

Early View

Correspondence

Pulmonary rehabilitation in Long-COVID – more than just natural recovery !?

Rainer Gloeckl, Daniela Leidl, Inga Jarosch, Tessa Schneeberger, Christoph Nell, Nikola Stenzel, Ayham Daher, Michael Dreher, Claus F. Vogelmeier, Klaus Kenn, Andreas R. Koczulla

Please cite this article as: Gloeckl R, Leidl D, Jarosch I, *et al.* Pulmonary rehabilitation in Long-COVID – more than just natural recovery !?. *ERJ Open Res* 2021; in press (<https://doi.org/10.1183/23120541.00454-2021>).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Copyright ©The authors 2021. This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Reply to Correspondence ERJOR-00398-2021

Title: Pulmonary rehabilitation in Long-COVID – more than just natural recovery !?

Authors: Rainer Gloeckl PhD ^{1,2}, Daniela Leitl MSc ^{1,2}, Inga Jarosch PhD^{1,2}, Tessa Schneeberger MSc^{1,2}, Christoph Nell PhD³, Nikola Stenzel PhD⁴, Ayham Daher MD⁵, Michael Dreher MD⁵, Claus F. Vogelmeier MD⁶, Klaus Kenn MD^{1,2}, Andreas R. Koczulla MD^{1,2,7}

Affiliations:

¹ Department of Pulmonary Rehabilitation, Philipps-University of Marburg, Member of the German Center for Lung Research (DZL), Marburg, Germany

² Institute for Pulmonary Rehabilitation Research, Schoen Klinik Berchtesgadener Land – Schoenau am Koenigssee; Germany

³ Department of Pulmonology, Philipps-University Marburg, Germany

⁴ Psychologische Hochschule Berlin (PHB), Berlin

⁵ Department of Pneumology and Intensive Care Medicine, University Hospital RWTH Aachen, Aachen, Germany

⁶ Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Centre Giessen and Marburg, Philipps-Universität Marburg, Germany. Member of the German Center for Lung Research (DZL), Marburg, Germany

⁷ Teaching hospital, Paracelsus Medical University, Salzburg, Austria

Take Home Message: In the light of missing randomized controlled trials, some arguments suggest that pulmonary rehabilitation has beneficial effects beyond natural recovery.

Reply

We thank Hussain et al. for their correspondence regarding our study on the ‘benefits of pulmonary rehabilitation in COVID-19’ [1].

Although a large proportion of COVID-19 patients recovers fully from the disease, approximately 5% to 10% experience prolonged symptoms for several months following the acute COVID-19 phase [2-4]. This results in millions of people suffering from COVID-19 sequelae worldwide. Therefore, beneficial interventions are urgently needed to counteract

these long-term consequences. A Cochrane review from April 2021 identified more than 50 studies that investigated rehabilitative interventions in post-COVID patients [5]. Amongst them are two randomized, controlled trials that included 72 and 140 post-acute patients, respectively, showing that respiratory techniques have superior benefits beyond natural recovery to improve pulmonary function, exercise performance, quality of life, and anxiety, especially in combination with group psychological interventions [6, 7]. However, we admit, that there is currently no randomized, controlled trial available that investigated the effects of a more comprehensive, multidisciplinary pulmonary rehabilitation (PR) program in COVID-19.

Due to the lack of a control group in our study, the impact of natural recovery cannot be determined. Therefore, we agree with Hussain et al. that the natural convalescence after the acute COVID-19 phase may have contributed to the effects of PR in our study (like we discussed in the limitation section). However, we would like to point out, why we believe that PR seems to have additional benefits beyond spontaneous recovery.

Effects of pulmonary rehabilitation versus natural recovery in *mild/moderate* COVID-19

Hussain et al. questioned why patients in the mild/moderate group without functional limitation were referred to PR “only” due to ongoing symptoms. The German COVID-19 rehabilitation guideline recommends referring patients to rehabilitation programs when symptoms or other impairments of activities of daily living are ongoing [8]. Hussain et al. also mentioned a 6-minute walk distance (6MWD) of 500m to 580m to be “normal”. Patients in our study reached a median 6MWD of 509m which corresponded to only 71% predicted (according to the reference equation by Troosters et al.[9]). We agree, that a higher baseline 6MWD leads to a certain ceiling effect that limits the chances to improve 6MWD after PR. Nevertheless, COVID-19 patients in the mild/moderate group were able to improve 6MWD by 48m (95%CI: 35m to 113m). This range is clearly beyond the expected minimal important difference of 30m [10] and well beyond common variabilities seen in 6MWD [11]. Furthermore, since the SARS-CoV-2 infection in the mild/moderate patient group had occurred 6 months before, the improvement in 6MWD during a comprehensive 3 week PR might be rather related to the intervention than to a spontaneous recovery after such a long period. Also, FVC did not influence 6-MWD in a relevant fashion - the correlations between

the improvements in FVC and 6MWD were low and not significant (mild/moderate: $r = -0.03$; severe/critical: $r = 0.33$).

Effects of pulmonary rehabilitation versus natural recovery in *severe/critical* COVID-19

A study by Huang et al. has shown that hospitalized COVID-19 patients had a median 6MWD of 495m 6-month after hospital discharge [12]. Patients in the severe/critical COVID-19 group in our study reached a comparable 6MWD (468m) already at PR discharge (which was only 6 weeks after hospital discharge). It seems that the recovery of exercise performance was accelerated by PR.

Even clearer is a comparison of our data with another COVID-19 cohort published by Daher et al. [13] which was comparable in age and lung function. These patients were followed up 6 weeks after hospital discharge. Assessments of COVID-19 patients in our study at the end of PR were also 6 weeks after hospital discharge. This makes the Daher cohort an interesting comparison group, although it remains unknown, if and how many patients in this cohort performed PR after hospital discharge. Although their patients had a shorter duration of hospitalization (37 versus 15 days), the median 6-MWD was markedly higher in our cohort (following PR) compared to the cohort of Daher et al. (468m versus 380m, Figure 1).

Figure Legend

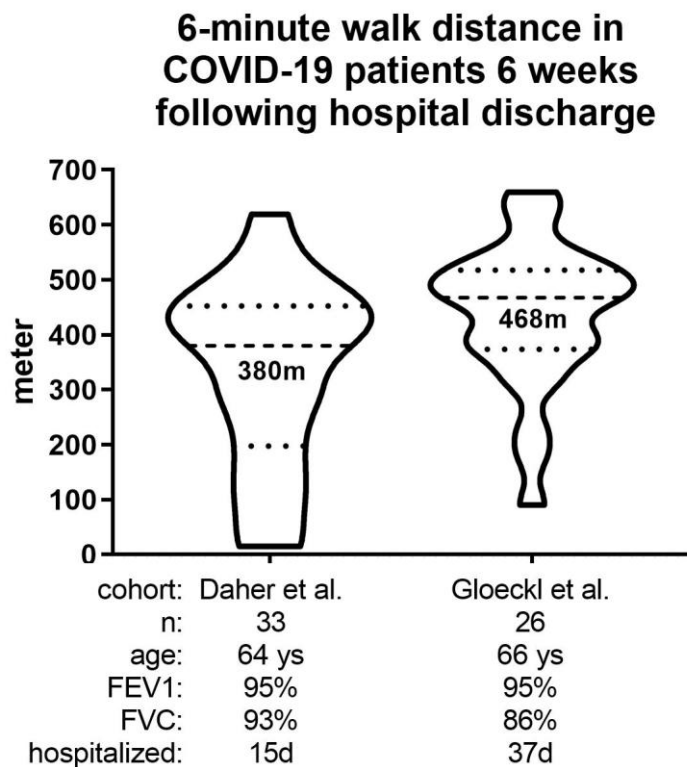


Figure 1. Comparison of the 6-minute walk distance between two cohorts of COVID-19 patients 6 weeks after hospital discharge. Patients in the cohort from Gloeckl et al. [1] performed comprehensive pulmonary rehabilitation. Original data from the comparison group was provided by courtesy of Daher et al. [13]. Values below the dashed lines within violin plots represent median; dotted lines represent interquartile ranges.

Another consideration of Hussain et al. was that our PR service was supposed to differ from standard practice because we offered “only” a 3 week PR program. We have not mentioned this in the manuscript clear enough, but a 3-week inpatient multidisciplinary PR is an obligatory procedure in Germany as well as in some other European countries like i.e. in Austria or Switzerland. Several studies have shown, that such a comprehensive PR program is highly beneficial to improve health status and quality of life in patients with chronic respiratory diseases [14-17].

In conclusion, based on all mentioned aspects we strongly believe that PR has beneficial effects beyond natural recovery. However, we agree with Hussain et al. that well-planned, randomized controlled trials (which were already initiated, e.g. NCT04821934, NCT04365738, NCT04718506) are necessary, to clarify the relevance of PR in COVID-19 on a higher evidence level.

References

1. Gloeckl R, Leidl D, Jarosch I, et al. Benefits of pulmonary rehabilitation in COVID-19: a prospective observational cohort study. *ERJ Open Res* 2021; 7: 00108-2021.
2. Greenhalgh T, Knight M, A'Court C, et al. Management of post-acute covid-19 in primary care. *Bmj* 2020; 370: m3026.
3. Vaes AW, Goertz YMJ, Van Herck M, et al. Recovery from COVID-19: a sprint or marathon? 6-month follow-up data from online long COVID-19 support group members. *ERJ Open Res* 2021; 7:
4. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med* 2021; 27: 626-631.
5. Negrini F, de Sire A, Andrenelli E, et al. Rehabilitation and COVID-19: update of the rapid living systematic review by Cochrane Rehabilitation Field as of April 30th, 2021. *Eur J Phys Rehabil Med* 2021;
6. Liu K, Zhang W, Yang Y, et al. Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. *Complement Ther Clin Pract* 2020; 39: 101166.
7. Liu Y, Yang YQ, Pei SL, et al. Effects of group psychological intervention combined with pulmonary rehabilitation exercises on anxiety and sleep disorders in patients with mild coronavirus disease 2019 (COVID-19) infections in a Fangcang hospital. *Psychol Health Med* 2021; 1-11.
8. AWMF SARS-CoV-2, COVID-19 und (Früh-) Rehabilitation. Available in German only: https://www.awmf.org/uploads/tx_szleitlinien/080-008l_S2k_SARS-CoV-2_COVID-19_und_Fr%C3%BCh- Rehabilitation_2020-11.pdf. Link accessed on 24.06.2021.
9. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999; 14: 270-4.
10. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014; 44: 1428-46.
11. Hernandez NA, Wouters EF, Meijer K, et al. Reproducibility of 6-minute walking test in patients with COPD. *Eur Respir J* 2010;
12. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021; 397: 220-232.
13. Daher A, Balfanz P, Cornelissen C, et al. Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. *Respir Med* 2020; 174: 106197.
14. Kenn K, Gloeckl R, Soennichsen A, et al. Predictors of success for pulmonary rehabilitation in patients awaiting lung transplantation. *Transplantation* 2015; 99: 1072-7.
15. Huppmann P, Sczepanski B, Boensch M, et al. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. *Eur Respir J* 2013; 42: 444-53.
16. Schultz K, Wittmann M, Wagner R, et al. In-Patient Pulmonary Rehabilitation to Improve Asthma Control. *Dtsch Arztebl Int* 2021; 118: 23-30.
17. Jarosch I, Gehlert S, Jacko D, et al. Different Training-Induced Skeletal Muscle Adaptations in COPD Patients with and without Alpha-1 Antitrypsin Deficiency. *Respiration* 2016; 92: 339-347.