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Early View

Research letter

Exercise capacity-impairment after COVID-19 pneumonia is mainly caused by deconditioning

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Exercise capacity-impairment after COVID-19 pneumonia is mainly caused by deconditioning

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Summary: Not pulmonary factors, but physical deconditioning is the main limiting factor of exercise capacity in patients after severe COVID-19 pneumonitis. This underscores the importance of an early rehabilitative intervention in these patients.

To the editor:

The new severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) can cause severe pneumonia characterized by dry cough, dyspnea, hypoxaemia, and diffuse ground glass opacities on chest computed tomography (CT) [1]. While much has been learnt concerning diagnosis and treatment of COVID-19 during the first year of the pandemic, only scarce data is available concerning post-COVID long-term pulmonary sequelae. Data about pulmonary function in the early convalescence demonstrated impaired diffusion capacity, lower respiratory muscle strength, and radiological abnormalities [2, 3]. Herein we report data of cardio-pulmonary exercise testing (CPET) three months after severe COVID-19 pneumonitis.

Between February 26 and May 3, 2020, 221 patients with RT-PCR-confirmed SARS-CoV-2 infection were admitted to the University Hospital Basel, Switzerland. A total of 50 (22.6%) patients suffered from severe COVID-19 pneumonitis, fulfilling ≥ 2 of the following criteria: respiratory rate > 30/min, SpO2 < 93% while breathing ambient air, C-reactive protein (CRP) levels > 75 mg/l (normal < 10.0 mg/l), ground glass opacities or diffuse infiltrates on CT- scan or progression of > 50% within 24-48 hours or typical findings ≥ 4 lobes [4]. Patients were treated according to local standard at that time, and only one patient received systemic corticosteroids (cumulative dose of 80 mg prednisone); all patients were included in an observational study (NCT04351503).
During hospitalization 5/50 (10%) patients died due to COVID-19. One further patient succumbed to pre-existing haematological disease after hospital discharge. Among the 44 COVID-19 survivors, four experienced prolonged hospitalization with oxygen dependency. Further five patients declined the performance of CPET. All patients received physiotherapy during their hospitalization; after discharge, 8/35 (23%) patients were transferred to further inpatient pulmonary rehabilitation, 3/35 (9%) patients underwent outpatient pulmonary rehabilitation. In all these patients, pulmonary rehabilitation programs were completed at the time of CPET.
In the context of this analysis, patients were followed-up including clinical status, bodyplethysmography and chest CT-scan three months after COVID-19 pneumonitis. All 35 patients underwent an incremental CPET using a cycle ergometer [5] (Ergoline Ergoselect 1000) in semi-recumbent position in continuous ramp mode (10-20W/min). CPET parameters were systematically computed according to breath-by-breath analysis and data were displayed online (Sentry Suite Version 3.10). Arterial blood gas analysis at rest and at maximal exercise level was performed (ABL 800 Flex). The level of dyspnea and exhaustion at peak exercise was objectified using the Borg modified scale [6]. The evaluation of the collected data was in accordance with Wassermann

algorithm [7] and the adaptation of Schmid et al. [8]. Health-related quality of life (QoL) was evaluated using the St. George Respiratory Questionnaire (SGRQ) and the King's Brief Interstitial Lung Disease (K-BILD) questionnaire. Chest CT scans were conducted on a dual source CT scanner (Somatom Definition Flash, Siemens Healthineers) using dual-energy acquisition after intravenous injection of iodine contrast material in the late pulmonary arterial phase. Mann-Whitney-U test was computed to assess statistical differences; a p-value <0.05 was considered statistically significant.

Baseline characteristics, underlying comorbidities, and concomitant medication of those 35 patients who agreed to perform CPET are shown in table 1. On chest CT scan, 15/35 patients (43%) exhibited residuals only, and 6/35 patients (17%) had additional fibrotic changes. Pulmonary function values were normal (total lung capacity [TLC] ≥ 80% predicted, diffusion capacity of carbon monoxide [DLCO] ≥ 80% predicted, Tiffeneau-index > 0.7) in 23/35 patients (66%). A normal maximal oxygen uptake (VO2max) during CPET (VO2max ≥ 82% predicted) was observed in 16/35 (46%) patients, 19/35 (54%) proved to have impaired VO2max (15 mild impairment [VO2max 61-81% predicted]; 4 moderate impairment [VO2max 51-60% predicted]). Main limiting factors in those patients with impaired VO2max were deconditioning in 9/19, cardiovascular in 5/19, and pulmonary limitations in 5/19 patients. In those patients with impaired VO2max, DLCO %pred at day 90 was significantly lower as compared to the patients with normal VO2max (p=0.006); no other parameter differed between the two groups (table 1). Detailed variables of CPET are shown in table 1.

Contrary to our expectations, both in patients with and without lung function impairment, the most common main limiting factor of VO2max was not of pulmonary nature, but general deconditioning. Of note, maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were normal in those patients with deconditioning (mean MIP 99.4% predicted, mean MEP 79.9% predicted), making it unlikely that neuro-muscular impairment caused the limitation. Three of the nine patients with deconditioning were obese. In 14% of the patients (5/35) cardiovascular limitation of CPET was observed. From those, three had previous CVD. Only one of the five patients with pulmonary limitation had a preexisting respiratory disease, i.e. severe obstructive sleep apnea. Health related QoL was not better in those with normal VO2max as compared to those with impaired maximal oxygen uptake. However, this finding is limited by the fact that 40% of patients did not complete the questionnaires, though equally distributed in both groups (42% vs 37.5%).

Our data on PFT impairment after COVID-19 pneumonitis are in line with previous publications [2, 9-11]. The low prevalence of respiratory comorbidities and active smoking in our population might partially explain the finding of 66% normal PFT three months after severe COVID-19. Impairment of physical performance in patients recovering from COVID-19 pneumonia has been described before [2, 3, 10, 12]. To date, there are accumulating data on CPET after SARS-CoV-2 infection [13-18], but only limited respective information on patients surviving severe COVID-19 pneumonitis. In our well-characterized patient group, almost half (46%) had normal VO2max in CPET. In those patients with impaired maximal oxygen uptake, the majority (47%) was limited by deconditioning. Thus, despite the severity of the acute COVID-19 pneumonitis, only 14% of survivors exhibited pulmonary limitation in CPET three months later, demonstrating a surprisingly good pulmonary recovery. This applies even more in the light of the predominant lung pathology observed in patients with severe COVID-19, i.e. diffuse alveolar damage, endothelitis, and pulmonary immunothrombosis [19].

In a previous issue of this journal, Skjorten et al. reported a reduced VO2max in one-third of COVID-19 patients three months after hospital discharge, with deconditioning being the major cause of exercise limitation [15]. Compared to these findings, we observed a higher proportion of patients with impaired peak oxygen uptake (54%), which is likely due to the more severe disease course in our patient group, as depicted by the longer length of hospital stay (median 14 day versus median 6 days) [15]. The study by Rinaldo et al. reported CPET-data in a mixed group of patients with critical, severe, and mild-moderate COVID-19 [13]. Even though we included only patients with severe COVID-19 pneumonia, the mean VO2max %pred of 82% in our study population is surprisingly similar to the one reported by Rinaldo et al. (83%). A striking disparity between the two patient groups is the portion of active smokers, being only 2.9% in our population as compared to 19% in the group studied by Rinaldo. This might – at least partially – explain the good outcome in our patients. Finally, in line with our data, Rinaldo et al. found muscle deconditioning to be the main cause of reduced exercise capacity [13]. In a very small group of 10 moderate and severe COVID-19 patients, Gao et al. performed CPET one month post-discharge [20]. In contrast to our data, Gao et al. found reduced peak oxygen uptake in all cases, an apparent contradiction which might be explained by the two months later follow-up time-point of our study. However, similar to us, Gao et al. showed that extrapulmonary factors were the main reason for exercise limitation [20]. Notably, our findings are in line with CPET-data from survivors of the 2002 coronavirus-induced SARS outbreak: three months after SARS, 41% of the patients showed reduced VO2max; none of these patients had

pulmonary limitation, but extrapulmonary disease – mainly impaired muscle function – caused reduced VO2max [21]. Furthermore, similar data were found in survivors of severe ARDS caused by various etiologies [22]. By performing CPET three months after severe COVID-19, a time point by which most radiological abnormalities related to the acute infection had vanished, we were able to demonstrate that half of the patients have reduced exercise capacity, yet, only a minority of patients have pulmonary limitation. Thus, CPET is a helpful tool to further dissect reduced exercise tolerance and interpret exertional dyspnea. With similar previous findings in survivors of SARS, physical deconditioning seems to be the main cause of impaired exercise capacity after severe coronavirus infections, and might even represent the natural course after severe lung injury with critical illness in general.

In summary, we demonstrate that physical deconditioning is the most common cause of impaired VO2max in patients after severe COVID-19 pneumonitis. Whether these findings are specific to SARS-CoV2 infection or contrariwise depict the common sequelae after ARDS caused by any insult has to be further explored. Finally, our findings underscore the importance of an early rehabilitative intervention in survivors of severe COVID-19 pneumonitis.

	Total	Impaired VO2max	Normal VO2max*	p-value
n	35	19	16	
Age, y (mean (SD))	58 (±13)	56 (±13)	60 (±14)	0.289
Ethnicity (%)				0.232
Caucasian	23 (65.7)	11 (57.9)	12 (75.0)	
Asian	9 (25.7)	5 (26.3)	4 (25.0)	
African	3 (8.6)	3 (15.8)	0	
Female sex (%)	6 (17.1)	2 (10.5)	4 (25.0)	0.379
Comorbidities (%)				
Hypertension	15 (42.9)	7 (36.8)	8 (50.0)	0.506
Diabetes	7 (20.0)	5 (26.3)	2 (12.5)	0.415
Asthma	3 (8.6)	2 (10.5)	1 (6.2)	1
Coronary heart disease	2 (5.7)	1 (5.3)	1 (6.2)	1
COPD	0	0	0	
Chronic kidney disease	3 (8.6)	2 (10.5)	1 (6.2)	1
Autoimmune disease	2	0	2	0.202
HIV	2 (5.7)	2 (10.5)	0	0.489
BMI, kg/m2 (mean (SD))	29 (±5)	28 (±3)	31 (±6)	0.2
Smoking (%)				0.517
Active smoker	1 (2.9)	0	1 (6.2)	
Former smoker	10 (28.6)	6 (31.6)	4 (25.0)	
Never smoker	24 (68.6)	13 (68.4)	11 (68.8)	
Any concomitant medication (%)	20 (57.1)	9 (47.4)	11 (68.8)	0.306
ACE-inhibitor	9 (25.7)	5 (26.3)	4 (25.0)	1
Statins	5 (14.3)	2 (10.5)	3 (18.8)	0.642
Antidiabetic drugs	8 (22.9)	6 (31.6)	2 (12.5)	0.244
Oral anticoagulation	0	0	0	
WHO scale at hospitalization (%)				0.745
3 Hospitalised, no oxygen therapy	18 (51.4)	10 (52.6)	8 (50.0)	
4 or 5 Hospitalised, oxygen by mask or nasal prongs; non-invasive ventilation or high-flow oxygen	14 (40.0)	8 (42.1)	6 (37.5)	
6 or 7 Hospitalised, intubation and mechanical ventilation; ventilation plus additional organ support	3 (8.6)	1 (5.3)	2 (12.5)	
CRP peak value during hospitalization, mg/l (median [IQR])	72 [91.5]	68.1 [93.4]	74.2 [105]	0.854
Hospital length of stay (days), median (IQR)	14 [15]	11 [20]	14.5 [11.25]	0.854
Pulmonary rehabilitation after hospital discharge (%)				
Inpatient pulmonary rehabilitation after discharge	8 (23)	5 (14)	3 (9)	0.7
Outpatient pulmonary rehabilitation after discharge	3 (9)	2 (6)	1 (3)	1
Pulmonary function tests day 90				
TLC %pred (mean (SD))	93 (±9)	91 (±9)	96 (±9)	0.153
FVC %pred (mean (SD))	91 (±13)	88 (±12)	94 (±14)	0.119
FEV1 %pred (mean (SD))	93 (±13)	90 (±11)	96 (±15)	0.226
FEV1/FVC % (mean (SD))	83 (±10)	84 (±12)	82 (±9)	0.703
DLCO %pred (mean (SD))	88 (±17)	80 (±13)	96 (±18)	0.006
Radiological findings day 90 (%)				
Residuals	21 (61.8)	11 (57.9)	10 (66.7)	0.728
Fibrosis	6 (17.6)	2 (10.5)	4 (26.7)	0.37
Embolism	0	0	0	
Disturbed microcirculation	11 (34.4)	6 (31.6)	5 (38.5)	0.721
Health related quality of life day 90				
SGRQ completed (%)	21 (60)	11 (31)	10 (29)	1
SGRQ total score (median [IQR])	13 [5, 27]	10 [6, 20]	22 [8, 30]	0.359
SGRQ symptoms (median [IQR])	12 [0, 21]	9 [2, 16]	17 [2, 29]	0.285
SGRQ activity (median [IQR])	30 [11, 48]	18 [6, 38]	39 [22, 52]	0.242
SGRQ impact (median [IQR])	6 [4, 15]	4 [3, 12]	14 [5, 17]	0.357
K-BILD completed (%)	21 (60)	11 (31)	10 (29)	1
K-BILD total score (median [IQR])	87 [72, 93]	89 [73, 92]	82 [72, 93]	0.75
K-BILD breathlessness/activity (median [IQR]	85 [62, 100]	89 [72, 98]	78 [64, 99]	0.668
K-BILD psychological (median [IQR])	80 [72, 88]	80 [64, 88]	78 [75, 87]	0.859
K-BILD chest symptoms (median [IQR])	91 [69, 100]	91 [69, 100]	91 [62, 100]	0.941
Cardiopulmonary exercise testing day 90				
Workload %pred (mean (SD))	97 (±22)	85 (±18)	110 (±18)	0.001
VO2max %pred (mean (SD))	82 (±16)	71 (±9)	96 (±10)	<0.001
Circulation				
Heart rate at rest, bpm (mean (SD))	74 (±14)	72 (±14)	76 (±14)	0.371
Heart rate at peak, bpm (mean (SD))	129 (±30)	126 (±37)	132 (±18)	0.529
Heart rate reserve at peak, 1/min (mean (SD))	34 (±20)	37 (±21)	29 (±19)	0.267
O2 pulse at rest, ml (mean (SD))	7 (±7)	6 (±2)	7 (±10)	0.064
O2 pulse at peak, ml (mean (SD))	14 (±2)	13 (±2)	15 (±2)	0.022
O2 pulse at peak %pred (mean (SD))	103 (±21)	91 (±13)	118 (±20)	<0.001
SBP at rest, mmHg (mean (SD))	135 (±18)	135 (±18)	135 (±19)	0.934
SBP at peak, mmHg (mean (SD))	166 (±31)	161 (±32)	172 (±31)	0.214
DBP at rest, mmHg (mean (SD))	83 (±12)	84 (±12)	83 (±12)	0.829
DBP at peak, mmHg (mean (SD))	93 (±18)	90 (±14)	96 (±22)	0.54
Ventilation				
Minute ventilation at rest, l/min (mean (SD))	13 (±6)	14 (±6)	12 (±5)	0.319
Minute ventilation at peak, l/min (mean (SD))	66 (±20)	66 (±24)	67 (±15)	0.573
Minute ventilation at peak %pred (mean (SD))	73 (±14)	68 (±15)	79 (±10)	0.018
Breathing rate at rest, 1/min (mean (SD))	19 (±9)	18 (±9)	21 (±8)	0.233
Breathing rate at peak, 1/min (mean (SD))	37 (±8)	36 (±9)	38 (±8)	0.446
Breathing reserve at peak (mean (SD))	39 (±15)	43 (±16)	34 (±13)	0.116
Gas exchange				
O2-saturation at rest, % (mean (SD))	97 (±2)	98 (±2)	97 (±2)	0.085
O2-saturation at peak, % (mean (SD))	97 (±2)	97 (±1)	97 (±2)	0.859
PaO2 at rest, kPa (mean (SD))	11 (±2)	11 (±2)	11 (±2)	0.987
PaO2 at peak, kPa (mean (SD))	14 (±1)	14 (±1)	14 (±1)	0.986
PaCO2 at rest, kPa (mean (SD))	5 (±0.5)	5 (±0.6)	5 (±0.4)	0.842
PaCO2 at peak, kPa (mean (SD))	4.9 (±0.5)	4.9 (±0.6)	5 (±0.5)	0.743
Lactate at rest, mmol/l (mean (SD))	1.4 (±0.6)	1.4 (±0.6)	1.5 (±0.6)	0.475
Lactate at peak, mmol/l (mean (SD))	7 (±3)	7 (±3)	7 (±2)	0.945
Borg dyspnea (mean (SD))	5 (±2)	4 (±2)	5 (±2)	0.181
Borg peripheral limitation (mean (SD))	5 (±2)	6 (±3)	5 (±2)	0.634
Workload limitation (%)				0.061
no limitation	28 (80.0)	12 (63.2)	16 (100)	
mild limitation	4 (11.4)	4 (21.1)	0	
moderate limitation	2 (5.7)	2 (10.5)	0	
severe limitation	1 (2.9)	1 (5.3)	0	
VO2 max limitation (%)				<0.001
no limitation	16 (45.7)	0	16 (100)	
mild limitation	15 (42.9)	15 (78.9)	0	
moderate limitation	4 (11.4)	4 (21.1)	0	
Pulmonary gas exchange (%)				0.215
Drop in PaO2	2 (5.7)	0	2 (12.5)	
Increase in PaCO2	5 (14.3)	3 (15.8)	2 (12.5)	
Desaturation (%)	3 (8.6)	2 (10.5)	1 (6.2)	1
Any cardiac limitiations (%)	19 (54.3)	10 (52.6)	9 (56.3)	1
Main limiting factor (%)				<0.0001
Cardiovascular	5 (14.3)	5 (26.3)	0	
Deconditioning	9 (25.7)	9 (47.4)	0	
Pulmonary	5 (14.3)	5 (26.3)	0	
No limitation	16 (45.7)	0	16 (100)	

Table 1: Baseline characteristics, underlying comorbidities, concomitant medication, and disease severity at hospital admission, pulmonary function testing, radiological outcome, quality of life and cardio-pulmonary exercise testing-data three months after severe COVID-19 pneumonitis. Data are n (%), median [IQR] or mean ±SD as appropriate. * Normal maximal oxygen uptake is defined as VO2max ≥ 82% predicted; mild impairment VO2max 61-81% predicted, moderate impairment VO2max 51-60% predicted. The St. George's Respiratory Questionnaire (SGRQ) is a 50-item questionnaire divided in three domains (symptoms, activity, impact); a total and three domain scores are calculated, each domain is scored separately; a score of zero represents best, a value of 100 represents worst quality of life. The King's Brief Interstitial Lung Disease (K-BILD) questionnaire is a 15-item questionnaire divided in three domains (breathlessness and activity, psychological aspects, chest symptoms); a score of 100 represents best, a value of zero represents worst quality of life. Ground glass opacities and reticulations were considered as residuals, coarse reticulations and traction bronchiectasis were interpreted as fibrosis; microcirculation was assessed based on Dual Energy Computed Tomography.

Definition of abbreviations: BMI = body mass index, bpm = beats per minute, CRP = C-reactive protein, COPD = chronic obstructive pulmonary disease, DBP = diastolic blood pressure, DLCO = diffusing capacity for carbon monoxide, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HIV = Human Immunodeficiency Virus, K-BILD = King's Brief Interstitial Lung Disease, SBP = systolic blood pressure, SGRQ = St. George Respiratory Questionnaire, TLC = total lung capacity, VO2 max = maximal oxygen uptake.

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