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

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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 (AaDO2) 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 (DLCO) of 73% was recognized in the cohort.

Cardiopulmonary exercise testing
Peak oxygen uptake (Peak-VO2) 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 (AaDO2) 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 EQCO2 and mean EQO2, at VT1 were measured with 35±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 (VO2max ≥ 85%) in two of the patients (No 3 and No 8), eight patients (beside No 1 and No 10) had elevated (≥30) EQCO2 values at VT1. Limitation was cardiac in one patient (No 5) and ventilatory (BR <30%) in two patients. AaDO2 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. AaDO2 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
| 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 / %predicted) | 6 min walk | CPET power | CPET FEV1 / CO slope / VO2 max | CPET VO2 AT / VO2 max | CPET max HR | CPET max VO2 (rest / exercise) | CPET max BR | CPET BR | CPET max ECOO / dead-space ventilation (exercise) | CPET max exercise (post-exercise) | CPET max lactate max (post-exercise) | CPET Lactate max |  
|------------------------------------------|------------------|--------------------------|---------------------------------------------|---------|---------------------------------------------|-----------|-----------|---------------------------------|-----------------|-------------|---------------------------------|-----------|--------|---------------------------------|-----------------|-----------------|-------------------|  
| 1 / nurse / former smoker since 2018 (10 py) | F / 52 a / 36.3 kg/m² | 0 days | No oxygen therapy | No abnormalities; non-pulmonary embolism | FB / PCT normal TLCO SB: 12% TLC: 16% | 0.0 | 411 m (91%) | 98 | 28 | 2 / 1 | 86 | 731 ml / min | 328 ml / min (70%) | 129 | 77 | 17 | 39 l/min | 22 | 10 | 23.0 | 27 | 7 | 9 | 58 |  
| 2 / smoker / no smoker | F / 52 / 17 kg/m² | 0 days | No oxygen therapy | No abnormalities; non-pulmonary embolism | FB / PCT normal TLCO SB: 28% TLC: 18% | 0.0 | n.a. | 99 | 85 | 31 | 2 / 1 | 86 | 600 ml / min | 1221 ml / min (70%) | 162 | 88 | 21 | 35 l/min | 51 | 50 | 31.3 | 34 | 32 | 18 | 17 |  
| 3 / clerk / former smoker since 2013 (10 py) | F / 54 / 20.7 kg/m² | 22 days / 6 days | Oxygen therapy | No abnormalities; non-pulmonary embolism | FB / PCT normal TLCO SB: 25% TLC: 13% | 0.0 | n.a. | 100 | 10 | 25 | 2 / 1 | 80 | 649 ml / min | 1355 ml / min (80%) | 128 | 79 | 21 | 35 l/min | 30 | 13 | 34.5 | 30 | 10 | 27 |  
| 4 / factory worker / no smoker | M / 59 / 21.1 kg/m² | 66 days / 42 days | Oxygen therapy | No abnormalities; non-pulmonary embolism | FB / PCT normal TLCO SB: 26% TLC: 18% | 0.0 | 395 m (50%) | 162 | 8 | 26 | 2 / 1 | 1080 ml / min | 1604 ml / min (80%) | 162 | 91 | 12 | 35 l/min | 50 | 11 | 24.7 | 30 | 10 | 27 |  
| 5 / nurse / no smoker | M / 54 / 23.0 kg/m² | 1 day / 0 days | No oxygen therapy | No abnormalities; non-pulmonary embolism | FB / PCT normal TLCO SB: 35% TLC: 20% | 0.0 | 393 m (50%) | 150 | 8 | 28 | 4 / 1 | 491 ml / min | 1670 ml / min (70%) | 116 | 79 | 11 | 29 l/min | 38 | 11 | 21.8 | 26 | 10 | 27 |  
| 6 / nurse / no smoker | F / 60 / 21.6 kg/m² | 0 days | No oxygen therapy | No abnormalities; non-pulmonary embolism | FB / PCT normal TLCO SB: 35% TLC: 20% | 0.0 | 102 m (48%) | 162 | 8 | 28 | 4 / 1 | 779 ml / min | 1300 ml / min (70%) | 117 | 79 | 10 | 7 l/min | 44 | 12 | 23.4 | 30 | 10 | 27 |  
| 7 / clerk / no smoker | M / 59 / 22.3 kg/m² | 7 days / 0 days | Oxygen therapy | No abnormalities; non-pulmonary embolism | FB / PCT normal TLCO SB: 35% TLC: 20% | 0.0 | n.a. | 102 | 0.5 | 38 | 3 / 1 | 1707 ml / min | 1630 ml / min (80%) | 127 | 79 | 25 | 45 l/min | 8 | 11 | 91 | 15 | 11 | 17 |  
| 8 / dentist / no smoker | F / 59 / 23.0 kg/m² | 20 days / 25 days | Oxygen therapy | No abnormalities; non-pulmonary embolism | FB / PCT normal TLCO SB: 35% TLC: 20% | 0.0 | n.a. | 168 | 0.1 | 38 | 3 / 1 | 1077 ml / min | 1850 ml / min (80%) | 127 | 79 | 25 | 45 l/min | 8 | 11 | 91 | 15 | 11 | 17 |  
| 9 / bank employee / no smoker | M / 58 / 32.0 kg/m² | 0 days | No oxygen therapy | No abnormalities; non-pulmonary embolism | FB / PCT normal TLCO SB: 35% TLC: 20% | 0.0 | 442 m (77%) | 150 | 8 | 33 | 3 / 1 | 937 ml / min | 1820 ml / min (70%) | 128 | 79 | 13 | 17 l/min | 21 | 11 | 23.6 | 30 | 10 | 27 |  
| 10 / student / no smoker | F / 51 / 30.4 kg/m² | 0 days | No oxygen therapy | No abnormalities; non-pulmonary embolism | FB / PCT normal TLCO SB: 35% TLC: 20% | 0.0 | 553 m (77%) | 112 | 8 | 24 | 2 / 1 | 576 ml / min | 1413 ml / min (80%) | 150 | 79 | 25 | 12 l/min | 60 | 5 | 15.8 | 20 | 10 | 27 |  

F: female; M: male; BMI: body mass index; ICU: intensive care unit; HR: heart rate; aHbO2: arterial hemoglobin oxygen saturation; ARDS: acute respiratory distress syndrome; BR: breathing reserve; n.a.: not available; TLC: total lung capacity; CO: carbon monoxide; VO2: oxygen uptake; VO2max: maximum oxygen uptake; %predicted: percentage of predicted value; TLC: total lung capacity; SB: single-breath; ECOO: end-exercise carbon dioxide output; CO2; VO2AT: anaerobic threshold; Lactate: lactate concentration; min: minute; py: pack years.
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-polynuropathy 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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