

Can Intermittent Hypoxic Conditioning Enhance the Benefits of Standard Long COVID-19 Rehabilitation?

Tim Kambič^{1,2}  | Tadej Debevec^{1,3} | Mitja Lainscak^{4,5}

¹Faculty of Sport, University of Ljubljana, Ljubljana, Slovenia | ²Department of Medical BioSciences, Exercise Physiology Research Group, Radboud University Medical Centre, Nijmegen, the Netherlands | ³Department of Automatics, Biocybernetics and Robotics, Jožef Stefan Institute, Ljubljana, Slovenia | ⁴Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia | ⁵Division of Cardiology, General Hospital Murska Sobota, Murska Sobota, Slovenia

Correspondence: Mitja Lainscak (mitja.lainscak@guest.arnes.si)

Received: 24 January 2025 | **Accepted:** 29 January 2025

Funding: T.K. is partially funded by Slovenian Research and Innovation Agency (programme no. P5-0147). M.L. is funded by the Slovenian Research and Innovation Agency (grant no.: P3-0456).

Keywords: exercise training | hypoxia exposure | post COVID-19 | pulmonary rehabilitation | SARS-CoV-2

Since the outbreak of the Coronavirus-19 (COVID-19) pandemic in December 2019, nearly 705 million people got infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 7 million people died [1]. Following recovery from acute COVID-19 infection, many individuals continue to suffer from long-term sequelae of SARS-CoV-2 infection (≥ 3 months) defined as long COVID-19 syndrome or post COVID condition [2–4]. Unsurprisingly, incidence of long COVID-19 syndrome is the highest among hospitalised unvaccinated individuals (50%–85%) and the lowest among vaccinated people (8–12%) and in most cases persisted more than 1 year [2]. The greater risk and most severe symptoms of long COVID-19 were manifested in females aged 35–50 years, patients with comorbidities (type 2 diabetes, allergies, lung diseases, heart failure, chronic kidney disease and obesity) and in unvaccinated individuals [2–5]. Sarcopenia is highly prevalent in patients with long COVID-19, particularly after longer hospitalisation [6].

Long COVID-19 is a heterogeneous, systemic and multiorgan syndrome that has been associated with > 200 different symptoms. The accumulation of SARS-CoV-2 in the tissues, dysregulated immune response, inflammation and endothelial dysfunction induce damage to pulmonary (lung fibrosis and alveolar epithelium injury), cardiovascular (peri-myocarditis, arterial inflammation, micro-thrombosis and coagulopathy), skeletal muscle (muscle fibre atrophy and disrupted mitochondrial function) [7, 8], neurological (postural orthostatic

tachycardia and dysautonomia) and autoimmune (onset of autoimmune diseases) systems (Figure 1) [2–4, 9]. These impairments are primarily manifested as fatigue, cough, shortness of breath at rest and after exercise, exercise intolerance, chest pain, joint and muscle pain, cognitive impairments (dizziness, brain fog) and sleep disorders, along with other less frequent symptoms [2–4, 7, 9, 10].

Multisystem involvement makes long COVID-19 management challenging. To date, only cognitive and exercise training interventions alone or combined have shown promise of improvement in cognitive, pulmonary and physical function over usual care; a plethora of other interventions, including drugs, food supplementation and neurological approaches, did not provide benefits (Figure 1) [11, 12]. With pulmonary symptoms at a centre stage, several exercise training modalities for patients with long-COVID were effectively translated from standard pulmonary rehabilitation [13], while the inspiratory muscle training alone demonstrated no added benefit. Therefore, the search for safe and effective pulmonary or systemic intervention that would additionally restore pulmonary function continues.

Over the recent years, the manipulations of ambient oxygen (O_2) (e.g., hypoxic and hyperoxic conditioning) have emerged as a therapeutic strategy from sports performance settings, which lead to development of different hypoxic interventions, including intermittent hypoxia conditioning (IHC; e.g., short

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2025 The Author(s). Journal of Cachexia, Sarcopenia and Muscle published by Wiley Periodicals LLC.

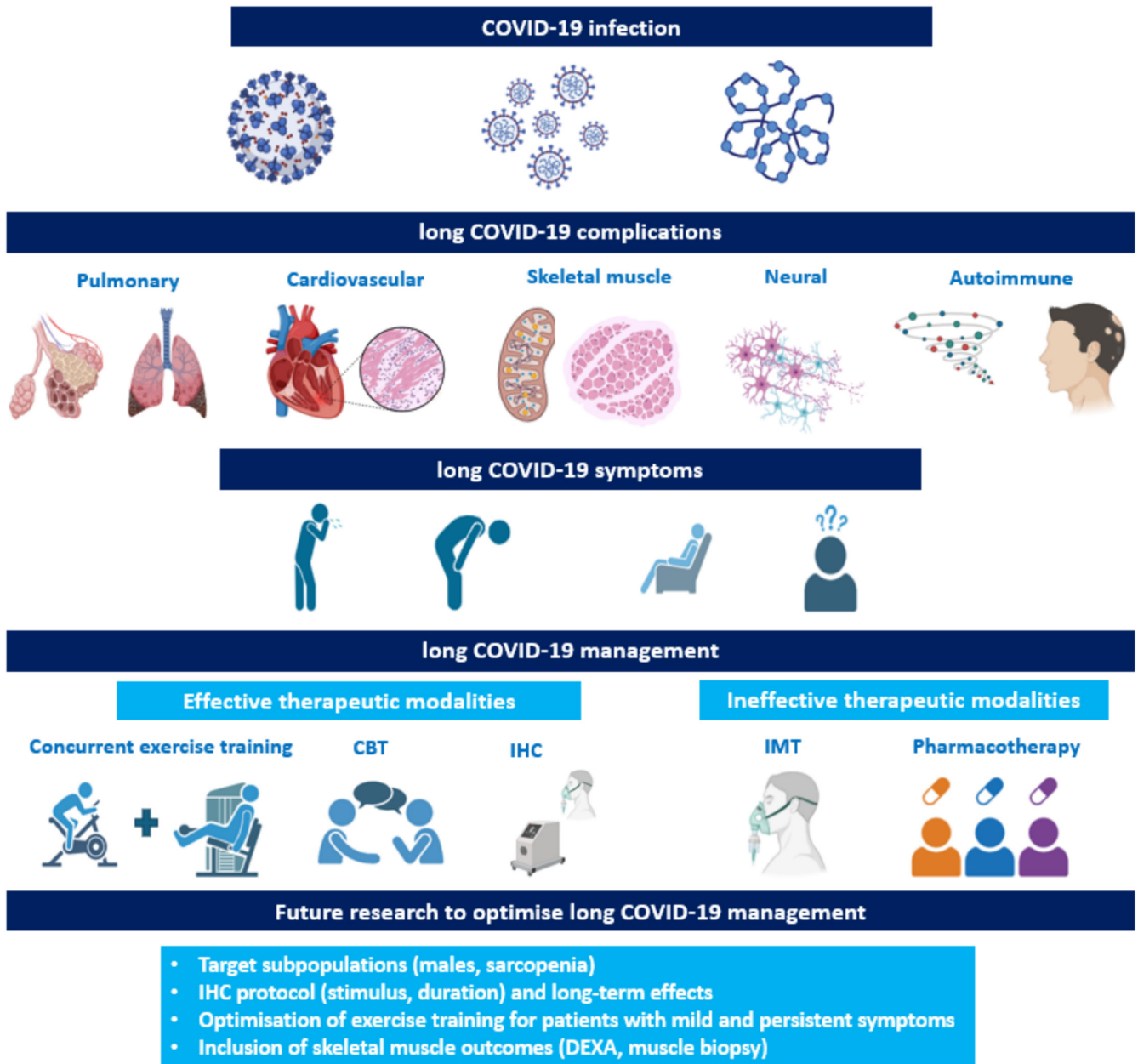


FIGURE 1 | Frontiers in management of long COVID-19. CBT, cognitive behavioural training; COVID-19, coronavirus-19; DEXA, dual-energy X-ray absorptiometry; IHC, intermittent hypoxic conditioning; IMT, inspiratory muscle training.

daily repeated bouts of breathing moderate hypoxia [$F_{I_{O_2}}$ usually 9–15% interspersed with intervals breathing ambient air) [14–16]. The application of IHC can provoke improvements in many physiological and functional systems (e.g., cardiopulmonary function, exercise performance, glucose metabolism and weight management) in both athletes and chronic disease patients [14–18]. In patients with cardiovascular disease, resting IHC reduced resting heart rate, systolic and diastolic blood pressure [17]. In addition, early studies from the Soviet Union also suggested potential improvements in myocardial function, blood pressure and sympathetic nervous system regulation [16].

As previous clinical studies in cardiometabolic patients [14, 16–18] suggested benefits of IHC for use in rehabilitation of patients with long COVID-19, Doehner et al. sought to determine whether such benefits can be translated to rehabilitation

of patients with long COVID-19 in a pilot trial recently published in the *Journal* [19]. The study included 145 overweight, middle-aged patients with long COVID-19 and coexisting arterial hypertension that were allocated to 5 weeks of either combination of IHC with extensive, multidisciplinary rehabilitation program (IHC + rehab, $n = 70$) or to extensive, multidisciplinary rehabilitation programme alone (rehab, $n = 75$). The IHC intervention was performed in three weekly sessions consisting of rather standardised six to eight intervals of 3–5 min of breathing a hypoxic air mixture (10%–12% of O_2) interspersed with 3–5 min of breathing a slightly hyperoxic air mixture (30%–35% of O_2). After 45 min of IHC, patients continued with multimodal rehabilitation consisting of *physical therapy* (inspiratory muscle training, electrotherapy, hydrotherapy, etc), *exercise training* (progressive aerobic, resistance, balance and coordination training), *occupational training* (cognitive and motor training

for improving activities of daily life) and *interdisciplinary educational counselling with psychosocial support* focused on improving self-management of long COVID-19 disease [19]. The primary study outcome was the change in (sub)maximal endurance (6-min walk test distance) along with integrative assessment of strength (hand grip strength, nine-hole peg test, timed up-and-go test and functional ambulatory capacity), pulmonary capacity, symptoms of dyspnoea, health-related quality of life, blood pressure and biomarkers of inflammation, glucose metabolism and kidney function [19]. The combination of IHC and multidisciplinary rehabilitation appeared safe, well-tolerated and showed a superior effect on improving 6-min walk test distance (+59 m), stair climbing time (−1.4 s), health-related quality of life (European Quality of Life Five Dimensions Questionnaire analogue scale: +28.4 points) and on long COVID-19 symptoms (Median COVID-19 Recovery Score: −10.2 points) compared with multidisciplinary rehabilitation alone.

While Doehner et al. [19] should be applauded for taking the first step in exploring the potential of IHC as added tool to standard, mainly exercise-based rehabilitation of patients with long COVID-19, there remain some important considerations for advancing our understanding and applicability of this approach. First, the study findings should be tested in future well-powered randomised, controlled trials, with special emphasis on the appropriate group allocation, which represents one of the limitations in the present study and might partially underscored primary outcome (6-min walk test). Future work should also aim to balance biological sex in the sample, as the present study enrolled mostly female patients likely due to higher prevalence of the syndrome compared to males [2, 3, 19]. Second, future studies should put special emphasis on improving prescription and progression of exercise training, particularly resistance training [20, 21], to counterbalance the cardiopulmonary and skeletal muscle impairments associated with long COVID-19 sequelae [7], which may accelerate sarcopenia in these patient group [2, 6]. Optimised resistance training should be complemented with the inclusion of advanced measurement of body composition (e.g., dual-energy X-ray absorptiometry) and skeletal muscle histology and metabolism (e.g., biopsies on *m. vastus lateralis*) to gain novel insights into the changes of muscle quality and quantity (Figure 1). Nevertheless, Doehner et al. [19] provide a strong foundation to optimise future exercise training interventions, as solely multidisciplinary rehabilitation approach demonstrated clinical meaningful improvements in 6-min walk test. Thirdly, the benefits of current somewhat standardised IHC protocol combined with pulmonary rehabilitation [13] can be enhanced with further IHC protocol adjustments (changes in hypoxia/hyperoxia ratio, extended exposure per set and within single session) [14], especially for long COVID-19 patient with severe exercise participation-limiting symptoms. Lastly, the benefits of combined IHC with standard pulmonary rehabilitation [13] should be tested in a longer intervention (8–12 weeks) with extended follow-up (≥ 1 year), to investigate whether IHC effects are maintained over longer period of time or whether long COVID-19 symptoms can present again [2].

The application of IHC, as suggested by Doehner et al. [19], should undoubtedly be considered in rehabilitation of patients with long COVID-19 syndrome and can be effectively combined within the current scheme of standard pulmonary rehabilitation

[13]. After extensive clinical assessment [13, 19], the IHC can be introduced in the early phases of long COVID-19 rehabilitation, preferably immediately after COVID-19 infection hospitalisation for patients with severe symptoms of breathlessness and exercise intolerance. Therefore, in early phases of rehabilitation (1–4 weeks), IHC can be added to inspiratory muscle training, low-to-moderate intensity continuous aerobic training (40%–60% of peak O_2 consumption, 45–60 min) and resistance training (3–5 sets of 15–20 repetitions at 40%–60% of maximal muscle strength), balance training and other cognitive and physical therapy interventions [11, 13]. In the later phases of long COVID-19 rehabilitation (5–12 weeks), the intensity of exercise training can be progressively increased (aerobic training: 60%–80% of peak O_2 consumption; resistance training: 70%–80% of muscle strength) [13, 21], while the use of IHC and balance training should be predominantly applied for patients with persistent moderate-to-severe symptoms of breathlessness, exercise intolerance and dizziness and vertigo, respectively. Such individualised approach may further optimise the intensive multidisciplinary rehabilitation of long COVID-19 and consequently help reduce the long-term burden of the syndrome [2, 3, 10, 21].

In summary, the future of multimodal long COVID-19 rehabilitation consisting of concurrent exercise training [21] and behavioural interventions [11] combined with effective IHC looks bright. Prospective work is nevertheless, warranted, to provide further insights into the question whether the short-term effects of IHC timely presented by Doehner et al. [19] can be maintained/enhanced by using a longer, individually tailored interventions for the most vulnerable patients' populations with persistent long COVID-19 syndromes (patients with pre-existing sarcopenia, after longer hospitalisation and/or with multiple metabolic and cardiopulmonary comorbidities).

Acknowledgements

T.K. is partially funded by Slovenian Research and Innovation Agency (programme no. P5-0147). M.L. is funded by the Slovenian Research and Innovation Agency (grant no.: P3-0456).

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Worldometers.info, “COVID-19 Pandemic Tracker,” 2024, <https://www.worldometers.info/coronavirus/>.
2. T. Greenhalgh, M. Sivan, A. Perlowski, and J. Ž. Nikolich, “Long COVID: A Clinical Update,” *Lancet* 404, no. 10453 (2024): 707–724.
3. M. Gyöngyösi, P. Alcaide, F. W. Asselbergs, et al., “Long COVID and the Cardiovascular System—Elucidating Causes and Cellular Mechanisms in Order to Develop Targeted Diagnostic and Therapeutic Strategies: A Joint Scientific Statement of the ESC Working Groups on Cellular Biology of the Heart and Myocardial,” *Cardiovascular Research* 119, no. 2 (2023): 336–356.
4. H. E. Davis, L. McCorkell, J. M. Vogel, and E. J. Topol, “Long COVID: Major Findings, Mechanisms and Recommendations,” *Nature Reviews. Microbiology* 21, no. 3 (2023): 133–146.
5. J. Benes, M. Jankowski, K. Szuldrzynski, et al., “SepsEast Registry Indicates High Mortality Associated With COVID-19 Caused Acute

- Respiratory Failure in Central-Eastern European Intensive Care Units,” *Scientific Reports* 12, no. 1 (2022): 14906.
6. A. M. Martone, M. Tosato, F. Ciciarello, et al., “Sarcopenia as Potential Biological Substrate of Long COVID-19 Syndrome: Prevalence, Clinical Features, and Risk Factors,” *Journal of Cachexia, Sarcopenia and Muscle* 13, no. 4 (2022): 1974–1982.
7. M. N. Soares, M. Eggelbusch, E. Naddaf, et al., “Skeletal Muscle Alterations in Patients With Acute Covid-19 and Post-Acute Sequelae of Covid-19,” *Journal of Cachexia, Sarcopenia and Muscle* 13, no. 1 (2022): 11–22.
8. C. Scheibenbogen and K. J. Wirth, “Key Pathophysiological Role of Skeletal Muscle Disturbance in Post COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Accumulated Evidence,” *Journal of Cachexia, Sarcopenia and Muscle* 16, no. 1 (2025): e13669.
9. L. Hiti, T. Markovič, M. Lainscak, J. F. Lainščak, E. Pal, and I. Mlinarič-Raščan, “The Immunopathogenesis of a Cytokine Storm: The Key Mechanisms Underlying Severe COVID-19,” *Cytokine & Growth Factor Reviews* (2025): 1–17, <https://doi.org/10.1016/j.cytogfr.2024.12.003>.
10. Collaborators GB of DLC, “Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021,” *Journal of the American Medical Association* 328, no. 16 (2022): 1604–1615.
11. D. Zeraatkar, M. Ling, S. Kirsh, et al., “Interventions for the Management of Long Covid (Post-Covid Condition): Living Systematic Review,” *BMJ* 387 (2024): e081318.
12. D. V. Pouliopoulou, J. C. Macdermid, E. Saunders, et al., “Rehabilitation Interventions for Physical Capacity and Quality of Life in Adults With Post–COVID-19 Condition: A Systematic Review and Meta-Analysis,” *JAMA Network Open* 6, no. 9 (2023): e2333838.
13. T. Troosters, W. Janssens, H. Demeyer, and R. A. Rabinovich, “Pulmonary Rehabilitation and Physical Interventions,” *European Respiratory Review* 32, no. 168 (2023): 220222.
14. J. Burtscher, T. Citherlet, A. Camacho-Cardenosa, et al., “Mechanisms Underlying the Health Benefits of Intermittent Hypoxia Conditioning,” *Journal of Physiology* 602, no. 21 (2023): 5757–5783.
15. G. P. Millet, T. Debevec, F. Brocherie, D. Malatesta, and O. Girard, “Therapeutic Use of Exercising in Hypoxia: Promises and Limitations,” *Frontiers in Physiology* 7 (2016): 224.
16. T. V. Serebrovskaya and L. Xi, “Intermittent Hypoxia Training as Non-Pharmacologic Therapy for Cardiovascular Diseases: Practical Analysis on Methods and Equipment,” *Experimental Biology and Medicine* 241, no. 15 (2016): 1708–1723.
17. G. S. Oleg, K. Y. Svetlana, Z. A. Maxim, D. N. Elena, S. G. Vlada, and S. Davide, “Safety and Efficacy of Intermittent Hypoxia Conditioning as a New Rehabilitation/Secondary Prevention Strategy for Patients With Cardiovascular Diseases: A Systematic Review and Meta-Analysis,” *Current Cardiology Reviews* 17, no. 6 (2021): 12–23.
18. C. C. L. Tee, M. B. Cooke, M. C. Chong, W. K. Yeo, and D. M. Camera, “Mechanisms for Combined Hypoxic Conditioning and Divergent Exercise Modes to Regulate Inflammation, Body Composition, Appetite, and Blood Glucose Homeostasis in Overweight and Obese Adults: A Narrative Review,” *Sports Medicine* 53, no. 2 (2023): 327–348.
19. W. Doehner, A. Fischer, B. Alimi, et al., “Intermittent Hypoxic–Hyperoxic Training During Inpatient Rehabilitation Improves Exercise Capacity and Functional Outcome in Patients With Long Covid: Results of a Controlled Clinical Pilot Trial,” *Journal of Cachexia, Sarcopenia and Muscle* 15, no. 6 (2024): 2781–2791.
20. T. Kambič, J. Farkaš, M. Lainscak, and M. Lainscak, “Comment on: “Effects of Resistance Training Intensity on Muscle Quantity/Quality in Middle-Aged and Older People: A Randomized Controlled Trial” by Otsuka et al.,” *Journal of Cachexia, Sarcopenia and Muscle* 13, no. 5 (2022): 2579–2580.
21. T. Kambic, V. Hadžić, and M. Lainscak, “Optimizing Cardiopulmonary Rehabilitation of Long COVID-19 Syndrome: Are We There Yet?,” *European Journal of Preventive Cardiology* 29, no. 8 (2022): e268–e269.