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

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To the Editor:

SARS-CoV-2 and the related disease COVID-19 have had a dramatic impact on the global healthcare system since their appearance in December 2019 [1]. The evidence of long-lasting sequelae in COVID-19 survivors has 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 ⩾2 months [2]. Nevertheless, recent literature has showed how some patients still presented SARS-CoV-2 sequelae with clinical and functional impairment even at a 2-year follow-up [3]. Cardiopulmonary exercise testing (CPET), which is the gold standard for the evaluation of pathophysiological response during exercise [4], allowed the unveiling of 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 a post-acute sequela of COVID-19 are still lacking.

In this observational, monocentric study, we prospectively enrolled consecutive patients who presented a reduced exercise capacity (V'_{O_2}Low) on CPET 3–6 months after hospital discharge (peak oxygen consumption (V'_{O_2peak}) <85% predicted) [4] and who repeated, at our post-COVID-19 clinic, CPET ⩾18 months following discharge. We also included a group of patients who already presented a normal exercise capacity (V'_{O_2}Normal) at the 3–6-month evaluation, for descriptive reasons. Other inclusion criteria were: 1) age >18 years; and 2) previous microbiological diagnosis of SARS-CoV-2 infection. Definition of diagnosis of SARS-CoV-2 infection, severity of the disease and SARS-CoV-2-related pneumonia were as previously described [7]. Exclusion criteria were the absence of 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, osteomuscular impairment compromising exercise performance) [4].

All patients had already been evaluated in our previous study on exercise capacity at 3–6 months after 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 index (AHRI) calculated as:

$$\text{AHRI} = \frac{\text{HR}_{\text{peak}} - \text{HR}_{\text{rest}}}{220 - \text{age} - \text{HR}_{\text{rest}}} \times 100$$

where HR_{peak} and HR_{rest} are peak and resting heart rate, respectively. Deconditioning was defined as reduced exercise capacity with normal breathing reserve, no evidence of cardiocirculatory pathology (assessed by ECG, ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) slope and oxygen pulse curve) with normal or low V'_{O_2} at the anaerobic threshold and/or the presence of a reduced slope or late plateau of the V'_{O_2} trajectory (*i.e.* a V'_{O_2}/work rate relationship ⩽8) [9, 10]. Dysfunctional breathing identification was based on visual pattern recognition [11].

Shareable abstract (@ERSpublications)
Post-COVID-19 exercise capacity sequalae on oxygen utilisation and ventilatory efficiency improve over time in most patients. Cardiopulmonary exercise testing is a valuable tool to identify those who may benefit from specific rehabilitative interventions. https://bit.ly/3qFd97x

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All tests were performed at the Respiratory Unit at ASST Santi Paolo e Carlo, Milan, Italy (March–June 2022). Written informed consent was obtained from 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 V'_{O_2peak}, in a population of subjects who had a reduced exercise capacity 3–6 months after acute SARS-CoV-2 infection. We hypothesised an improvement of ⩾10% of V'_{O_2peak} over time as a significant outcome in respiratory patients [12]. A *post hoc* analysis of V'_{O_2peak} confirmed a statistical power >85% (α-error of 5%) for such an outcome in 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.

Three patients were excluded for submaximal test (one V'_{O_2}Normal patient), new diagnosis of atrial fibrillation during the test (one V'_{O_2}Low patient) and excessive air loss through the mouthpiece (one V'_{O_2}Normal patient). We eventually included 20 V'_{O_2}Low patients and 19 V'_{O_2}Normal patients at 3–6 months. Mean±SD time from hospital discharge was 24±1 months for both groups. No patient had undergone a structured programme of rehabilitation after discharge. IPAQ scores of physical activity were comparable between the V'_{O_2}Low and V'_{O_2}Normal groups (low/moderate/high: 4/8/8 *versus* 4/6/9; p=0.853). One V'_{O_2}Low and one V'_{O_2}Normal patient reported a new asymptomatic SARS-CoV-2 infection between tests.

The most frequent comorbidities were arterial hypertension (41%), asthma (13%) and diabetes (5%). One V'_{O_2}Normal patient had a major medical event between tests (non-ST elevation myocardial infection treated with revascularisation and stent placement).

V'_{O_2}Low patients significantly improved their peak exercise capacity, while V'_{O_2}Normal patients reported comparable values at the repeated test. CPET and functional parameters are reported in table 1.

V'_{O_2}Low patients had a significant improvement in V'_{O_2peak}, although they still had lower levels of exercise capacity compared to V'_{O_2}Normal patients (V'_{O_2peak} 88±12% *versus* 98±14% predicted, p=0.021). At 24 months, 13 (65%) V'_{O_2}Low patients had recovered to a preserved exercise capacity. Among the seven patients who still presented a reduced exercise capacity, four had an increase in V'_{O_2peak} (range 4–12% predicted), while three presented a decrease (range −1– −4% predicted). The final diagnoses for exercise intolerance were five patients with deconditioning and two with chronotropic incompetence. Three (16%) patients in the V'_{O_2}Normal group presented a V'_{O_2peak} <85% predicted at 24 months. Out of the eight (40%) V'_{O_2}Low and nine (47%) V'_{O_2}Normal patients who showed dysfunctional breathing at the early evaluation, one and two had a complete resolution, two and three had a significant improvement in their breathing pattern, and five and four showed an unchanged pattern at 24 months, respectively, resulting in 14 (35%) patients still presenting dysfunctional breathing in the combined cohort. Overall, five (12%) patients with preserved exercise capacity at 24 months reported an mMRC score ⩾1 with no evident sign of altered physiology on CPET, pointing to a final diagnosis of long COVID, as per the World Health Organization definition.

This is, to our knowledge, the first study assessing peak exercise capacity in COVID-19 survivors 24 months after hospital discharge. In our study, we report a significant improvement in anaerobic threshold, V'_{O_2}/work slope and peak oxygen pulse in V'_{O_2}Low 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*. [14] had showed an initial improvement in V'_{O_2peak} between 3 and 6 months. Recently, Ingul *et al*. [9] demonstrated that V'_{O_2peak} increases from 3 to 12 months post-COVID-19, as well as a proportion of patients considered as normal of 77%. 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 recovery from the disease-related limitation of activity and consequent deconditioning [13]. Although already above the limit of normal, our group showed a further improvement in ventilatory and gas exchange responses. We interpreted this improvement as likely further resolution of parenchymal abnormalities still observed on computed tomography at 3–6 months [15]. However, the evidence of a residual ventilatory inefficiency in COVID-19 survivors is mixed in the literature [5, 6]; Noureddine *et al*. [16] have shown a prevalence ranging 50–56% of intensive care unit-admitted patients presenting a V'_E/V'_{CO_2} slope above normal even at 12 months from the infection, independently of a preserved or reduced peak exercise capacity. Of note, as previously pointed out also at earlier time-points from the infection, some degree of dysfunctional

TABLE 1 Differences in lung function and cardiopulmonary exercise testing (CPET) 3–6 months and 24 months after hospital discharge

	V'_{O_2}Low at 3–6 months[#]			V'_{O_2}Normal at 3–6 months[¶]		
	3–6 months	24 months	p-value	3–6 months	24 months	p-value
Male/female, n (%)	13/7 (65/35)[§]			10/9 (53/47)[§]		
Age, years	55±11			58±8		
BMI, kg·m^{-2}	28.3±4.8	29.3±5.1	**0.008**	29.3±4.3	30.1±4.5	**0.023**
Never/current/ex-smoker, n (%)	12/2/6 (60/10/30)			10/0/9 (53/0/47)		
mMRC 0/1/2/3/4 at the time of CPET, n	8/10/2/0/0	10/10/0/0/0	0.344	7/8/4/0/0	12/6/1/0/0	**0.031**
FEV_1, % 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
D_{LCO}, % predicted	71±14	74±13	0.162	72±12	76±15	0.144
V'_{O_2peak}, % predicted	74±6	88±12	**0.001**	98±10	98±14	0.905
V'_{O_2peak}, mL·min^{-1}·kg^{-1}	19.5±5.5	21.9±6.4	**<0.001**	23.3±6.1	22.2±5.9	0.218
Peak work rate, % predicted	78±11	80±13	0.388	97±10	100±12	0.234
Anaerobic threshold, % V'_{O_2max} predicted	47±4	53±9	**0.019**	61±13	60±13	0.578
V'_{O_2}/work rate slope, mL·min^{-1}·W^{-1}	9.8±1.0	10.9±1.2	**0.001**	10.7±1.1	11.2±1.1	0.102
Peak respiratory exchange ratio	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
Peak O_2 pulse, % predicted	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
V'_E at peak, L·min^{-1}	63±21	71±21	**0.009**	73±22	72±23	0.826
V'_E/V'_{CO_2} slope	29.2±4.8	27.7±3.5	**0.035**	28.4±2.9	27.1±3.5	**0.050**
V'_E/V'_{CO_2} slope >30, n (%)	3 (15)	3 (15)	1.000	2 (10)	2 (10)	1.000
Alveolar–arterial O_2 gradient[+], mmHg, median (interquartile range)	29 (23–37)	23 (16–26)	**0.009**	26 (23–32)	26 (17–32)	0.245
P_{aCO_2peak}[+] mmHg	34±3	31±5	**0.038**	34±5	33±5	0.245
Peak lactate[+], mmol·L^{-1}	7.3±2.7	8.2±2.9	0.169	8.5±2.5	8.8±2.4	0.511
Borg scale for dyspnoea at peak	3.4±2.2	4.9±2.6	**0.032**	4.1±1.6	3.3±2.2	0.099
Borg scale for perceived exertion at peak	5.0±1.8	5.2±2.7	0.707	5.3±1.8	5.3±1.7	1.000

Data are presented as mean±SD unless otherwise stated. V'_{O_2}Low: reduced exercise capacity; V'_{O_2}Normal: normal exercise capacity; BMI: body mass index; mMRC: modified Medical Research Council scale for dyspnoea; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V'_{O_2peak}: peak oxygen consumption; V'_{O_2max}: maximal oxygen consumption; V'_{O_2}: oxygen consumption; V'_E: ventilation; V'_{CO_2}: carbon dioxide output; P_{aCO_2peak}: peak arterial carbon dioxide tension. [#]: n=20; [¶]: n=19; [+]: blood gas analysis data available for 16 V'_{O_2}Low and 17 V'_{O_2}Normal patients; [§]: V'_{O_2}Low *versus* V'_{O_2}Normal, p=0.433. Bold indicates statistically significant p-values.

breathing was still present in our cohort [11]. Interestingly, our V'_{O_2}Low patients showed an increase in Borg scale for dyspnoea at peak, despite a better performance. This could be related to the resolution of a blunted perception of dyspnoea that characterises the acute and early phases of recovery from the disease [17].

The main limitations of our study are the monocentric nature, which impacts the generalisability of our data, 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 oxygen 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-CoV-2 infection.

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