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

Arno Mohr,1 Laura Dannerbeck,1 Tobias J. Lange,2 Michael Pfeifer,1,2 Stefan Blaas,1 Bernd Salzberger,3 Florian Hitzenbichler,3 Myriam Koch 2

1Center for Pneumology, Donaustauf Hospital, Donaustauf
2Department of Internal Medicine 2, University Medical Center, Regensburg
3Department of Infection Control and Infectious Diseases, University Medical Center Regensburg, Germany

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.

Correspondence: Dr. Myriam Koch, Klinik und Poliklinik für Innere Medizin II, Universitätsklinikum Regensburg, Franz-Josef-Strauß Allee 11, D-93053 Regensburg, Germany. Tel. +49.941/944-0. E-mail: myriam.koch@ukr.de

Contributions: All authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the manuscript.

Conflict of interest: LD, MP and MK have nothing to disclose; AM reports grants from Gilead Sciences, outside the submitted work; TJL reports personal fees from Actelion, personal fees from Janssen-Cilag, personal fees from BMS, personal fees from MSD, personal fees from Pfizer, personal fees from GSK, personal fees from Acceleron Pharma, outside the submitted work; SB reports personal fees and non-financial support from Roche, personal fees and non-financial support from Boehringer Ingelheim, non-financial support from Teva, personal fees and non-financial support from Bayer, non-financial support from Gilead, personal fees and non-financial support from Novartis, personal fees from Merck Serono, non-financial support from Lucane Pharma, non-financial support from Actelion, non-financial support from CSL Behring, non-financial support from Vertex, outside the submitted work; BS reports personal fees from Roche Ag, personal fees from Sanofi, personal fees from Falk Foundation, outside the submitted work; FH reports grants from Gilead Sciences, personal fees from MSD, outside the submitted work.

Funding: The authors received no specific funding for this work.

Availability of data and materials: The dataset analysed during the current study is available from the corresponding author upon reasonable request.

Ethics approval and consent to participate: The retrospective study was approved by the local ethics committee (No. 20-1773-104) at the University of Regensburg.

Consent for publication: Not applicable.
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.

Cardiopulmonary exercise testing

Peak oxygen uptake (Peak-VO2) was measured by CPET with 151±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 35.4±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 (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
Table 1. Detailed characteristics of all 10 patients.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 / nurse / former smoker since 2018 (30 py)</td>
<td>F / 52 a / 36.3 kg/m²</td>
<td>0 days</td>
<td>No oxygen therapy</td>
<td>No abnormalities; no pulmonary embolism</td>
<td>FB / PVC normal TLCO SB: 123 Hb: 115 g/dl</td>
<td>441 m (91%)</td>
<td>98%</td>
<td>26.2 l / 2 l / min</td>
<td>70 ml / min / 190 ml / min (78%)</td>
<td>129 l / min / 77%</td>
<td>17 min/hg +</td>
<td>29 month</td>
<td>10 ml / 102%</td>
<td>23 l</td>
<td>17.7</td>
<td>9%</td>
</tr>
<tr>
<td>2 / smoker / no smoker</td>
<td>F / 30 a / 201 kg/m²</td>
<td>0 days</td>
<td>No oxygen therapy</td>
<td>No abnormalities; no pulmonary embolism</td>
<td>FB / PVC normal TLCO SB: 88 Hb: 143 g/dl</td>
<td>n.a.</td>
<td>90%</td>
<td>33 l / 41 l / min</td>
<td>600 ml / min / 1221 ml / min (78%)</td>
<td>163 l / min / 88%</td>
<td>21 min/hg +</td>
<td>25 month</td>
<td>51%</td>
<td>40 ml</td>
<td>73 l / 80%</td>
<td>31.3</td>
</tr>
<tr>
<td>3 / clerk / former smoker since 2013 (50 py)</td>
<td>M / 54 a / 291 kg/m²</td>
<td>22 days / 6 days</td>
<td>Oxygen therapy: high-flow therapy No invasive ventilation No noninvasive ventilation CT scan: CT scan No abnormalities</td>
<td>No abnormalities</td>
<td>FB / PVC normal TLCO SB: 83% Hb: 143 g/dl</td>
<td>n.a.</td>
<td>100%</td>
<td>25 l / 2 l / min</td>
<td>639 ml / min / 1555 ml / min (80%)</td>
<td>129 l / min / 78%</td>
<td>21 min/hg +</td>
<td>35 month</td>
<td>30%</td>
<td>61 l</td>
<td>11.2 ml / 119%</td>
<td>34.5</td>
</tr>
<tr>
<td>4 / factory worker / no smoker</td>
<td>M / 63 a / 335 kg/m²</td>
<td>56 days / 12 days</td>
<td>Oxygen therapy: No high-flow therapy No invasive ventilation No noninvasive ventilation LTCL: CRCT; CT scan: No abnormalities</td>
<td>No abnormalities</td>
<td>FB / PVC normal TLCO SB: 79% Hb: 143 g/dl</td>
<td>621 m (76%)</td>
<td>54W</td>
<td>36 l / 3 l / min</td>
<td>1080 ml / min / 1480 ml / min (88%)</td>
<td>160 l / min / 91%</td>
<td>10 min/hg +</td>
<td>20 month</td>
<td>58%</td>
<td>69 l</td>
<td>11.6 ml / 115%</td>
<td>24.7</td>
</tr>
<tr>
<td>5 / nurse / no smoker</td>
<td>M / 44 a / 21.0 kg/m²</td>
<td>1 day / 0 days</td>
<td>No oxygen therapy</td>
<td>No abnormalities</td>
<td>FB / PVC normal TLCO SB: 73% Hb: 163 g/dl</td>
<td>395 m (56%)</td>
<td>162W</td>
<td>36 l / 2 l / min</td>
<td>1080 ml / min / 1690 ml / min (80%)</td>
<td>160 l / min / 91%</td>
<td>12 min/hg +</td>
<td>20 month</td>
<td>58%</td>
<td>69 l</td>
<td>11.6 ml / 115%</td>
<td>24.7</td>
</tr>
<tr>
<td>6 / nurse / no smoker</td>
<td>M / 63 a / 48 days / 290 kg/m²</td>
<td>0 days</td>
<td>Oxygen therapy: No high-flow therapy No invasive ventilation No noninvasive ventilation</td>
<td>No abnormalities</td>
<td>FB / PVC normal TLCO SB: 52% Hb: 143 g/dl</td>
<td>534 m (79%)</td>
<td>150W</td>
<td>289 l / 4 l / min</td>
<td>819 ml / min / 1670 ml / min (76%)</td>
<td>116 l / min / 72%</td>
<td>11 min/hg +</td>
<td>29 month</td>
<td>38%</td>
<td>72 l</td>
<td>16.9 l / 106%</td>
<td>23.8</td>
</tr>
<tr>
<td>7 / clerk / no smoker</td>
<td>M / 58 a / 22.3 kg/m²</td>
<td>7 days / 0 days</td>
<td>Oxygen therapy: No high-flow therapy No invasive ventilation No noninvasive ventilation CT scan: No abnormalities</td>
<td>No abnormalities</td>
<td>FB / PVC normal TLCO SB: 63% Hb: 143 g/dl</td>
<td>n.a.</td>
<td>102W</td>
<td>38 l / 3 l / min</td>
<td>779 ml / min / 1330 ml / min (56%)</td>
<td>117 l / min / 72%</td>
<td>10 min/hg +</td>
<td>7 month</td>
<td>14%</td>
<td>88 l</td>
<td>11.4 l / 80%</td>
<td>54.4</td>
</tr>
<tr>
<td>8 / dentist / no smoker</td>
<td>M / 59 a / 23.0 kg/m²</td>
<td>30 days / 25 days</td>
<td>Oxygen therapy: High-flow therapy No invasive ventilation</td>
<td>No abnormalities</td>
<td>FB / PVC normal TLCO SB: 54% Hb: 143 g/dl</td>
<td>n.a.</td>
<td>168W</td>
<td>38.1 l / 3 l / min</td>
<td>1107 ml / min / 1850 ml / min (89%)</td>
<td>127 l / min / 79%</td>
<td>25 %/ 25 month</td>
<td>8%</td>
<td>91 l</td>
<td>15.4 l / 119%</td>
<td>29.0</td>
<td>35.7</td>
</tr>
<tr>
<td>9 / back employee / no smoker</td>
<td>M / 58 a / 32.0 kg/m²</td>
<td>0 days</td>
<td>No oxygen therapy</td>
<td>No abnormalities</td>
<td>FB / PVC normal TLCO SB: 50% Hb: 143 g/dl</td>
<td>442 m (77%)</td>
<td>150W</td>
<td>33 l / 2 l / min</td>
<td>937 ml / min / 1820 ml / min (74%)</td>
<td>129 l / min / 80%</td>
<td>13 min/hg +</td>
<td>17 month</td>
<td>21%</td>
<td>90 l</td>
<td>14.3 l / 94%</td>
<td>23.6</td>
</tr>
<tr>
<td>10 / student / no smoker</td>
<td>F / 21 a / 32.0 kg/m²</td>
<td>0 days</td>
<td>No oxygen therapy</td>
<td>No abnormalities</td>
<td>FB / PVC normal TLCO SB: 79% Hb: 143 g/dl</td>
<td>555 m (87%)</td>
<td>128W</td>
<td>24.9 l / 2 l / min</td>
<td>276 ml / min / 1413 ml / min (60%)</td>
<td>150 l / min / 79%</td>
<td>25 l / 12 month</td>
<td>68%</td>
<td>40 l</td>
<td>93 l / 80%</td>
<td>15.8</td>
<td>28.3</td>
</tr>
</tbody>
</table>
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.

References