Feasibility and Efficacy of Cardiopulmonary Rehabilitation After COVID-19

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Abstract: The COVID-19 pandemic affects a large number of patients with a rapid progression of respiratory failure often requiring hospitalization or intensive care unit treatment in some patients. Survivors of severe COVID-19 experience persistent weakness and cardiorespiratory failure. Feasibility and potential benefit of cardiopulmonary rehabilitation after COVID-19 remains unclear. Therefore, we retrospectively analyzed a cohort of COVID-19 patients in a single-center inpatient rehabilitation clinic and describe performance and outcome during cardiopulmonary rehabilitation.

Patients were referred from acute care hospitals for rehabilitation after severe COVID-19. The cohort (N = 28) was divided in ventilated or not ventilated patients for further analysis. Fifty percent were female, the mean age was 66 yrs, and patients stayed in the acute hospital for 19.3 ± 10.7 days before referral for cardiopulmonary rehabilitation. Seventeen patients (61%) needed previous intensive care unit treatment in the acute care hospital. Risk factors, assessments, and questionnaires on admission were comparable in both groups. Significant enhancements were observed in 6-min walking test and feeling thermometer, which were independent of previous ventilation status.

In conclusion, comprehensive cardiopulmonary rehabilitation after COVID-19 is safe, feasible, and effective. Improvements in physical performance and subjective health status were independent of previous ventilation.

Key Words: COVID-19, Rehabilitation, Outcome, 6-MWT, Feeling Thermometer

Infection with the severe acute respiratory syndrome coronavirus 2, hereafter referred as COVID-19, often affects patients with chronic health conditions and takes a more severe course in patients with comorbidities such as cardiovascular disease, diabetes mellitus, and obesity.1 A feature of severe COVID-19 is the rapid progression of respiratory failure often requiring hospitalization or even intensive care unit (ICU) treatment.2 Severe outcome of COVID-19 is particular driven by a so called systemic endotheliitis, a severe cytokine storm and activated coagulation, and mortality of severe COVID-19 is high.3,4 Survivors experience reduced lung function, critical illness polyneuropathy and myopathy, and cardiorespiratory deconditioning that could be described as a form of postintensive care unit syndrome.5,6 Survivors of severe COVID-19 are significantly impaired in all activities of daily living and are in need of multimodal rehabilitation with particular knowledge in cardiovascular and pulmonary medicine. After acute respiratory distress syndrome associated with COVID-19 and subsequent ICU treatment, most patients experience reduced lung function, critical illness polyneuropathy, critical illness myopathy, and cardiorespiratory deconditioning.7 In addition, high prevalence of anxiety and depression has been reported after ICU treatments and hospital admission for COVID-19 might be associated with fear of survival of patient and families.8–10

However, as the whole COVID-19 condition is so new, there are scarce data available about feasibility, safety, and success of in-patient cardiopulmonary rehabilitation (CR) in COVID-19 patients. We hypothesized that CR for COVID-19 is safe and feasible and therefore aimed to characterize patients referred to in-patient rehabilitation and describe performance and outcome during rehabilitation.

METHODS

Participants and Procedures

The cohort presents patients referred for CR to the Zürcher RehaZentren Wald, Switzerland after hospitalization in acute care hospitals for COVID-19 between March and May 2020. Patients were retrospectively analyzed to describe potential differences, performance, and outcome during rehabilitation. Patients were eligible for rehabilitation as soon as they were hemodynamically and respiratory stable (no catecholamine or invasive ventilation) and without the need for permanent monitoring. In the initial phase of the corona crisis in Switzerland, patients were admitted after being asymptomatic for 2 days and 10 days after onset of infection. Initially patients were admitted after 2 days of no symptoms and 10 days after onset of infection, and later, patients were required to have at least one negative swab before transfer. For these patients, isolation was not necessary according to the current guidelines in Switzerland and patients were cared for on a normal ward. All patients gave written informed consent, and local ethics committee approved the study protocol (BASEC-No 2020-01061).

The cohort was divided into mechanically ventilated patients (n = 12) or not ventilated patients (n = 16) in the acute hospital setting in order to analyze the impact of very severe COVID-19. Within 2 days after admission for rehabilitation, all patients were assessed with questionnaires, such as Chronic Respiratory...
Questionnaire, Hospital Anxiety and Depression Scale (HADS), Cumulative Illness Rating Scale, and Functional Independence Measure. To measure changes during rehabilitation, functional assessments with 6-min walk test (6-MWT) and feeling thermometer (FT) were performed on admission and before discharge. All patients were deemed cognitively able to provide valid responses to the questionnaires by treating physicians. Co-morbidities, lung function, and laboratory values including blood gas analysis were assessed.

**Cardiopulmonary Rehabilitation Intervention**

The patients participated in a multimodal 2- to 4-wk inpatient CR, which was carried out according to a protocol adapted to the severity of the disease. This program normally included a total of 25–30 therapy sessions, which took place on 5–6 days per week. It consisted of an individualized exercise training including aerobic exercise and strength training.

Training intensity for aerobic exercise was mainly derived from an initial 6-MWT, and only in some patients, exercise cycle ergometer tests were performed. The aerobic program consisted primarily of supervised indoor and outdoor walking or stationary cycling. Patient were monitored using pulse oxymetry during their exercise. Criteria for stopping or reducing exercise intensity were SpO2 level of less than 88%, symptom limited (Borg > 6), or/and reaching their submaximal heart rate.

Strength training was performed 3 × 20 repetitions with the maximum tolerated load. The intensity of the monitored

| TABLE 1. Baseline characteristics and results of CR in severe COVID-19 patients |
|---------------------------------------------------------------|
| **Total Group (N = 28)** | **+ Ventilation (n = 12)** | **− Ventilation (n = 16)** | **P** |
| Age, mean (SD) | 66.04 (9.3) | 64.3 (8.9) | 67.4 (9.7) | 0.390 |
| Sex, male, n (%) | 14/28 (50.0) | 9/12 (75.0) | 5/16 (31.3) | 0.054 |
| BMI, mean (SD) | 27.6 (4.9) | 26.9 (3.5) | 28.1 (5.7) | 0.553 |
| ICU stay, n (%) | 17/28 (60.7) | 12/12 (100.0) | 5/16 (31.3) | <0.001 |
| Hospitalization days (acute), mean (SD) | 19.3 (10.7) | 27.6 (9.1) | 12.7 (6.5) | <0.001 |
| Hospitalization days (ICU), mean (SD) | 13.9 (7.3) | 17.0 (5.9) | 6.4 (3.8) | 0.002 |
| Comorbidities previous COVID-19, n (%) | 4/28 (14.3) | 1/12 (8.3) | 3/16 (18.8) | 0.613 |
| Coronary artery disease | 1/28 (3.6) | 0/12 (0.0) | 1/16 (6.3) | 1.000 |
| Hypertension | 14/28 (50.0) | 5/12 (41.7) | 9/16 (56.3) | 0.704 |
| Type 2 diabetes | 7/28 (25.0) | 4/12 (33.3) | 3/16 (18.8) | 0.418 |
| Dyslipidemia | 6/28 (21.4) | 2/12 (16.7) | 4/16 (25.0) | 0.673 |
| Peripheral artery disease | 2/28 (7.1) | 0/12 (0.0) | 2/16 (12.5) | 0.492 |
| Chronic renal failure (eGFR <60 ml/min) | 5/28 (17.9) | 3/12 (25.0) | 2/16 (12.5) | 0.002 |
| Previous smoker | 7/28 (25.0) | 5/12 (41.7) | 2/16 (12.5) | 0.103 |
| COPD (all stages) | 6/28 (21.4) | 0/12 (0.0) | 6/16 (37.5) | 0.024 |
| CIRS points | 9.9 (5.1) | 9.3 (4.2) | 10.3 (5.7) | 0.592 |
| Questionnaires/assessments | 6-MWT, meters at entry, mean (SD) | 230.9 (153.6) | 241.3 (154.4) | 223.1 (157.7) | 0.764 |
| | 6-MWT, meters at discharge, mean (SD) | 360.9 (134.6) | 386.7 (135.7) | 341.6 (134.7) | 0.391 |
| | 6-MWT, meters change, mean (SD) | 130.0 (78.0) | 145.4 (59.1) | 118.5 (89.8) | 0.376 |
| | FT, points at entry, median (IQR) | 4.0 (3.4–4.9) | 4.3 (3.0–5.5) | 4.0 (3.4–4.9) | 0.877 |
| | FT, points at discharge, median (IQR) | 4.0 (4.0–5.0) | 4.5 (4.0–5.0) | 4.0 (3.4–4.9) | 0.536 |
| | FT, points change, median (IQR) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.066 |
| | CRQ, score points, median (IQR) | 4.0 (3.4–4.9) | 4.3 (3.0–5.5) | 4.0 (3.4–4.9) | 0.434 |
| | FIM, total points, median (IQR) | 107.0 (103.0–122.0) | 106.0 (103.0–122.0) | 113.5 (103.0–122.8) | 0.451 |
| | HADS A, points, median (IQR) | 4.0 (2.5–6.8) | 3.0 (2.5–6.8) | 3.0 (2.5–6.8) | 0.779 |
| | HADS D, points, median (IQR) | 4.0 (1.0–7.0) | 4.0 (1.0–7.0) | 1.0 (1.0–7.0) | 0.281 |
| | Laboratory values, mean (SD) | 122.4 (94.6) | 171.0 (107.7) | 85.2 (64.6) | 0.024 |
| | Leucocytes, G/l | 7.9 (3.2) | 10.3 (3.4) | 6.3 (3.7) | 0.002 |
| | Creatinine, μmol/ml | 91.6 (74.4) | 116.8 (106.4) | 72.6 (28.0) | 0.185 |
| | Hemoglobin, g/l | 116.7 (21.7) | 108.8 (22.9) | 122.6 (19.3) | 0.096 |
| | Creatine kinase, U/l | 114.0 (79.8) | 136.0 (79.2) | 94.2 (78.9) | 0.266 |
| | D-dimer, ng/ml | 4.1 (3.5) | 4.3 (3.5) | 3.9 (3.7) | 0.785 |

*P value for the comparison with the total group of the extern cohort.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, c-reactive protein; CRQ, Chronic Respiratory Questionnaire; extern, referred to CPR; FIM, Functional Independence Measure; HADS A, Hospital Anxiety and Depression Scale Anxiety; HADS D, Hospital Anxiety and Depression Scale Depression; in-house infected, infection occurred during rehabilitation.
endurance training sessions was adjusted continuously, with the aim of achieving the maximum tolerated exercise load during each training session. When a drop in oxygen saturation was observed, oxygen was added with a maximum of 4 L via nasal cannula to keep the oxygen saturation at more than 90%. Respiratory physiotherapy consisted of teaching breath control (pursed lip breathing, secretion mobilization, and diaphragmatic breathing), energy saving techniques, and controlled coughing exercises. Twice a week (1 hr each), all patients participated in educational sessions, which in addition to self-management, included coping skills and nutrition interventions, self-medication, management of infections and exacerbations, dyspnea, use of oxygen, and activities of daily living. To the underweight and overweight patients, a nutritional advice and diabetes advice were offered.

If needed, the patients took part in a structured smoking cessation program and received psychosocial support.

Noninvasive ventilation using breathing support administered through a face mask to reduce the work load of breathing and improve gas exchange was initially used in three patients during night time only and not during exercise training.

Hygiene Concept During Rehabilitation

For the treatment and management of COVID-19 patients, the recommendations of the Swiss Nos (Swiss National Institute of Infection-Prevention) and the Health Department of the Kanton Zurich were applied. An assessment of the hygienic risk was made for the individual patient. If isolation was indicated, the patients were transferred to the isolation ward where they were supervised in a single room. The staff in close contact with these patients (especially nursing staff and physiotherapists) had to wear FFP-2 masks, long-sleeved disposable fluid repellent gowns or disposable fluid repellent coveralls, eye protection, and gloves. Temporary isolation was stopped after negative COVID-19 swab. In some cases, the viral RNA was still detected in the polymerase chain reaction although being asymptomatic leading to the continued isolation until at least one test was negative. In isolated patients, individual therapies were carried out 1–2 times a day for 15–45 mins depending on the level of performance, according to the severity of the illness, and were adjusted in the course of time. Therapies took place in the patients’ room and instructions for self-training were given as well as smaller therapy devices, such as elastic resistance bands and/or breathing training devices such as RC-Cornet or VRP1-flutter. Some training devices were stored in a central location in the isolation ward and were disinfected after each therapy, such as motorized training devices, stepper, ergometer, etc. Respiratory therapies, psychological support, massages, nutrition and diabetes counseling, social services, etc. were provided. The frequency of these treatments was adapted to the individual and diagnosed limitations and needs of the patients.

Exercise Capacity

Exercise capacity was measured at hospital admission and discharge using the 6-MWT, performed once at the beginning and once at the end of the CR program after 20 days, according to the guidelines of the American Thoracic Society and carried out by experienced, well-instructed examiners.11

Quality of Life

As standardized health-related quality of life measurement tool, the German version of the Chronic Respiratory Questionnaire was used. The questionnaire measures eight dimensions of health-related quality of life and allows calculation of two summary scales of physical and mental health.12

Functional Independence Measure

The Functional Independence Measure is an 18-item measurement tool that explores an individual’s physical, psychological, and social function.13 We used this tool to assess a patient’s level of disability as well as change in patient status in response to rehabilitation.

Cumulative Illness Rating Scale

The Cumulative Illness Rating Scale was used as an indicator of health status and predicted 18-mo mortality and rehospitalization especially in hospitalized elderly patients.14

Hospital Anxiety and Depression Scale

The HADS was originally designed as a short, easy-to-use, 14-item screening tool for depression and anxiety symptoms in the hospital outpatient setting.15 It is composed of two 7-item subscales (both ranging from 0 to 21 with higher scores indicating more severe distress.

FIGURE 1. A and B, Change during rehabilitation. Improvement in 6-MWT (A) and FT (B).
Feeling Thermometer

We used the FT to determine and compare patients’ feelings about their actual well-being by applying a numeric rating of their feelings toward an imaginary scale in terms of degrees, with their attitudes corresponding to temperatures.

Lung Function, Blood Gas Analysis, and Oxygen Therapy

Spirometry and body plethysmography (Master Screen Body; Jaeger GmbH, Hoechberg, Germany) were performed on CR discharge according to recent guidelines. Blood gases were taken at rest under room air condition (Radiometer ABL800, Willich, Germany) at the admission to CR.

Statistics

Binary variables were presented as frequencies, and the Fisher exact test was used for group comparison. Normally distributed continuous variables were presented as mean with standard deviation (SD) and the *t* test was used for comparison between groups. Not normally distributed continuous variables were presented as median with interquartile range (IQR) and the Mann-Whitney *U* test was used for group comparison. A *P* value of less than 0.05 was considered as statistically significant.

RESULTS

Fifty percent were female, the mean age was 66 yrs, and duration of stay was 19.3 ± 10.7 days before referral for CR (Table 1). Seventeen patients (61%) needed ICU treatment and 12 patients needed ventilation in the acute hospital setting with a mean duration of 10.8 ± 6.3 days. Ventilated patients had a longer ICU stay in days (17.0 [5.9] vs. 6.4 [3.8], *P* < 0.002) and total duration of the hospitalization in days (27.6 [9.1] vs. 12.7 [1.7], *P* < 0.001). All patients performed a CR with a mean duration of 20 days. Partially, CR was provided with limited intensity because of hygiene concept and necessary isolation. Twenty-one patients (75%) still needed nasal oxygen therapy and 3 (11%) received noninvasive ventilation during the night on admission to CR. None died or had to be retransferred to the acute hospital setting. Eighty-five percent of the patients were still isolated on admission, where 15% of them had least one negative severe acute respiratory syndrome coronavirus 2 swab taken in the acute clinic before transfer to the rehabilitation clinic.

Risk factors were comparable in both groups according to the comorbidities. At admission to CR, Cumulative Illness Rating Scale, HADS, and Functional Independence Measure scores were similar for the ventilation group in comparison with the nonventilated group. This was also true for the questionnaires (HADS, Chronic Respiratory Questionnaire), 6-MWT, and FT (Table 1).

### TABLE 2. Respiratory parameters of COVID-19 patients before discharge from rehabilitation

| Respiratory parameters | Total Group (N = 28) | + Ventilation (n = 12) | − Ventilation (n = 16) | *P* value |
|------------------------|----------------------|-----------------------|-----------------------|------------|
| **BGA pO2, mean (SD), kPa** | 9.4 (2.9) | 9.9 (3.5) | 8.9 (2.3) | 0.451 |
| **BGA pCO2, mean (SD), kPa** | 4.9 (1.2) | 4.7 (0.8) | 5.1 (1.4) | 0.460 |
| **SpO2 admission, mean (SD), %** | 92.7 (2.7) | 92.4 (2.2) | 92.9 (3.1) | 0.665 |
| **SpO2 discharge, mean (SD), %** | 96.0 (2.3) | 96.0 (2.8) | 96.1 (2.1) | 0.946 |
| **O2 therapy at admission, n (%)** | 21/28 (75.0) | 11/12 (91.7) | 10/16 (62.5) | 0.184 |
| **O2 therapy at discharge, n (%)** | 8/28 (25.0) | 4/16 (28.6) | 3/16 (18.8) | 0.418 |
| **NIV at admission, n (%)** | 3/27 (11.1) | 2/27 (7.4) | 1/26 (3.8) | 0.549 |

#### Obstruction

- None, n (%) | 8/21 (38.1) | 3/9 (33.3) | 5/12 (41.7) | 1.000 |
- Mild, n (%) | 2/21 (9.5) | 0/9 (0.0) | 2/12 (16.7) | 0.486 |
- Moderate, n (%) | 0/21 (4.8) | — | — | — |
- Severe, n (%) | 0/21 (4.8) | — | — | — |
- Very severe, n (%) | 1/21 (4.8) | 0/9 (0.0) | 1/12 (8.3) | 1.000 |

#### Restriction

- Non, n (%) | 8/21 (38.1) | 2/9 (22.2) | 6/12 (50.0) | 0.367 |
- Mild, n (%) | 2/21 (9.5) | 1/9 (11.1) | 1/12 (8.3) | 1.000 |
- Moderate, n (%) | 9/21 (42.9) | 6/9 (66.7) | 3/12 (25.0) | 0.087 |
- Severe, n (%) | 1/21 (4.8) | 0/9 (0.0) | 1/12 (8.3) | 1.000 |

#### CO diffusion

- Normal, n (%) | 1/21 (4.8) | 0/9 (0.0) | 1/12 (8.3) | 1.000 |
- Mild, n (%) | 8/21 (38.1) | 4/9 (44.4) | 4/12 (33.3) | 0.673 |
- Moderate, n (%) | 7/21 (33.3) | 4/9 (44.4) | 3/12 (25.0) | 0.397 |
- Severe, n (%) | 4/21 (19.0) | 1/9 (11.1) | 3/12 (25.0) | 0.603 |

*P* value for the comparison with the total group of the extern cohort.

BGA, blood gas analysis; extern, referred to CPR; in-house infected, infection occurred during rehabilitation; NIV, noninvasive ventilation.
Significant enhancements were observed in 6-MWT (+130 m) and FT (+40 points) for total cohort with no significant differences in the intergroup comparison between ventilated and nonventilated patients (Fig. 1). Chest x-ray was performed in 27 patients before discharge showing persistent bilateral infiltrations in 20 patients (74%). Lung function testing before discharge showed persistent obstructed ventilation in just a few cases, but predominantly restricted ventilation and reduced diffusion capacity were observed in most of the patients, without significant differences between both groups (mean forced expiratory volume in one second 56% pred [+12], mean forced expiratory volume in one second% forced vital capacity 81% [+9], mean total lung capacity 62% pred [+8], mean transfer factor of the lung for carbon monoxide 56% pred [+12]). Seven patients (25%) still required supplemental oxygen at discharge from CR. However, all patients were able to return back home without professional nursing support.

The findings in the laboratory results indicated that patients with previous ventilation had significant higher inflammation markers (c-reactive protein, leucocytes) on admission to CR, whereas there were no significant differences between both groups in the level of creatinine, hemoglobin, D-dimer, blood gas analysis, and respiratory parameters (Tables 1, 2).

DISCUSSION

We demonstrated that CR could be performed safely and with beneficial effect in a rehabilitation cohort of COVID-19 patients. All patients with severe COVID-19 being referred for CR were stable enough to participate in a comprehensive program irrespective of restrictions due to hygiene safety requirements. Functional capacity and subjective health status improved significantly, as assessed by 6-MWT and FT. Interestingly, patients with previous mechanical ventilation showed identical improvements in 6-MWT and FT as patients without ventilation and no major differences in patient’s baseline characteristics including risk factors, respiratory parameters, and functional measures. However, the intergroup comparison of the 6-MWT showed an increase of 26.9 meters for the ventilated group compared with nonventilated patients. Although statistically not relevant, this result was above the minimal important difference of 25 m in pulmonary patients. An explanation might be their longer stay in the acute hospital with more time to recover, which possibly also explains the missing difference in the 6-MWT on admission to CR. We would have expected, in contrast to the observation that patients with the lowest initial distance walked in 6-MWT have a higher probability of reaching the minimal important difference. The almost identical improvements in both groups suggest a classic deconditioning rather than the muscle dysfunction that is often discussed in context with COVID-19. At discharge, we found in most patients a restricted ventilation according to their lung function, which is in line with data from 2005 of 97 SARS survivors, showing in 24% persistent reduction of lung diffusion and exercise capacity at 1-yr follow-up.

The need for rehabilitation during the COVID-19 pandemic has been published recently. We demonstrate that inpatient CR is apparently feasible and safe in COVID-19 patients, as long as proper safety precautions, close medical management, and supplemental oxygen are available and used if needed.

Limitations

Like all retrospective analyses, the validity of the data is already limited by the study design itself. Referring the severe and very severe COVID-19 patients to this CR program leads to a one-sided view of COVID-19, which is why the results cannot be transferred to the total cohort of COVID-19 patients, probably leading to a selection bias. Another limitation is the short observation period of an average of 20 days. It is unsure that all patients received exactly the same CR content, as the program had to be varied or limited in some patients because of isolation. In addition, the single-center approach and the lack of a control group limit the validity of the data.

CONCLUSIONS

Comprehensive CR after COVID-19 is safe, feasible, and effective. Improvements were significant according to physical performance and subjective health status regardless of previous ventilation. Safety issues regarding a strict hygiene concept addressing contact isolation and personal protection equipment was important but could also be implemented within CR.

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