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Impact of SARS Cov2 Infection in Pulmonary Gas Exchange and Exercise Capacity in Patients with Mild to Severe COVID-19

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Abstract

Background: Since beginning of 2020, SARS-CoV2 pandemic has been prevailing in humans causing COVID-19. Airways are strongly impacted during virus mediated inflammation and damage. Exact pathomechanisms during COVID-19 are still under investigation. We now further characterized limitations in exercise capacity in outpatient patients after symptomatic infection with SARS-CoV2 using bicycle cardiopulmonary exercise testing (CPET). 45 patients (21female/24 male) underwent standard pulmonary function testing (PFT) including spirometry, bodyplethysmography, CO-diffusion-measurement (DLCO, DLCO/VA), capillary blood gas-analysis (BGA) and symptom limited CPET on a bicycle. Patients' disease history was evaluated in advance. Severity of the disease was quantified according to reported data.

At rest, there were no statistically relevant abnormalities in spirometry, bodyplethysmography, CO-diffusion-measurement or blood gas-analysis, even in those patients less than 40 days post infection. We found significantly impaired alveolar-arterial oxygen gradients ($AaDO_2$) and decreased peak $V'O_2$ level post-COVID-19 patients up to up to 80days post infection. Reevaluating 10 patients 3 month later, a markedly increase in peak oxygen-uptake ($V'O_2$) and a normalized $AaDO_2$ at rest was noted. We conclude that COVID-19 resulted in decreased cardiopulmonary exercised capacity as demonstrated by CPET (significantly decreased peak $V'O_2$). The underlying mechanism is limitation of oxygen-diffusion indicated by significantly elevated $AaDO_2$ level in post-COVID-19 patients. Limitation was temporary and patients reached age-appropriate level 3 month later.

Keywords: COVID-19 • Pulmonary • SARS CoV2

Introduction

During spring 2020, we were confronted with the first patients that got sick from newly identified "Severe Acute Respiratory Syndrome-like Coronavirus-2" (SARS-CoV2) [1, 2]. which is spreading rapidly in humans via airborne transmission causing "Coronavirus Disease 2019, COVID-19". SARS-CoV2 has been first identified and sequenced 12-2019 in Wuhan [3]. It has some similarities with the SARS-CoV [4, 5] and the "Middle East Respiratory Syndrome Coronavirus" (MERS-CoV) [5]. However, while latter two only caused smaller and almost self-limitating endemic outbreaks until now a couple of SARS-CoV2 variants of interests and variants of concerns spread around the world causing repetitive waves of different stages of COVID-19 infections among population in almost every country of the world [6]. Until today, WHO reported more than 305 million confirmed cases [7] with more than 5.5 million death worldwide.

Different COVID-19 disease stages have been reported. Although many cases remain mild to asymptomatic, there is a large amount of severe courses requiring hospitalization and complex ICU-treatment including mechanical ventilation and extracorporeal membrane oxygenation, ECMO. A couple of risk factors have been identified predisposing for severe courses which include older age and a couple of pre-existing chronic diseases [8]. In contrast to many other respiratory pathogens and infections, COVID-19 is associated with a significant number of patients suffering from upcoming new symptoms days and weeks after acute COVID-19 ("post-COVID-syndrome") or from protracted symptoms and physical disabilities remaining after acute infection ("long-COVID-syndrome"). Scientist worldwide have been studying underlying pathomechanisms in SARS-CoV2-mediated infection and inflammation but biological properties underlying this phenomenon as well as possible therapeutic approaches remain largely unclear. Most symptoms during COVID-19 are mainly based on severe SARS-CoV2-triggered inflammatory reaction in susceptible cells expressing one or both of the human SARS-CoV2 receptors ACE2 and neuropilin1 [9,10].

Several studies have demonstrated that lung function is (highly) impaired at different courses of disease in hospitalized patients due to and discharged after COVID-19 [11-13]. Impairment has been demonstrated by different methods of lung function testing and imaging like high resolution computer tomography (CT), lung volume measurement (total lung capacity, TLC), spirometry (FVC, FEV1), lung diffusion capacity for carbon monoxide (DLCO), respiratory muscle strength and 6-minute walking distance (6MWD) [14-18]. However, it was difficult to perform pulmonary function tests (PFT) during pandemic because many laboratories and (private) clinics have been closed completely or reduced their PFT capacities due to massive aerosol formation during testing and thereby largely increased risks of contagion [19].

Patients assessed for lung function during a routine follow-up visit three months after discharge from hospitalisation due to COVID-19 indicated abnormal pulmonary function testing as well as impaired bloodgas diffusion during recovery. Different studies confirmed that almost 50% of patients included showed impaired diffusion-capacity for carbon monoxide (DLCO) values up to several month after acute infection and dismissal for hospital, deviations strongly correlated with increased degrees of severity [11,13,20]. Anastasio et al demonstrated that lung damage due to an infection with SARS-CoV2 was associated with reduced pulmonary function four months after acute COVID-19 infection [12]. Patients with severe disease stages had more

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impaired pulmonary function marker and decreased oxygen saturation values (SpO_2) during 6-minute-walking-tests compared to patients without pneumonia [12].

Data were confirmed by Huang et al. demonstrating that patients with severe courses of disease had more severe limitations of diffusion capacity for carbon monoxide as well as altered radiological findings [14]. During 6-minute-walk-test, 24% of patients on severity scale 3, 22% on severity scale 4 and 29% on severity scale 5-6 reached less than the lower limit of the normal range [14]. Furthermore, six months after discharge from hospital, patients still suffered from a couple of additional none-pulmonary symptoms such as fatigue and muscle weakness [14]. Moreover, almost all studies reported significantly enhanced weakness and impairment in body function with subsequently prolonged reduction in quality of life after SARS-CoV2-induced acute lung injury [21]. So far, most post-COVID-19 studies included patients which had severe COVID-19 disease stages requiring hospitalization and/or ICU-treatment. Until now little is known about prolonged restriction or limitation of lung function or mechanisms of pulmonary dysfunction after mild to of pulmonary diffusion capacity in post-COVID-19 patients without clearly differentiating between different measurement methods (blood gas analysis, carbon monoxide diffusion capacity (DLCO) or alveolar carbon monoxide uptake efficiency (DLCO/VA)).

In this study, we therefore investigated long-term effects after COVID-19 on different lung function parameters at rest and during exercise after mild to moderated course of COVID-19. All patients included in our study had been treated at home using standard treatment for acute respiratory infection, mostly nonsteroidal anti-inflammatory drugs. None of them required high-flow oxygen treatment, mechanical ventilations, oral steroids or antibiotic treatment of pulmonary superinfection. All patients reported a profound and prolonged reduced exercise capacity even after the infection has subsided. Until know there is little published data on possible mechanisms of lung function disorientation in post-COVID-19 patients during exercise testing. We therefore determined different lung function parameter in 45 post-COVID-19 patients at rest and during exercise using standardized bicycle cardiopulmonary exercise testing (CPET). In addition, 10 patients underwent follow up CPET to evaluate possible changes/improvements about 118 days after first examination.

Methods and Methodology

Study subjects

Subjects were evaluated post COVID-19 infection. Infection was confirmed by positive PCR for SARS-CoV2 with onset of first symptoms. All patients had been infected by wildtype variant of SARS-CoV2 during second wave in Berlin, Germany. 45 Patients were included, 24 female and 21 males (median age 55, range 13-82 yrs.). Subjects volunteered to participate investigation. None of them had needed mechanical ventilation during infection. All subjects underwent standard pulmonary workout within a regular ambulatory evaluation for a possible lung damage after COVID-19, 10 patients an additional follow up check 3 month later. Patients had to be able to perform bicycle ergometry. Patients with evidence of left heart failure, primary valvular disease, peripheral arterial disease, underlying muscular diseases, relevant orthopedic limitations or significant anemia were excluded from our study. All subjects gave written informed consent. CPET results were compared to previously published reference data [22-24].

Assessment of disease severity

Assessment of disease severity was done according to a 5 point clinical assessment score from 1 (mild, no pneumonia), 2 moderate (mild pneumonia), 3 severe (severe pneumonia), 4 critical (ARDS, Hyperinflammation, septic shock, multi organ failure) [25].

Pulmonary Function Testing (PFT)

Each subject underwent PFT immediately prior to CPET. PFT consisted of spirometry, bodyplethysmography, carbon monoxide (CO-) diffusion-measurement (DLCO, and DLCO/VA as corrected for ventilated area), capillary blood gas-analysis from hyperemic earlobe (BGA) and symptom limited cardiopulmonary exercise-testing (CPET) on a bicycle.

Cardiopulmonary Exercise Testing (CPET)

Each subject performed CPET on a bicycle. A ramp test with an exercise increment of 5 Watt per minute was used for with all patients. Protocol started with a resting period of 3 minutes to reach steady state conditions for heart rate, blood pressure and gas exchange, followed by an unloaded cycling period of 3 minutes at 10 Watt. In the absence of chest pain, ECG abnormalities or critical blood pressure changes, tests were continued with a linear increase of load until symptom-limited end (volitional exertion, dyspnea or muscle-fatigue/exhaustion). All tests were done according to international standardized guidelines for CPET [26,27] with continuous monitoring of gas exchange, ECG, blood pressure and oxygen saturation as published before [24].

Gas exchange variables

Respiratory gas exchange was measured continuously throughout all periods of exercise testing using a Jaeger®/Vyaire® Masterscreen CPX system with Oxycon Pro and BMI-adapted Rudolph's mask. Prior to each test, equipment was calibrated with reference gas and volume calibration. Standard 12-lead ECG was obtained during whole investigation; blood pressure was measured with a standard cuff sphygnomanometer. Minute ventilation (V'E), tidal volume (V't), oxygen uptake ($V'O_2$), carbon dioxide output ($V'CO_2$) and end-tidal partial pressures for oxygen ($petO_2$) and carbon dioxide ($petCO_2$) were acquired on a breath-by-breath basis and averaged over 10 second intervals. Peak oxygen uptake ($peakV'O_2$) was defined as the highest 10-sec average of $V'O_2$ during the last minute of exercise. Ventilatory efficiency, expressed as the relation of V'E and $V'CO_2$, has been assessed as slope of regression of both parameters excluding excess hyperventilation at the end of exercise. Aerobic threshold (AT) was determined according to Wasserman [28]. Breathing reserve (VE'/MVV) was calculated as maximal V'E in relation to maximal voluntary ventilation (MVV). MVV was calculated by FEV1 x 35.

During exercise dynamic flow volume loops were documented at early, middle and maximal exercise-levels. Each maneuver was finished by maximal deep inspiration to place the flow volume loop to the resting spirometry (intrabreath-measurement of end-expiratory lung volume, EELV). After the test, each maneuver was evaluated for V't and inspiratory capacity (IC). Special attention was paid to register a sufficient flow volume loop during last third of exercise. Capillary blood gas samples from hyperemic ear lobe were obtained at rest and at AT.

Statistical analysis

Between-group comparisons was made using Mann-Whitney U test and multifactorial ANOVA. Statistical analysis of follow-up examinations was done by Wilcoxen signed rank test. A 2-tailed P-value of less than 0.05 was considered statistically significant. The associations between time after diagnosis to $AaDO_2$ were tested by Spearman´s rank correlation. P-values (2-tailed) below 0.05 were considered statistically significant.

Results

45 participants were included in the study. Two of them were not able to perform CPET according to defined guidelines and quality standards due to orthopedic limitations. All patients had had PCR-confirmed SARS-CoV2 infection and clinically relevant, highly symptomatic COVID-19 but could be treated outpatient. None of these patients needed more than symptomatic treatment with e.g., nonsteroidal anti-inflammatory drugs, no oral or inhaled steroids were used, neither antibiotics in any patient for any kind of bacterial superinfection. Demographics and major clinical characteristics as well as results from lung function screening are listed in (Table 1). Disease stages indicated as mean values. FEV1: forced expiratory volume in 1 second in litre and percent predicted; Raw: resistance of airways in ($kPa * s * l^{-1}$); FVC: forced vital capacity in litre and percent predicted; RV: residual volume in litre; TLC: total lung capacity in litre; DLCO and DLCO/VA: diffusion-capacity for carbon

monoxide/corrected for ventilated area, single breath; peakV'O_2: peak-oxygen uptake in ml/minute and ml/minute/kg bodyweight; V'O_2/HR: oxygen pulse in ml; BR: breathing reserve; A-aO_2 rest/AT: alveolar-arterial oxygen gradient at rest/aerobic threshold in mmHg; pO_2 rest/AT: partial pressure for oxygen at rest/aerobic threshold in mmHg.

Patients presented after different time points post infection/quarantine in our practice, so four groups of patients in 40-day intervals post-infection (p.i.) were made (randomly): Group 1 included patients ≤ 40 days post infection, group 2 patients between 40-80 days post infection, group 3 patients between 80-120 days post infection, and group 4 patients with more than 120 days post infection. Disease severity in all patients was assessed [25] and was not significantly different between all groups (Table 1). As refered to age-adapted reference values, no significant difference in lung function parameters at rest could be evaluated by spirometry and bodyplethysmography among patients in either group.

Patients in group 1 (40days post infection) and group 2 (40 - 80 days post infection), however, demonstrated a significantly decreased peak V'O_2 and increased AaDO_2 level at rest compared to age-adapted reference values (table 1) although DLCO and DLCO/VA and blood gases analysis at rest, before CPET were noticeable in all groups. AaDO_2 improved during exercise and reached almost normal level at the aerobic threshold. In group 3 (80 - 120 days post infection) and group 4 (more than 120 post infection), no conspicuous peak V'O_2 or AaDO_2-level could be noticed (Figure 1). AaDO_2 at rest demonstrated a significant negative correlation to time post infection (Figure 2). However, there was no correlation between disease severity and deviation of CPET marker from age-adapted predicted values (data not shown). Moreover, static and dynamic lung function parameters as demonstrated by spirometry, bodyplethysmography, DLCO and remained noticeable in all groups and all follow up PFT-examinations independent of severity of illness (Table 1). A subgroup of 10 patients agreed to a reevaluation procedure 3 month after the first pulmonary workout (Table 2). FE_{V1}: forced expiratory volume in 1 second in litre and percent predicted; Raw: resistance of airways in (kPa * s * l^{-1}); VC: vital capacity in litre and percent predicted; RV: residual volume in litre; TLC:

Table 1. Demographic and clinical characteristic of patient groups. Four groups of patients in 40 day intervals post-infection (p.i.) have been made as described above (* p ≤ 0.05, ** p ≤ 0.01).

Characteristics	Total	≤ 40δ π.ι.	40-80d p.i.	80-120d p.i.	> 120d p.i.
Patients (n)	45	12	11	8	14
Female/male (n)	24/21	07-May	03-Sep	05-Mar	09-Apr
Age (years)	46 (13-82)	47,5 (19-75)	48 (19-82)	45,5 (38-56)	36 (13-61)
Disease stage (1-3)	1,622 (1-3)	1,9 (1-3)	1,46 (1-3)	1,625 (1-3)	1,54 (1-3)
FEV1 (l)	3.23 (1.62-5.25)	3.06 (1.73-3.98)	3.34 (2.02-4.09)	3.195 (2.02-5.06)	3.57 (1.62-5.25l)
FEV1 (%pred.)	97% (64-129)	89.5% (66-115%)	94% (64-116%)	104.5% (64-129%)	103.6% (64-121%)
Raw (kPa × s × l^{-1})	0.23 (0.12-0.0.51)	0.25 (0.15-0.42)	0.23 (0.12-0.29))	0.205 (0.14-0,28)	0.24 (0.13-0.51)
FVC (l)	3.76 (2.08–6.46)	3.58 (2.08-4.89)	3.85 (2,76-5.19)	3.895 (3.37-6.34)	3.81 (2.67-6.62)
FVC (%pred.)	96% (63.9-128)	87% (63.9-106%)	90% (71-114%)	103% (93-128%)	102% (72-115%)
RV (l)	2.72 (1.3-4.63)	3.15 (1.55-3.98)	2.72 (1.89-3.79)	3.67 (1.3-4.63)	2.26 (1.33-3.49)
TLC (l)	6.68 (4.87-10.97)	6.65 (4.94-8.85)	6.63 (5.25-8.3)	7.79 (4.87-10.97)	6.49 (5-8.68)
DLCO (ml/min/kPa)	6.98 (2.66-11.88)	7.75 (2.66-10.03)	6.71 (4.69-10.6)	6.79 (6-11.68)	7.29 (4.64-11.76)
DLCO/VA (%pred.)	83.5% (49-111%)	85.4% (49-105%)	84% (63-111%)	71.75% (63-110%)	93% (50-106,7%)
peakV'O_2 (ml/min)	1694 (1059-3244)	1606 (1059-2447)	1916 (1191-2828)	2205 (1063-2638)	1797 (1078-3244)
peakV'O_2 (ml/min/kg)	25.5 (13.2-44)	18.9* (13.2-30.6)	19.2* (15.3-44)	29.8 (16.3-42)	26.9 (13.5-36.6)
V'E vs. V'CO_2 slope	29 (24-38)	30 (24-38)	30 (25.6-35)	27 (25-33)	28 (27-32)
V'O_2/HR (ml)	10.9 (6.2-19.7)	9.5 (7.8-15.3)	13.1 (8.1-15.4)	13 (9.2-16.3)	9.3 (6.2-19.7)
BR (%pred.)	37 (0-67)	46 (32-63)	37 (17-62)	34 (26-67	38 (0-66)
A-aO2 rest (mmHg)	20.05 (0.5-41)	32.2** (11.5-41)	26.6** (7-33.2)	14 (10-37.2)	14.4 (0.5-31.9)
A-aO2 AT (mmHg)	17.81 (7-56.2)	25 (8-56.2)	23 (11.2-40.8)	14 (10-37.2)	16.2 (7-38.5)
pO2 rest (mmHg)	84.8 (60.3-105)	82.3 (60.3-97.3)	77.9 (68-94)	92 (82.3-103)	87.4 (70-105)
pO2 AT (mmHg)	91.8 (59.4-104)	87.6 (59.4-96.6)	82 (70.2-99.8)	92.1 (74.6-104)	95.4

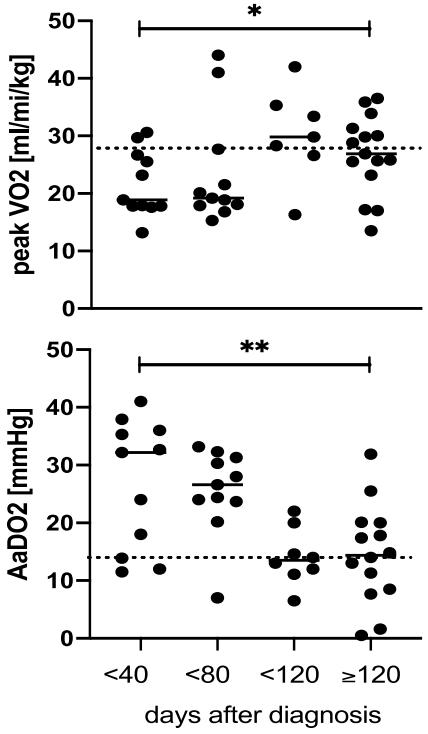

Figure 1. Time-dependent changes of peak V'O_2 [ml/min/kg body weight], upper figure and A-aO_2 [mmHg] lower figure. Patients were grouped in 40-day intervals according to time frames patients presented to the practice post-infection (p.i.)/quarantine. Dashed lines represent calculated/age adjusted standard value (* p ≤ 0.05 and ** p ≤ 0.01).

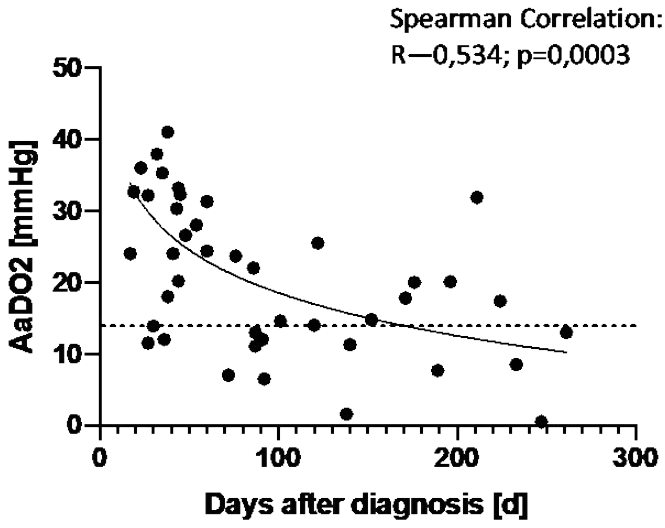

Figure 2. Time-dependent decline of COVID-19-mediated increased A-aO_2 level [mmHg] days after diagnosis [d]. Dashed line represents calculated/age adjusted standard value.

Table 2. Demographic and clinical characteristic of reevaluated patients. Ten patients agreed to second evaluation cycle and were reevaluated three months after first set of pulmonary function testing and CPET (* $p \leq 0.05$, ** $p \leq 0.01$).

Characteristics	1. examination	2. examination
patients (n)	10	10
female/male (n)	05-May	/
age (years, mean)	40.5(19-59)	/
days after diagnosis (mean)	46.9 (17-101)	168.8 (102-263)
Severity (1-3; mean)	1.9 (1-3)	/
FEV1 (l)	3.53 (2.28-3.89)/	3.26 (2.21-4)
FEV1 (%pred.)	91.01% (64-115%)	93.06% (65-117%)
Raw (kPa × s × l^{-1})	0.235 (0.19-0.42)	0.25 (0.18-0.44)
FVC (l)	4.14 (2.92-4.89) 92.3% (71-112%)	3.82 (3.05-4.68)
FVC (%pred.)		92.5% (76-113)
RV (l)	2.84 (1.55-3.96)	2.53 (1.81-4.01)
TLC (l)	6.96 (4.94-8.85)	6.34 (4.86-8.59)
DLCO (ml/min/kPa)	7.8 (6.6-10.03)	7.82 (6.14-10.16)
DLCO/VA (%pred.)	79% (63-105%)	86%* (75-105%)
peakV'O_2 (ml/min)	2011.4 (1415-2828)	2147.7** (1050-3175)
peakV'O_2 (ml/min/kg)	29 (1415-2828)	32.1** (12,7-46)
V'E vs. V'CO_2 slope	28.5 (24-35)	28.5 (25-33)
V'O_2/HR (ml)	14.5 (8.6-15.6)	13.6 (8.2-18.8)
BR (%pred.)	25.45 (17-46)	25.1 (15-49)
A-aO2 rest (mmHg)	23.15 (7-41)	16.5** (1.6-40)
A-aO2 AT (mmHg)	24 (8-37.2)	20.7 (11.1-35.7)
pO2 rest (mmHg)	89.65 (60.3-97.3)	91 (63.5-102)
pO2 AT (mmHg)	85 (74.6-94.8)	92.85 (70.6-104)

total lung capacity in litre; DLCO and DLCO/VA: diffusion-capacity for carbon monoxide/corrected for ventilated area, single breath; peakV'O_2: peak-oxygen uptake in ml/minute and ml/minute/kg bodyweight; V'O_2/HR: oxygen pulse in ml; BR: breathing reserve; A-aO_2 rest/AT: alveolar-arterial oxygen gradient at rest/aerobic threshold in mmHg; pO_2 rest/AT: partial pressure for oxygen at rest/aerobic threshold in mmHg.

We noted a significant decrease in AaDO2 levels at rest and AT as well as a significantly increased peak V'O_2 reaching age-adapted predicted values independent of severity of illness (Table 2). In these subgroups also a significant increase in DLCO could be demonstrated.

Discussion and Conclusion

Until now, more than 200 million confirmed cases of SARS-CoV2 induced COVID-19 have been reported by WHO. Although most of the SARS-CoV2 infections remain mild, there is a relevant number of severe courses requiring hospitalization and graduated stages of medical treatment. Mortality is significantly increased in those patients requiring hospitalization leading to almost 4.5 million fatal courses (> 90.000 in Germany) [7]. Patients suffering from different kind of signs and symptoms like shortness of breath or difficulty breathing, fatigue, cough, joint-/muscle-/chest-pain, headache, loss of smell or taste, memory, concentration or sleeping problems, depression or anxiety, and worsened symptoms after physical or mental activities partly weeks or months after acute COVID-19 infection. Symptoms are often independent of initial stage of disease. The mechanisms still remain under investigation [29,30]. Long-COVID is relevant condition with million people suffering from it. This syndrome can occur in different ways. The symptoms here are not limited to the respiratory tract, but manifest themselves in various organ systems. It is still unclear which risk factors, such as gender, age, severity of the disease course, etc., are involved [29].

In our study, we examined the impact of a mild to moderate course of disease of SARS-CoV2 induced COVID-19 on lung function at rest and during exercise in outpatient subjects. We therefore routinely examine all post-COVID-19 patients using a standardized pulmonary function testing protocol including body plethysmography, lung diffusion capacity for carbon monoxide (DLCO), blood gas analysis and cardiopulmonary exercise testing (CPET) on a bicycle. For our study, we included 45 highly post-COVID-19 patients with different stages of severity and at different time points after infection. We retrospectively grouped all patients in four groups regarding elapsed time between acute COVID-19 and examination (group 1 ≤ 40 days, group 2 40-80 days, group 3 80-120 days, group 4 ≥ 120 days post infection).

Using pulmonary function testing (body plethysmography, DLCO-testing, BGA), we were not able to demonstrate any pathological findings, regardless of time interval to acute COVID-19 and disease severity. This suggests that even moderate to more severe stages of disease in our patient group did not cause any sustained restrictive or obstructive ventilation disorders. Using CPET we could demonstrate a time-dependent significant increased of $AaDO_2$ and a decreased peak V'O_2 up to 80 days post infection. $AaDO_2$ and V'O_2 normalized again after at least 120 days post infection. Interestingly $AaDO_2$ values at rest were more impaired than at the aerobic threshold (AT) during exercise. We speculate that this might be explained by preserved ventilatory capacity. In contrast to our results, Rinaldo et al. reported “deconditioning” as main mechanism of impaired exercise response in COVID-19 survivors [31]. Therefore, most patients considered in those studies had a critical or severe course of disease after the infection with SARS-CoV-2 [31].

In our study, we were able to demonstrate reduced peak VO_2 after an infection with SARS-CoV2. By means of reduced peak VO_2 values, we can prove the subjective resilience here. As limiting factor in CPET, we could show elevated $AaDO_2$. It is interesting to observe that the $AaDO_2$ values at rest are more impaired than the $AaDO_2$ during the exercise. The altered values of $AaDO_2$ are probably caused by endothelial inflammation, microthrombi, alveolitis and pulmonary oedema [10,32,33]. Despite this, we could not detect any changes in DLCO as well as PFD, since the values were within the normal range. This indicates that no change in lung function, neither due to restriction or obstruction, was observed. The severity of the proband's disease is not critical enough to see impaired levels of DLCO. However, in our patient group with measurements at different timepoints (Table 2) we could see a significant improvement of DLCO. Nevertheless, those values are not pathological. The recommendation of measurement of DLCO is easy and might provide limitations in some patients but needs not show pathological values of DLCO in all subjects. In special issues, CPET-examination should be considered as increased $AaDO_2$ could be demonstrated by this technic.

Pathophysiological processes during COVID-19 and as well as the long-term effects post COVID-19 infection are still under investigation. Some studies describe the regeneration process after a cleared infection with SARS-CoV-2 for up to one year. In one study, the regeneration process after a severe course of infection with SARS-CoV-2 after 3, 6, 9 and 12 months was observed. The dyspnea scores as well as walking distance in six minutes improved during the recovery period [34]. However, they also discovered that even after one year in the aftermath of the clearance of the infection, there was consisting physiological, regarding reduced DLCO values, as well as radiological changes [34]. Those changes were also observed in another study in patients without a severe disease progression [35]. In another study, scientists investigated the effects of an already cleared infection with hospitalization 3 months after discharge [36]. At this point, the subjects showed improved function of the lung [36]. Other articles also described the regeneration process at different states after the remission of the infection [37-38]. Our study shows the timeline of consequences caused by a mild to moderate without mechanical ventilation COVID-19 infection. We were able to show in this study that the impairments due to a COVID-19 infection frequently improve und normalize after 4 months [39].

Nevertheless, there are some (in part unavoidable) limitations in our study. All data were obtained from retrospective analysis of real life data of patients which came for regular examination after having had a COVID-19 infection. Study therefore, unlike many previous studies, was difficult to plan in advance, as SARS-CoV2 pandemic only started a couple of months before. Moreover, due to hygienic restrictions and limitations, examinations of the individuals were more difficult.

Competing Interests

All contributing authors state to have no competing financial or non-financial interests.

Author's Contributions

All authors approved and read the final version of the manuscript.

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