO$_2$/work slope, ml/min/W	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**
Peak heart rate, bpm	145 (19)	138 (22)	0.136
Oxygen pulse peak % predicted	110 (15)	85 (19)	**<0.001**
Peak ventilation, /min	67 (21)	58 (18)	0.068
VE/VCO$_2$ slope, L/L	28.1 (3.2)	28.7 (3.1)	0.453
VE/VCO$_2$ slope >30, n (%)	5 (15)	6 (15)	0.993
Alveolar-arterial gradient for O$_2$[§†], mmHg	26 (19-31)	26 (16-31)	0.719
PaCO$_2$ at peak[§], mmHg	35 (4)	35 (4)	0.955

Lactate at peak[§], mmol/L	7.5 (2.7)	7.1 (2.5)	0.464
Borg scale of dyspnea 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 mean (SD), unless otherwise specified; in bold: $p < 0.05$; † median (IQR); reduced exercise capacity when peak VO_2 <85% predicted; °DLCO available respectively for 32 pts with normal exercise capacity and 37 patients with reduced exercise capacity #CT imaging available for 30 pts with normal exercise capacity and 41 with reduced exercise capacity; § BGA data available for 33 pts with normal exercise capacity and 34 with reduced exercise capacity; 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; $P_{ET}CO_2$: End tidal pressure for carbon dioxide; $PaCO_2$: partial arterial pressure for carbon dioxide.

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