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Early View

Research letter

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SARS-CoV-2 infection sequelae on exercise response: persistent or reversible? A 2 year perspective

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To the Editor:

SARS-CoV2 and the related disease COVID-19 had a dramatic impact on global healthcare system since its appearance in December 2019 [1]. The evidence of long-lasting sequelae in COVID-19 survivors have rapidly grown, leading to the current definition of "long COVID", an entity defined as the persistence or development of new symptoms 3 months after the acute infection lasting at least 2 months [2]. Nevertheless, recent literature showed how a share of patients still presented SARS-CoV2 sequelae with clinical and functional impairment even at a 2-year follow-up [3]. Cardiopulmonary exercise test (CPET), which is the gold standard for the evaluation of pathophysiological response during exercise [4], allowed to unveil mechanisms of exercise intolerance in the early post-acute phase, mainly involving deconditioning and peripheral oxygen utilisation impairment, but also alteration of the breathing pattern and possibly chronotropic incompetence [5, 6]. However, data on the long-term outcome of patients presenting altered exercise capacity as post-acute sequelae of COVID-19 are still lacking.

In this observational monocentric study, we prospectively enrolled consecutive patients who presented a reduced exercise capacity (VO_2Low) at CPET 3-6 months after hospital discharge (peak oxygen consumption - peakVO_2 <85% predicted)[4], and who repeated, at our post-COVID-19 clinic, a CPET at least 18 months following discharge. We also included a group of patients who presented a normal exercise capacity (VO_2Normal) already at the 3-6 months evaluation, for descriptive reasons. Other inclusion criteria were: 1) age >18 years, 2) previous microbiological diagnosis of SARS-CoV-2 infection. Definition of diagnosis SARS-CoV2 infection, severity of the disease and SARS-CoV2 related pneumonia were previously described [7]. 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 (i.e. acute or unstable cardio-respiratory conditions, osteo-muscular impairment compromising exercise performance) [4].

All patients had already been evaluated in our previous study on exercise capacity at 3-6 months from COVID-19 [7]. The Italian version of modified Medical Research Council dyspnoea during daily

living scale (mMRC) was administered for quantification of dyspnoea. The International Physical Activity Questionnaire (IPAQ) was administered to assess daily physical activity [8]; the questionnaire identifies three levels of physical activity: low, moderate and high. Pulmonary function testing and CPET procedures were previously described [7]. We defined an abnormal chronotropic response as <80% of the adjusted heart rate reserve (AHRR) calculated as follows: (HRpeak-HRrest)/(220-age-HRrest). Deconditioning was defined as reduced exercise capacity with normal breathing reserve, no evidence of cardiocirculatory pathology (assessed by ECG, VE/VCO_2 slope, and O_2-pulse curve) with normal or low VO_2 at anaerobic threshold (AT) and/or the presence of a reduced slope or late plateau of the VO_2 trajectory (i.e. a reduced VO_2/work-rate relationship ⩽8) [9, 10]. Dysfunctional breathing (DB) identification was based on visual pattern recognition [11].

All tests were performed at the Respiratory Unit at ASST Santi Paolo e Carlo, Milan, Italy (March 2022-June 2022). Written informed consent was obtained by each participant. The study was approved by Milan Area 1 Ethics Committee with the registration number 2022/ST/127.

The primary objective was to assess the change in peak exercise capacity, expressed as peakVO_2, in a population of subjects who had a reduced exercise capacity at 3-6 months from acute SARS-CoV2. We hypothesized an improvement of at least 10% of peak VO_2 through time, as significant outcome in respiratory patients [12]. A post-hoc analysis of peak VO_2 confirmed a statistical power >85% (alpha error of 5%) for such an outcome with our population. Student's t-test for two independent or paired groups and Mann-Whitney test or Wilcoxon signed-rank test were used when appropriate. Qualitative data were analysed with Pearson's chi-squared test. A p-value <0.05 was considered statistically significant.

3 patients were excluded for: submaximal test (1 VO_2Normal), newly diagnosis of atrial fibrillation during the test (1 VO_2Low), excessive air-loss through mouthpiece (1 VO_2Normal). We eventually included 20 VO_2Low patients and 19 VO_2Normal patients at 3-6 months. Mean (standard deviation – SD) time from hospital discharge was 24(1) months for both groups. No patient had

undergone a structured program of rehabilitation after the discharge. IPAQ levels of physical activity were comparable between VO_2Low and VO_2Normal (4/8/8 vs. 4/6/9 low/moderate/high; p=0.853). One VO_2Low and one VO_2Normal patient reported a new asymptomatic SARS-CoV2 infection between tests.

Most frequent comorbidities were: arterial hypertension (41%), asthma (13%) and diabetes (5%). 1 VO_2Normal patient had a major medical event between tests (non-ST elevation myocardial infection treated with revascularisation and stent placement).

VO_2Low patients significantly improved their peak exercise capacity, while VO_2Normal ones reported comparable values at the repeated test. CPET and functional parameters are reported in **table 1**.

VO_2Low patients had a significant improvement in peakVO_2, although they still featured lower levels of exercise capacity compared to VO_2Normal (peak VO_2 88(12)% vs. 98(14)% predicted; p=0.021). At 24 months 13 (65%) VO_2Low patients had recovered to a preserved exercise capacity. Among the 7 patients who still presented a reduced exercise capacity, 4 featured an increase in peakVO_2 (range 4-12% predicted), while 3 presented a decrease (range -1--4% predicted). The final diagnosis for exercise intolerance were: 5 deconditioning, 2 chronotropic incompetence. 3 (16%) patients in the VO_2Normal group presented a peakVO_2<85% predicted at 24 months. Out of the 8 (40%) VO_2Low and 9 (47%) VO_2Normal patients who showed DB at the early evaluation, respectively 1 and 2 had a complete resolution, 2 and 3 had a significant improvement in their breathing pattern and 5 and 4 showed an unchanged pattern at 24 months, resulting in 14 (35%) patients still presenting DB in the combined cohort. Globally, 5 (12%) patients with preserved exercise capacity at 24 months reported an mMRC≥1 with no evident sign of altered physiology at CPET, pointing to a final diagnosis of long COVID, as per WHO definition.

This is, to our knowledge, the first study assessing peak exercise capacity in COVID-19 survivors at 24 months from hospital discharge. In our study, we reported a significant improvement in anaerobic threshold, VO_2/work slope and peak oxygen pulse in VO_2Low patients, although they reached the same load at peak as at 3-6 months. We interpreted this response as an overall improvement in the transport/peripheral utilisation of oxygen, which was found to be impaired in our cohort, as well as in several studies, in the early post-acute phase [6, 7, 13]. Previously, Cassar et al. had showed an initial improvement in peakVO_2 already between 3 and 6 months [14]. Recently, Ingul et al. demonstrated that peakVO_2 increases from 3 to 12 months post-COVID, as well as a share of patients considered as normal of 77% [9]. Further studies, including invasive CPET, may be of use in understanding the limitation in those still presenting an overt impairment, particularly the role of a true residual myopathy beyond a recover from the disease-related limitation of activity and consequent deconditioning [13]. Although already in the limit of normal, our group showed a further improvement in ventilatory and gas exchange response. We interpreted this improvement as likely further resolution of parenchymal abnormalities still observed at the computed tomography at 3-6 months [15]. However, the evidence on a residual ventilatory inefficiency in COVID-19 survivors is mixed in literature [5, 6]; Noureddine et al. have shown a prevalence ranging 50-56% of ICU admitted patients presenting a VE/VCO_2 slope above normal even at 12 months from the infection, independently of a preserved or reduced peak exercise capacity [16]. Of note, as previously pointed out also at earlier time-points from the infection, some degree of DB was still present in our cohort [11]. Interestingly, our VO_2Low patients showed an increase in BORG scale for dyspnoea at peak, despite a better performance. This could be related to the resolution of blunted perception of dyspnoea that characterised the acute and early phases of recover from the disease [17].

The main limitations of our study are the mono-centric nature, which impact on the generalizability and the absence of a baseline pre-COVID-19 assessment.

In conclusion, our study shows that patients with an impairment in exercise capacity at 3-6 months recover to a normal exercise capacity in most cases, even without a specific rehabilitating intervention, through an overall improvement in the physiology of O_2 transport/peripheral utilisation of oxygen with a more efficient ventilatory response to exercise. Further studies are warranted to confirm our findings on the long-term consequences of SARS-CoV2 infection.

Table 1. Differences between lung function and CPET at 3-6 months and 24 months from hospital discharge.

	Reduced exercise capacity (VO_2Low) at 3-6 months (n= 20)			**Normal exercise capacity (VO_2Normal) at 3-6 months** (n= 19)		
	3-6 months	**24 months**	**p-value**	**3-6 months**	**24 months**	**p-value**
Male/Female n (percentage)		13/7 (65/35) †			10/9 (53/47) †	
Age years		55 (11)			58 (8)	
BMI kg/m²	28.3 (4.8)	29.3 (5.1)	**0.008**	29.3 (4.3)	30.1 (4.5)	**0.023**
Smoking status never/current/ex-smoker (%)		12/2/6 (60/10/30)			10/0/9 (53/0/47)	
mMRC at the time of CPET (0/1/2/3/4)	8/10/2/0/0	10/10/0/0/0	0.344	7/8/4/0/0	12/6/1/0/0	**0.031**
FEV1 %predicted	100 (17)	102 (19)	0.433	108 (14)	108 (28)	0.974
FVC %predicted	97 (17)	101 (18)	0.079	104 (13)	106 (29)	0.808
DLCO° %predicted	71 (14)	74 (13)	0.162	72 (12)	76 (15)	0.144
VO_2 peak %predicted	74 (6)	88 (12)	**0.001**	98 (10)	98 (14)	0.905
VO_2 peak absolute ml/min/kg	19.5 (5.5)	21.9 (6.4)	**<0.001**	23.3 (6.1)	22.2 (5.9)	0.218
Work peak %predicted	78 (11)	80 (13)	0.388	97 (10)	100 (12)	0.234
Anaerobic Threshold %VO_2 max predicted	47 (4)	53 (9)	**0.019**	61 (13)	60 (13)	0.578
VO_2/work slope ml/min/W	9.8 (1.0)	10.9 (1.2)	**0.001**	10.7 (1.1)	11.2 (1.1)	0.102
Respiratory Exchange Ratio peak	1.20 (0.11)	1.19 (0.11)	0.529	1.20 (0.10)	1.20 (0.09)	0.798
Heart rate reserve %	16 (12)	16 (11)	0.850	8 (10)	6 (8)	0.234
Oxygen pulse peak %pred	86 (20)	105 (17)	**<0.001**	110 (15)	105 (14)	0.205
Breathing reserve %	46 (13)	38 (15)	**0.003**	37 (13)	38 (15)	0.761
Ventilation at peak L/min	63 (21)	71 (21)	**0.009**	73 (22)	72 (23)	0.826
VE/VCO_2 slope L/L	29.2 (4.8)	27.7 (3.5)	**0.035**	28.4 (2.9)	27.1 (3.5)	**0.050**
VE/VCO_2 slope >30 n (%)	3 (15)	3 (15)	1.000	2 (10)	2 (10)	1.000
Alveolar-arterial gradient for O_2§∞ mmHg	29 (23-37)	23 (16-26)	**0.009**	26 (23-32)	26 (17-32)	0.245
$PaCO_2$ peak§ mmHg	34 (3)	31 (5)	**0.038**	34 (5)	33 (5)	0.245
Lactate peak§ mmol/L	7.3 (2.7)	8.2 (2.9)	0.169	8.5 (2.5)	8.8 (2.4)	0.511
BORG scale of dyspnea peak	3.4 (2.2)	4.9 (2.6)	**0.032**	4.1 (1.6)	3.3 (2.2)	0.099

BORG scale of perceived exertion peak	5.0 (1.8)	5.2 (2.7)	0.707	5.3 (1.8)	5.3 (1.7)	1.000

All quantitative data mean (SD), unless otherwise specified; ∞ median (IQR); in bold: $p<0.05$; † VO_2Low vs. VO_2Normal $p=0.433$; § BGA data available for 16 VO_2Low and 17 VO_2Normal patients; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; 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; PaO_2: partial arterial pressure for carbon dioxide.

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