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Short Report

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Cardiopulmonary exercise pattern in patients with persistent dyspnoea after recovery from COVID-19

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ABSTRACT

Cause and mechanisms of persistent dyspnoea after recovery from COVID-19 are not well described. The objective is to describe causal factors for persistent dyspnoea in patients after COVID-19. We examined patients reporting dyspnoea after recovery from COVID-19 by cardiopulmonary exercise testing. After exclusion of patients with pre-existing lung diseases, ten patients (mean age 50±13.1 years) were retrospectively analysed between May 14th and September 15th, 2020. On chest computed tomography, five patients showed residual ground glass opacities, and one patient showed streaky residua. A slight reduction of the mean diffusion capacity of the lung for carbon monoxide was noted in the cohort. Mean peak oxygen uptake was reduced with 1512±232 ml/min (72.7% predicted), while mean peak work rate was preserved with 131±29 W (92.4% predicted). Mean alveolar-arterial oxygen gradient ($AaDO_2$) at peak exercise was 25.6±11.8 mmHg. Mean value of lactate post exercise was 5.6±1.8 mmol/l. A gap between peak work rate in (92.4% predicted) to peak oxygen uptake (72.3% pred.) was detected in our study cohort. Mean value of lactate post exercise was high in our study population and even higher (n.s.) compared to the subgroup of patients with reduced peak oxygen uptake and other obvious reason for limitation. Both observations support the hypothesis of anaerobic metabolism. The main reason for dyspnoea may therefore be muscular.

Key words: CPET; COVID-19; postdischarge dyspnoea; post-COVID-19 syndrome.

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Introduction

COVID-19 has led to more than 2 millions deaths in less than 12 months [1]. Mankind is challenged by this new disease, which in many aspects and characteristics is different to other respiratory viral infections [2-4]. Manifestations range from asymptomatic infection to severe ARDS. Some survivors suffer from symptoms, attributable to ICU care and some show persisting symptoms which are still unclear [5]. Some patients do not report dyspnoea despite hypoxemia in severe COVID-19 [2,6]. Interestingly after recovery from acute infection with SARS-CoV2 dyspnoea and fatigue are the most frequent symptoms [7-10]. However, the cause and pathophysiologic mechanisms of persistent dyspnoea after recovery from COVID-19 are not well described. In this study we sought to analyse our cohort of post COVID-19 patients with persistent dyspnoea using a thorough clinical workup including cardiopulmonary exercise testing (CPET).

Methods

Study population, study design and data collection

The study was conducted at the Centre of Pneumology in Donaustauf, Germany. The hospital is a quaternary care provider for pneumology, where patients from the eastern region of Bavaria are seen for specialized care.

All available medical reports from patients, that presented to the outpatient's clinic or on Non-ICU ward with persistent symptoms after recovery from COVID-19 (post-COVID-19) between May 14th and September 15th 2020 were retrospectively analysed.

Statistics

Summary statistics of continuous variables are presented as mean ± standard deviation. Data were analysed using Microsoft Excel (version 2016, Redmond, USA) and IBM SPSS (version 24.0, IBM, Armonk, USA).

Patients

The following eligibility criteria were applied: 18 years of age or older, post COVID-19, still symptomatic with dyspnoea. Patients were excluded from the study if any of the above criteria was not fulfilled or if no CPET was performed or any other reason for dyspnoea became evident. Abnormal spirometry was not a strict exclusion criterion except reflecting an underlying lung disease judged responsible for patient's dyspnoea.

Examinations

Patients received a comprehensive assessment of dyspnoea including blood gas analysis, lung function test, 6-min walk test, echocardiography, computed chest tomography (CT) scan, thoracic sonography, and CPET. Due to the retrospective nature of our study, examinations mentioned (except CPET) were not performed in the entire patient population.

Results

Baseline characteristics

In the time period 42 patients post COVID-19 were seen at our hospital, 31 patients were excluded because no CPET was performed. Ten patients met the eligibility criteria. Mean age of these patients was 50±13.1 years and four patients were female. In the acute phase of COVID-19 six patients had been hospitalized, five patients needed oxygen, two patients needed high-flow oxygen therapy, and in two patients invasive ventilation was necessary. Mean hospital stay was 23.4±22.0 days; mean time to presentation to our outpatient's clinic after hospital discharge were 115 days. None of the participants had a history of lung disease, congestive heart failure, diabetes mellitus or malignancy. There were five patients with known "arterial hypertension", one patient had an ACE inhibitor in his regular medication.

Ejection fraction in transthoracic echocardiography was normal in all patients. One patient showed a slightly dilated right ventricle with a mild tricuspid valve insufficiency (PAP elevation 60 mmHg over central venous pressure). No other patient showed signs of an acute right heart strain. Thorax sonography was performed in two patients showing normal diaphragm function. Chest CT scan was performed in all patients. Five patients showed ground glass opacities and one patient showed streaky residua. Pulmonary embolism, as possible reason for the dyspnoea, was excluded by CT scan in nine patients (one patient had a CT scan without contrast agent but a low likelihood in Wells-Score and negative d-dimer testing).

No participant had obstructive lung disease. A nominal reduction of the diffusion capacity of the lung for carbon monoxide (DL_{CO}) of 73% was recognized in the cohort.

Cardiopulmonary exercise testing

Peak oxygen uptake (Peak-VO_2) was measured by CPET with 1512±232 ml/min (72.7% predicted) at a mean peak work rate of 131±29 W (92.4% pred.). Mean alveolar-arterial oxygen gradient ($AaDO_2$) at peak exercise was 25.6±11.8 mmHg, mean peak ventilation was 64.7 l/min and mean breathing reserve (BR) was 35.1±19.0%. Mean heart rate during exercise was 133±19 /min (78.1±7.3 pred.), oxygen pulse 11.9±2.6 (96.0±15.5% pred.). Mean $EQCO_2$ and mean EQO_2 at VT1 were measured with 35.4±6.5 and 28.7±10.4. Mean value of lactate post exercise was 5.6±1.8 mmol/l. A detailed description of all patients is presented in Table 1.

In detail CPET detected a nearly normal performance ($VO_2max \geq 85\%$) in two of the patients (No 3 and No 8), eight patients (beside No 1 and No 10) had elevated (>30) $EQCO_2$ values at VT1. Limitation was cardiac in one patient (No 5) and ventilatory (BR <30%) in two patients. $AaDO_2$ was elevated in three patients (No 3, No 4 and No 8). Dyspnoea during CPET was quantified *via* RPE scale (range 3-9).

Discussion

To our knowledge, this is the first study examining patients with persistent dyspnoea after COVID-19. Persistent dyspnoea in patients, who recovered from acute COVID-19 infection has been described [7-9].

The gap between reached peak work rate (92.4% predicted) to peak oxygen uptake (72.3% pred.) in our study population can most likely be explained by an early switch to anaerobic metabolism. This would explain why mean value of lactate post exercise was high in our study population and even higher (n.s.) compared to the subgroup of patients with reduced peak oxygen uptake and other obvious reason for limitation.

In two patients the limitation was ventilatory. Critical-illness-polyneuropathy may have contributed in patient Nos 7 and 8. $AaDO_2$ was elevated in three patients (No 3, No 4 and No 8), all of them had ground-glass opacity or streaky residua on the CT-scan. Finally, even with the use of CPET, dyspnoea could not be

Table 1. Detailed characteristics of all 10 patients.

Patient number / occupation / smoking status	Gender / age / BMI	Time in hospital / on ICU	Oxygen / high-flow NIV / invasive ventilation	CT scan	Lung function Z-scores and TLCO SB / haemoglobin	6 min walk	CPET: power	CPET: VE/VCO_2 slope / VE/VCO_2 intercept	CPET: $V'O_2$ AT / VO_2max	CPET: max. HR	CPET: $aado_2$ (rest / exercise)	CPET: BR	CPET: RMV	CPET: oxygen pulse	CPET: EOO_2, $EOCO_2$, dead space ventilation (exercise)	CPET:RER max. (post-exercise)	CPET: Lactate max. (post-exercise) [mmol/l]
1 / nurse / former smoker since 2018 (30 py)	F / 52 a / 36.3 kg/m²	0 days	No oxygen therapy	No abnormalities; no pulmonary embolism	FEV / FVC: normal TLC: -2.23 TLCO SB: 76% Hb 13.6 g/dl	441 m (91%)	98 W 106%	28. 2 / 2 l / min	731 ml / min 1288 ml/min (78%)	129 / min 77%	17 mmHg / 29 mmHg	19%	40 l/min	10 ml 102%	23.0 27.7 9%	1.5	5,93
2 / innkeeper / no smoker	F / 36 a / 20.7 kg/m²	0 days therapy	No oxygen therapy	No abnormalities; no pulmonary embolism	FEV / FVC: normal TLC: normal TLCO SB: 88% Hb 15.1 g/dl	n.a.	99 W 85%	31. 2 / 4 l / min	660 ml/min 1221 ml/min (74%)	162 / min 88%	21 mmHg / 25 mmHg	51%	49 l/min	7.5 ml 83%	31.3 42.4 13%	1.7	3,35
3 / clerk / former smoker since 2013 (10 py)	F / 54 a / 29.0 kg/m²	22 days / 6 days	Oxygen therapy high-flow-therapy No noninvasive ventilation No invasive ventilation	Ground-glass opacity; no pulmonary embolism	FEV / FVC: normal TLC: normal TLCO SB: 63% Hb 14.2 g/dl	n.a.	100 W 107%	25.8 / 2 l / min	649 ml/min 1355 ml/min (85%)	129 / min 78%	21 mmHg / 35 mmHg	36%	61 l/min	11.2 ml 116%	34.5 38.1 15%	1.3	4,17
4 / factory worker / no smoker	M / 58 a / 33.0 kg/m²	56 days / 42 days	Oxygen therapy No high-flow-therapy No noninvasive ventilation Invasive ventilation	Ground-glass opacity; CT-scan without contrast agent	FEV / FVC: normal TLC: -1.71 TLCO SB: 70% Hb 14.4 g/dl	621 m (126%)	154 W 108%	26.7 / 3 l / min	839 ml/min 1368 ml/min (64%)	107 / min 66%	4.8 mmHg / 37 mmHg	43%	67 l/min	13.7 ml 102%	26.7 35.5 16%	1.9	8,78
5 / nurse / no smoker	M / 44 a / 21.0 kg/m²	1 day / 0 days	No oxygen therapy	No abnormalities; no pulmonary embolism	FEV / FVC: normal TLC: normal TLCO SB: 79% Hb 16.3 g/dl	395 m (54%)	162 W 78%	30.7 / 2 l / min	1080 ml / min 1840 ml/min (68%)	160 / min 91%	12 mmHg / 20 mmHg	58%	69 l/min	11.6 75%	24.7 36.7 14%	1.6	5,00
6 / n / a / no smoker	M / 61 a / 49 days / 29.0 kg/m²	0 days	Oxygen therapy No high-flow-therapy No noninvasive ventilation No invasive ventilation	Ground-glass opacity; no pulmonary embolism	FEV / FVC: normal TLC: normal TLCO SB: 92% Hb 16.7 g/dl	534 m (97%)	150 W 98%	28.9 / 4 l / min	891 ml/min 1670 ml/min (74%)	116 / min 73%	11 mmHg / 29 mmHg	38%	72 l/min	14.9 106%	23.8 31.3 16%	1.6	6,15
7 / clerk / no smoker	M / 58 a / 22.3 kg/m²	7 days / 0 days	Oxygen therapy No high-flow-therapy No noninvasive ventilation No invasive ventilation	Ground-glass opacity; no pulmonary embolism	FEV / FVC: normal TLC: normal TLCO SB: 63% Hb 14.6 g/dl	n.a.	102 W 59%	38.5.1 / 3 l / min	779 ml / min 1320 ml/min (56%)	117 / min 73%	10 mmHg / 7 mmHg	14%	68 l/min	11,4. ml 77%	54.4 48.5 17%	1.1	3,97
8 / dentist / no smoker	M / 59 a / 23.0 kg/m²	26 days / 23 days	Oxygen therapy High-flow-therapy No noninvasive ventilation Invasive ventilation	Streaky residua; no pulmonary embolism	FEV / FVC: normal TLC: -2.44 TLCO SB: 54% Hb 12.7 g/dl	n.a.	168 W 113%	38.1 / 3 l / min	1107 ml/min 1850 ml/min (89%)	127 / min 79%	25 mmHg / 45 mmHg	8%	91 l/min	15.4 ml 119%	29.0 35.7 17%	1.7	4,69
9 / bank employee / no smoker	M / 58 a / 32.0 kg/m²	0 days	No oxygen therapy	Ground-glass opacity; no pulmonary embolism	FEV / FVC: normal TLC: normal TLCO SB: 93% Hb 15.5 g/dl	442 m (77%)	150 W 89%	33.1 / 3 l / min	937 ml/min 1820 ml/min (74%)	129 / min 80%	13 mmHg / 17 mmHg	21%	90 l/min	14.3 ml 94%	23.6 30.1 12%	1.6	8,43
10 / student / no smoker	F / 21 a / 32.0 kg/m²	0 days	No oxygen therapy	No abnormalities; no pulmonary embolism	FEV / FVC: normal TLC: normal TLCO SB: 79% Hb 15.5 g/dl	553 m (71%)	128 W 81%	24.9 / 2 l / min	576 ml/min 1413 ml/min (66%)	150 / min 75%	23 / 12 mmHg	63%	40 l / min	9,3 ml 86%	15.8 28.3 11%	1,6	5,78

F, female M, male; BMI, body-mass-index; ICU, intensive care unit; HR, heart rate; AaDO2, alveolar-arterial oxygen gradient; ARDS acute respiratory distress syndrome; BR, breathing reserve; n.a., not available; TLCO, diffusion capacity of the lung for carbon monoxide; CPET, spiroergometry; RMV, respiratory minute volume, py, pack years.

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explained by cardiac, pulmonary or ventilatory limitation in all patients. Muscular deficiency and thus metabolic limitation might have contributed to dyspnoea in most patients. As in other viral diseases in adults (*e.g.*, EBV) and in acute respiratory distress syndrome (ARDS), complete clinical recovery might be prolonged in COVID-19 [7,11-13]. However, the reason for muscular deficiency itself is unclear. It could either be due to atrophy as a consequence of insufficient physical load or critical-illness-polyneuropathy or direct damage of muscle or central nervous system by SARS-Cov2 [14].

Limitations

Our study has many limitations. First of all, it is retrospective and the number of patients being included is very small. Second, it is a single centre study; on the other hand, this is the first study at all analysing persistent dyspnoea in patients with COVID-19 *via* CPET.

Conclusion

Despite the use of CPET, dyspnoea could not be explained by cardiac, pulmonary or ventilatory limitation in all patients. A gap between peak work rate in (92.4% predicted) to peak oxygen uptake (72. % pred.) was detected in our study cohort. Mean value of lactate post exercise was high in our study population and even higher (n.s.) compared to the subgroup of patients with reduced peak oxygen uptake and other obvious reason for limitation. Both observations support the hypothesis of anaerobic metabolism. Muscular deficiency and thus metabolic limitation might contribute to dyspnoea in most patients. Further prospective studies with more participants are needed to evaluate the aetiology of dyspnoea post COVID-19.

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