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## **Effectiveness of pulmonary rehabilitation in COVID-19 respiratory failure patients post-ICU**

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None.

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## **Abstract**

**Introduction.** Some COVID-19 patients develop respiratory failure requiring admission to intensive care unit (ICU). We aim to evaluate the effects of pulmonary rehabilitation (PR) post-ICU in COVID-19 patients. **Methods.** Twenty-one COVID-19 patients were evaluated pre- and post-PR and compared retrospectively to a non-COVID-19 group of 21 patients rehabilitated after ICU admission due to respiratory failure. **Results.** PR induced greater 6-min walking distance improvement in COVID-19 patients (+205±121m) than in other respiratory failure patients post-ICU (+93±66m). The sooner PR was performed post-ICU, the better patients recovered. **Conclusions.** PR induced large functional improvements in COVID-19 patients post-ICU although significant physical and psychosocial impairments remained post-PR.

## **Introduction**

The emergence of SARS-CoV-2 has led to significant mortality, morbidity and unprecedented stress on healthcare systems worldwide [1]. Critically ill patients exhibiting respiratory failure were admitted to the intensive care unit (ICU) for prolonged stays, subsequently requiring a rehabilitation program to deal with the consequences of artificial ventilation and prolonged inactivity [2-4]. Pulmonary rehabilitation (PR) has proven to be effective in respiratory patients following mechanical ventilation [5] and in patients with the most common pulmonary disease, chronic obstructive pulmonary disease, at all stages and recovering from acute exacerbations [6]. Although PR has been suggested following severe COVID-19 [7], there is still a lack of data demonstrating its effectiveness on recovery of physical and psychosocial parameters in severe COVID-19 patients following an ICU stay.

The aim of this study was to evaluate the impact of PR in severe COVID-19 patients and to compare their outcomes to non-COVID-19 patients rehabilitated after ICU admission due to respiratory failure.

## **Methods**

The present study was conducted in a dedicated PR center (Dieulefit Santé) in Dieulefit, France. We extracted for analysis data collected systematically in an ongoing prospective cohort study including PR patients rehabilitated from 2019 to 2022. We analyzed data from all COVID-19 patients admitted to Dieulefit Santé during the current pandemic and from a non-COVID-19 group of patients after ICU admission due to respiratory failure. Both groups performed PR consisting in respiratory exercises, muscle strengthening, balance and walking when possible, cycling and gymnastics according to current ATS/ERS recommendations [8]. The following multidimensional testing battery was performed at admission and discharge: pulmonary function test, psychosocial evaluations, muscle strength and balance measurements, and six-minute walking test (6MWT, also performed weekly during PR). Only pulmonary function (pre-

PR) and 6MWT data were available in non-COVID-19 patients. The study was part of an ongoing cohort of pulmonary rehabilitation approved by a French independent ethics committee (ID-RCB number: 2019-A02104-53). One-way and two-way ANOVA analysis was used to compare the groups using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA)

## **Results**

We included a total of 21 severe COVID-19 patients rehabilitated post-ICU, and 21 non-COVID-19 respiratory failure patients rehabilitated post-ICU. Details of the groups' characteristics are provided in table 1. All COVID-19 patients had at least one of the following comorbidities: cardiovascular, respiratory, diabetes, cancer, or obesity. The non-COVID-19 group was in majority chronic respiratory patients. There was no significant difference in age, sex and body mass index between groups, but COVID-19 patients needed longer ICU and intubation duration. COVID-19 patients had less severe airway obstruction than the non-COVID-19 patients. COVID-19 patients had severe exercise impairment (6-min walking distance at admission was  $19.7 \pm 22.1$  % predicted, with 7 patients walking less than 50 m), desaturated severely during exercise and reported severe dyspnea similar to non-COVID-19 respiratory patients (table 1).

Adherence to PR was excellent in COVID-19 patients since all patients attended all the proposed sessions without adverse effects or specific limitation. COVID-19 patients showed significant improvement post-PR in all physical and psychosocial evaluations (table 1). Both groups started PR with severe limitation in 6-min walking distance without significant difference between groups. PR induced a significantly ( $p < 0.001$ ) greater 6MWT improvement in COVID-19 patients ( $+205 \pm 121$  m) than in non-COVID-19 patients ( $+93 \pm 66$  m). Post-PR, COVID-19 showed 6-min walking distance greater than non-COVID-19 respiratory patients. However, at discharge, both groups still showed significant impairment in respiratory function and physical performance.

In COVID-19 patients, a significant correlation between 6MWT improvement (in meters/day) and the number of days post-ICU ( $r = -0.59$ ,  $p = 0.01$ ) and a trend for a

significant correlation between 6MWT improvement (in meters) and the number of days in PR ( $r=0.41$ ,  $p=0.09$ ) were observed.

## **Discussion**

Our results show that long stays in ICU in COVID-19 patients are associated with severe short-term sequelae including severe muscle function impairment, exercise capacity limitations and low quality of life. These results emphasize the severe debilitating consequences of COVID-19 as recently underlined [9].

In contrast, we observed a large and rapid recovery in exercise capacity among COVID-19 patients compared to non-COVID-19 patients rehabilitated after ICU admission due to respiratory failure as well as large improvements in muscle strength, balance and psychosocial status suggesting that PR might limit post-traumatic stress disorder in this population. Hence, our results provide support for the recent guidelines proposed for rehabilitation in COVID-19 patients [7]. COVID-19 patients showed significantly greater improvement in 6-min walking distance for a similar PR program compared to non-COVID-19 respiratory failure patients post-ICU. This recovery was probably related to PR but also to the natural recovery process of the disease. Another important finding was that the earlier PR was introduced post-ICU and the longer the duration of PR, the better patients recovered their physical capacity. This observation corroborates previous results in COPD and respiratory failure patients emphasizing the need for early PR following ICU [5].

Our study has several limitations, firstly the small sample size of COVID-19 patients that were rehabilitated, secondly the lack of a control group of COVID-19 patients post-ICU who were not rehabilitated and thirdly the availability of 6MWT data only post-PR in the group of non-COVID-19 patients retrospectively analyzed as comparative group.

In conclusion, compared to non-COVID-19 respiratory patients, severe COVID-19 patients needed prolonged ICU stay and intubation, therefore had more functional impairment post-ICU, but recovered better following PR. However, the recovery was

limited with significant physical and psychosocial impairment remaining, possibly requiring longer rehabilitation, but the sooner patients were admitted post-ICU, the better they recovered. This suggests that some aspects of PR could be initiated while in the ICU or the pulmonary ward. Further controlled and long-term studies are required to better understand the role of PR post-COVID-19.

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**Table 1.** Characteristics and effect of PR in the COVID-19 vs non-COVID-19 groups.

	COVID-19 post-ICU (n = 21)		Non-COVID-19 Respiratory failure post-ICU (n = 21)	
Sex	14 ♂ / 7 ♀		13 ♂ / 8 ♀	
Age (years)	70.9 ± 10.6		69.1 ± 9.4	
BMI (Kg/m <sup>2</sup> )	26.9 ± 5.4		24.7 ± 7.2	
<b>Hospitalization</b>				
Days in ICU	23.4 ± 8.5		16.2 ± 26.9	
Intubation, n (%)	16 (76)		6 (29)*	
Days intubated	22.3 ± 5.7		1.6 ± 2.9*	
Days in pulmonary ward	13.0 ± 8.1		9.5 ± 11.4	
Duration of PR	27.6 ± 14.2		29.9 ± 17.3	
<b>Evaluations</b>				
Oxygen therapy, n (%)	Pre-PR	Post-PR	Pre-PR	Post-PR
	18 (86)	5 (24)	16 (76)	13 (62)
<b>Pulmonary function</b>				
FEV1 (% predicted)	66.7 ± 16.0	81.2 ± 14.2 <sup>+</sup>	35.17 ± 13.9 <sup>*</sup>	----
FVC (% predicted)	59.1 ± 15.2	72.9 ± 15.2 <sup>+</sup>	53.5 ± 11.5	----
<b>Respiratory pressures</b>				
Plmax (cmH <sub>2</sub> O)	42.7 ± 17.5	62.9 ± 13.0 <sup>+</sup>	----	----
PEmax (cmH <sub>2</sub> O)	68.2 ± 30.3	87.1 ± 30.3 <sup>+</sup>	----	----
<b>Walking performance</b>				
Tinetti balance test	25.0 ± 3.0	27.5 ± 1.0 <sup>+</sup>	----	----
6MWD (m)	138.7 ± 144.4	343.4 ± 139.6 <sup>+</sup>	136.6 ± 151.9	223.2 ± 170.5 <sup>**</sup>
Minimal SpO <sub>2</sub> (%)	85 ± 7	89 ± 11	83 ± 10	82 ± 8
End-of-test dyspnea (Borg)	4.4 ± 2.3	4.1 ± 1.8	5.9 ± 1.9	6.1 ± 2.0
<b>Muscle strength</b>				
Handgrip (Kg)	18.1 ± 8.0	23.5 ± 8.5 <sup>+</sup>	----	----
Quadriceps isometric (Kg)	14.2 ± 10.6	25.5 ± 11.7 <sup>+</sup>	----	----
<b>Psychosocial evaluation</b>				
Quality of life	37.2 ± 22.8	22.3 ± 15.9	----	----
Fatigue	12.1 ± 8.4	4.3 ± 6.5 <sup>+</sup>	----	----
Anxiety	6.9 ± 4.6	2.2 ± 3.2 <sup>+</sup>	7.1 ± 3.3	----
Depression	6.5 ± 4.8	1.4 ± 2.4 <sup>+</sup>	6.5 ± 2.3	----
Post-traumatic stress	29.7 ± 14.1	22.7 ± 12.1	----	----

Data are mean ± SD. Respiratory failure: 15 COPD patients with respiratory decompensation, 6 other patients with respiratory distress: stroke, cirrhosis and cardiac patients; ICU: intensive care unit; BMI: body mass index; PR: pulmonary rehabilitation; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; Plmax: maximal inspiratory pressure; PEmax: maximal expiratory pressure; 6MWD: six-minute walking distance. Quality of life was assessed using Saint George respiratory questionnaire; fatigue was assessed using the Pichot questionnaire (normal values < 22); anxiety and depression were assessed using the Hospital Anxiety and Depression questionnaire (normal values < 8).; Post-traumatic stress was measured using the PCLS: Post-traumatic stress disorder Checklist scale (normal values < 44). \* p < 0.05 vs COVID-19 group; <sup>+</sup> p < 0.05 vs pre-PR.

**Figure legend.**

**Figure 1.** Weekly 6-min walking distance in COVID-19 patients post-ICU. Each line represents a patient and each point represents a week. Day 0 is the day of extubation. The first point of each curve is the 6-min walking distance at admission in pulmonary rehabilitation (3 patients have 0 m at admission and 1 patient has 0 m throughout 5 weeks, i.e. they could not perform the walking test due to severe disability).

