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Case Report

Effect of cardiopulmonary and metabolic rehabilitation in patients with exercise-induced oxyhemoglobin desaturation after hospital discharge from COVID-19: case series

Efeito da reabilitação cardiopulmonar e metabólica em pacientes que apresentaram dessaturação da oxihemoglobina induzida pelo exercício após alta hospitalar pela COVID-19: série de casos

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ABSTRACT | INTRODUCTION: Exercise-induced oxyhemoglobin desaturation in post-COVID-19 patients appears to be associated with reduced diffusion and lung volumes, greater dyspnea and low functional capacity, being related to higher mortality and worse prognosis. Cardiopulmonary and metabolic rehabilitation (CPMR) is relevant, as it aims to restore functionality, exercise tolerance and quality of life (QoL). **OBJECTIVE:** To verify the effects of CPMR in patients who presented exercise-induced oxyhemoglobin desaturation after hospital discharge due to COVID-19 and also to observe the difference between moderate-intensity continuous training (MICT) and high intensity interval training (HIIT) on effort tolerance, symptoms and QoL. **METHODS:** This is the report of a series of 4 cases who were hospitalized for COVID-19 and who, after hospital discharge, presented exertion-induced oxyhemoglobin desaturation during the 6-minute step test (6MST). Patients were assessed using spirometry at rest, measurement of inspiratory muscle strength, 6MST, 6-minute walk test (6MWT), quadriceps and biceps brachii maximum repetitions test, and answered the SF-36 QoL questionnaire. Submitted to a training protocol containing training of the inspiratory muscles and resistance training for large muscle groups, additionally, 2 patients underwent CMIT (with 60-80% of heart rate reserve) and 2 HIIT (with 40% of HR reserve in the off, for 4 minutes and 80 to 100%, in the on phase, for 2 minutes) on a treadmill for 30 minutes, finally, after 3 months, they were reassessed. **RESULTS:** There was an increase in effort tolerance, inspiratory and peripheral muscle strength, in addition to an improvement in QoL and a reduction in symptoms in all patients after CPMR, but there were greater increments in patients submitted to HIIT compared to CMIT in the distance covered in meters (case 1 - 156 (23% increment); case 3 - 168 (40%)) versus (case 2 and 4 - 60 meters, with increments of 9% and 14%, respectively) and greater number of steps (case 1 - 28 (23% increase); case 3- 37 (34%)) versus (case 2 – 2 (2% increment); case 4 - 15 (21%)). **CONCLUSION:** CPMR had positive effects, with an increase in functional capacity and improvement in QoL, in addition to a reduction in symptoms during exertion, particularly in patients undergoing HIIT.

KEYWORDS: COVID-19. Hypoxemia. Rehabilitation. Physical Exercise. Quality of Life. Physiotherapy.

RESUMO | INTRODUÇÃO: A dessaturação da oxihemoglobina induzida pelo exercício em pacientes pós-COVID-19 parece estar associada à redução da difusão e dos volumes pulmonares, à maior dispneia e baixa capacidade funcional, sendo relacionada à maior mortalidade e pior prognóstico. A reabilitação cardiopulmonar e metabólica (RCPM) é relevante, pois visa restaurar a funcionalidade, tolerância ao esforço e a qualidade de vida (QV). **OBJETIVO:** Verificar os efeitos da RCPM em pacientes que apresentaram dessaturação da oxihemoglobina induzida pelo exercício após alta hospitalar pela COVID-19 e ainda observar a diferença entre os treinamentos contínuo de moderada intensidade (TCMI) e o intervalado de alta intensidade (TIAI) na tolerância ao esforço, nos sintomas e na QV. **MÉTODOS:** Trata-se do relato de uma série de 4 casos que foram hospitalizados por COVID-19 e que após alta hospitalar apresentaram dessaturação da oxihemoglobina induzida pelo esforço durante o teste do degrau de 6 minutos (TD6). Os pacientes foram avaliados por meio de espirometria de repouso, mensuração da força da musculatura inspiratória, TD6, teste da caminhada de 6 minutos (TC6), teste de repetições máximas do quadríceps e bíceps braquial e responderam ao questionário SF-36 de QV. Submetidos a um protocolo de treinamento contendo treino da musculatura inspiratória e treino resistido para grandes grupos musculares, adicionalmente, 2 pacientes fizeram TCMI (com 60-80% da frequência cárdica de reserva (FCR)) e 2 TIAI (com 40% da FCR na fase *off*, durante 4 minutos e 80 a 100%, na fase *on*, durante 2 minutos) em esteira por 30 minutos e, por fim, após 3 meses foram reavaliados. **RESULTADOS:** Observou-se aumento da tolerância ao esforço, da força muscular inspiratória e periférica, além da melhora da QV e redução dos sintomas em todos os pacientes após a RCPM, porém houve incrementos maiores nos pacientes submetidos ao TIAI comparados ao TCMI na distância percorrida em metros (caso 1- 156 (23% de incremento); caso 3 - 168 (40%)) versus (caso 2 e 4 - 60 metros, com incrementos de 9% e 14%, respectivamente) e maior número de degraus (caso 1- 28 (23% de aumento); caso 3- 37 (34%)) versus (caso 2 – 2 (2% incremento); caso 4 - 15 (21%)). **CONCLUSÃO:** A RCPM apresentou efeitos positivos, com incremento da capacidade funcional e melhora da QV, além da redução dos sintomas durante o esforço, particularmente nos pacientes submetidos ao TIAI.

PALAVRAS-CHAVE: COVID-19. Hipoxemia. Reabilitação. Exercício Físico. Qualidade de Vida. Fisioterapia.

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Introduction

The decline in functional capacity and tolerance for exertion are frequent conditions in patients after the acute phase of the 2019 coronavirus disease (COVID-19) until the long term, especially in those patients who were hospitalized and who evolved with changes in lung function.[1] The outcomes in lung function after COVID-19 are still unclear, but some data suggest a reduction in diffusion and lung volumes associated with greater dyspnea and oxyhemoglobin desaturation resulting in worsening of functional capacity, being more expressive the higher the disease severity.[2-3]

Exercise-induced oxyhemoglobin desaturation is a frequent complication in patients with chronic lung diseases, especially interstitial diseases with restricted lung volumes and low lung diffusion capacity, being a fact associated with higher mortality and worse prognosis and is considered a drop in saturation peripheral oxygen (SpO2) when the difference between peak exertion and rest is ≥ 4%.[4] The drop in SpO2 during exercise in post-COVID-19 patients may be due to ventilation/perfusion disorders such as increased ventilation wasted in dead space, causing ventilatory inefficiency and consequently greater dyspnea on exertion or in response to low physical conditioning.[5-6] In this way, cardiopulmonary and metabolic rehabilitation (CPMR) with an emphasis on physical exercises is of paramount importance to restore the functionality, tolerance to effort and quality of life (QoL) of post-COVID-19 patients.[6-7]

The benefits, precautions, as well as the criteria for prescribing exercise in CPMR in post-COVID-19 conditions, especially for patients with exercise-induced oxyhemoglobin desaturation, are not yet well established in the literature.[5-6]

Therefore, the objective of this case series was to elucidate the effect of CPMR in patients who presented exercise-induced oxyhemoglobin desaturation after hospital discharge due to COVID-19. Additionally, we sought to verify the difference between continuous moderate intensity training (CMIT) and high-intensity interval training (HIIT) in effort tolerance, symptoms and QoL.

Case descriptions

This case series reports the CPMR of four patients who were hospitalized for COVID-19 and after hospital discharge had exercise-induced oxyhemoglobin desaturation during the 6-minute step test (6MST), characterized by a ≥ 4% drop in SpO2 at the end of the test.[4]

The study was approved by the Ethics and Research in Human Beings Committee of the Escola Paulista de Ciências Médicas, with CAAE 58060122.2.0000.9887. And then the patients signed the Informed Consent Form.

Patient data

Case 1

Male, 58 years old, with systemic arterial hypertension (SAH), diabetes mellitus (DM), obesity, former smoker, and using Januvia and Irbesartan Hidrochlorothiazide. He was admitted to the intensive care unit (ICU) due to cough, fatigue, myalgia, fever, tachypnea and drop in SpO2 associated with mild hypoxemia and involvement of 50% of the lung parenchyma seen on chest computed tomography (CT). Non-invasive ventilation (NIV) was performed with an inspired fraction of oxygen (FIO2) of 50-55% for 1 hour, 2 to 3 periods a day, and a nasal cannula (NC) of 2 to 4 L/minute of O2 was also used. He remained in the ICU for 7 days and was discharged on the ninth day.

Case 2

Male, 60 years old, with SAH, dyslipidemia (DLP), obesity and using Enalapril and Rosuvastatin. He was admitted to the inpatient unit (IU) due to cough, fever, low SpO2, dyspnea at rest, and a ground-glass pattern in more than 50% of the lung parenchyma on CT. It was necessary to use a mask with a reservoir (MR) at 10 L/minute, he used NIV for periods (2-4 hours daily), however, he always maintained mild hypoxemia. After 2 days, there was a worsening of the ventilatory pattern, and he was transferred to the ICU, requiring orotracheal intubation (OTI),

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vasoactive drugs, evolving with septic shock with a pulmonary focus and pulmonary thromboembolism (PTE). He remained intubated for 7 days and was extubated successfully, after 16 days in the ICU he was discharged to the IU, where he stayed for another 49 days due to his evolution with renal lithiasis and the need for ureterolithiasis with the placement of a double J, urinary focus sepsis and difficult O2 weaning. Totaled 68 days of hospitalization until discharge from hospital.

Case 3

Woman, 56 years old, with SAH, DM, peripheral vascular insufficiency and using Gliclazide, Janumet, Amlodipine and Hydrochlorothiazide. She was hospitalized in the ICU for symptoms of dyspnea and fatigue associated with vomiting, tachypnea, borderline SpO2 with mild hypoxemia, even using 15 L/minute of RM, and had a chest CT showing 50% involvement of the lung parenchyma. She remained in the ICU for 8 days, where spontaneous prone position and O2 weaning were performed, and then she was transferred to the ICU, remaining for another 4 days until hospital discharge.

Case 4

Woman, 51 years old, with hypothyroidism, ankylosing spondylitis, DLP, obesity, anxiety and taking Pregabalin, Puran, Naproxen, Pantoprazole, Pitavastatin and Venlafaxine. She presented symptoms of anosmia, myalgia, headache, malaise, cough and after 5 days she was hospitalized in the IU due to dyspnea, drop in SpO2, chest CT showing 50-75% involvement of the lung parenchyma, requiring the use of high concentrations of O2 and use of NIV for periods (1-3 hours a day). After 5 days, she progressed with a significant worsening of the ventilatory pattern and was transferred to the ICU with an indication for OTI. During the OTI period, he presented: difficult-to-control refractory hypoxemia associated with 2 cycles of pronation; PTE; septic shock with a pulmonary focus and prolonged weaning with the need for a tracheostomy. He remained in the ICU for 22 days and was discharged to the IU, where he was weaned and the tracheostomy decannulated. After 41 days of hospitalization, the patient was discharged.

All patients underwent physiotherapy (respiratory and motor) during the entire hospitalization and after discharge were referred to the physiotherapy outpatient clinic due to functional limitations.

Assessment and intervention

The initial assessment took place between 15 and a maximum of 20 days after hospital discharge, according to medical guidance and the Brazilian Cardiology Guideline.[8]

In the evaluation, the patients were submitted to: 1) anamnesis and collection of anthropometric data; 2) application of the SF-36 QoL questionnaire; 3) spirometry at rest using the *MiniSPIR equipment, Mir Medical International Research, Italy*, following the procedures of the *Brazilian Society of Pneumology and Phthisiology*[9]; 4) assessment of the strength of the inspiratory muscles, by obtaining the maximum inspiratory pressure (MIP), with the *PowerBreathe Medic KH2* according to the *American and European Thoracic Society*[10]; 5) 6SWT, in which the patients went up and down a 20 cm high and 50 cm long step for 6 minutes, and their heart rate (HR) and SpO2 were monitored with a portable *Alfamed* oximeter, at the end of which subjective effort scale (BORG) was applied to check for dyspnea and lower limb (LL) fatigue[11]; 6) 6-minute walk test (6MWT) taking into account the guidelines for such a test[12] and the test of maximum repetitions of the quadriceps and biceps brachii of the non-dominant limb to determine 1 maximum repetition (1MR).[13]

Subsequently, they underwent a physical training protocol for 3 months with the use of supplemental oxygen (O2) through a NC (whenever necessary) and were divided into 2 types of training on a treadmill, CMIT or HIIT as shown in table 1. Cases 2 and 4 underwent the CTMI and cases 1 and 3 the HIIT. At the end of the protocol, they were reassessed using the same initial criteria. The predicted values for the 6MST, 6MWT and MIP took into account the values for the Brazilian population.[14-16]

Data are presented in number, percentage of predicted, difference between assessment and reassessment, and percentage increment (difference between assessment and reassessment/ reassessment X 100).

Table 1. Cardiopulmonary and metabolic rehabilitation training protocol

Procedure	**Protocol**	
Inspiratory muscle training	With *PowerBreathe Medic Plus*	
Load	50% of MIP[17]	
Volume	2 times per week 2 sets of 30 breaths	
Aerobic training	On a treadmill with O_2 supplementation for an $SpO_2 \geqq 93\%$.	
Load	**CMIT** 60 to 80% of reserve HR (*Karvonen*)[18]	**HIIT** 40% of HR reserve in the *off* phase, for 4 minutes and 80 to 100%, in the *on* phase, for 2 minutes, totaling four cycles[19]
Volume	2 times a week for 30 minutes	
Resistance training	With shin guards, dumbbells and weight machines	
Load	60 to 80% of 1 maximum repetition	
Volume	2 times per week 2 sets of 12 repetitions	

Source: The authors (2023).

Results

All four patients shown in this case series had some similar baseline characteristics, namely: a) they were admitted to the ICU for more than 7 days with pulmonary involvement on chest CT of 50% or more; b) used high concentrations of O2 (>7L/min or FIO2 >50%); c) were over 50 years of age; d) reduced inspiratory capacity (IC) and slow vital capacity (SVC); e) 6MWT footage and 6MST step number <80% of predicted; f) oxyhemoglobin desaturation during 6MST and h) low QoL scores. In addition, 3 were obese; 2 were diabetic and hypertensive and only one case had a reduced peak (Table 2).

In the assessment of exercise tolerance, patients who underwent HIIT showed greater gain in distance covered in meters (case 1 - 156 (23% increment); case 3 - 168 (40%)) versus (case 2 and 4 - 60, with increments of 9% and 14%, respectively) and greater number of steps (case 1- 28 (23% increase); case 3- 37 (34%)) versus (case 2 – 2 (2% increment); case 4 - 15 (21%)), as shown in Figure 1.

With regard to respiratory and peripheral muscle strength, the CMIT patients showed more expressive increments. The MIP increased by 19% and 34% in the CMIT versus 17% and 13% in the CMIT, as shown in table 2. In the 1 MR, cases 1 and 3 (CTMI) achieved greater gains, both in the upper and lower limbs compared to the cases 2 and 4 (CMIT), 33% and 43% versus 33% and 0%, 51% versus 52% X 41% and 0%, respectively, such data are shown in Figure 2.

Supplementary O2 during exercise was withdrawn over approximately 8 CPMR sessions in 3 patients, only case 2 used it for 12 sessions.

Cases 1, 3 and 4 did not present oxyhemoglobin desaturation during the 6MST in the reassessment, only case 2 continued with oxyhemoglobin desaturation. It can be seen that this patient's lung capacities remained at values below 80% (Table 2).

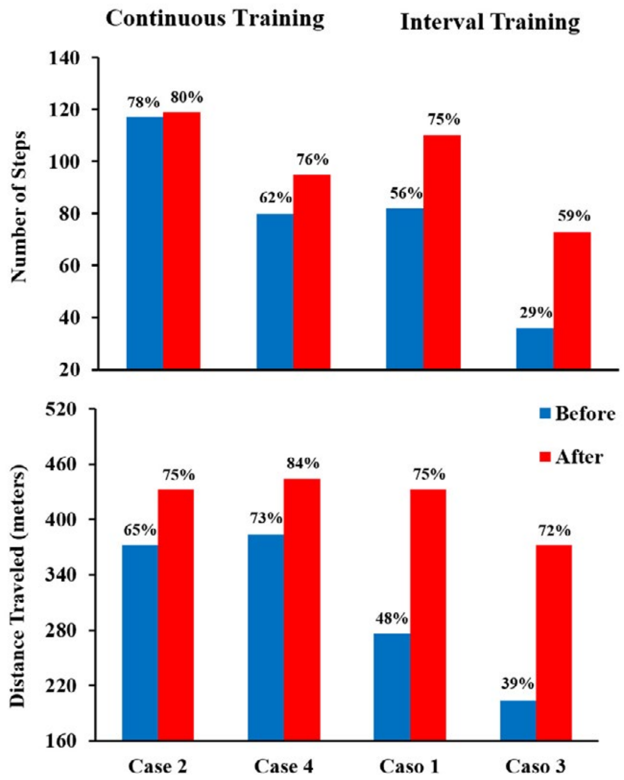
In table 2 we can see that there were gains in lung volumes and capacities and absence of oxyhemoglobin desaturation at the end of 6MST (in 3 cases, except case 2). The QoL assessed by the SF-36 questionnaire improved and the symptom of dyspnea at the peak of 6SWT was lower in all patients, however LL fatigue was reduced in 2 cases, 2 and 3 (Figure 4).

Table 2. Data before and after the cardiopulmonary and metabolic rehabilitation program in four post-COVID 19 patients

	Case 1		**Case 2**		**Case 3**		**Case 4**	
	Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Inspiratory muscle function								
Maximum inspiratory pressure, cmH_2O (% predicted)	103 (83)	127 (103)	112 (100)	135 (120)	44 (53)	67 (81)	87 (102)	100 (117)
Rest Spirometry								
FVC, L (% predicted)	3,08 (67)	4,21 (93)	2,41 (53)	3,18 (72)	1,65 (55)	2,37 (81)	2,55 (82)	2,80 (90)
FEV_1, L (% predicted)	3,06 (119)	3,60 (143)	2,08 (58)	2,81 (114)	1,53 (66)	2,07 (87)	2,26 (89)	2,45 (96)
FEV_1/ FVC, %	99,4	85,5	86,3	88,4	92,3	87,3	88,6	87,5
$FEF_{25-75\%}$, L (% predicted)	5,16 (165)	4,78 (155)	2,43 (80)	3,70 (121)	1,78 (79)	2,73 (121)	3,05 (126)	3,81 (158)
SVC, L (% predicted)	2,94 (64)	5,28 (115)	2,20 (48)	2,99 (68)	1,30 (45)	2,34 (80)	2,13 (68)	2,68 (86)
IC, L (% predicted)	1,61 (47)	3,22 (94)	0,97 (30)	1,79 (55)	0,58 (27)	0,99 (47)	1,41 (65)	1,70 (78)
6 minute walk test								
Δ Travelled distance $_{(before-after)}$	156		60		168		60	
6 minute step test								
HR_{pico} (%of the maximum)	105 (65)	129 (80)	157 (98)	141 (88)	134 (82)	116 (71)	143 (85)	149 (88)
SpO_{2peak}	87	98	87	90	91	100	91	95
Δ $SpO_{2(peak-rest)}$	11	0	10	8	5	0	7	2
Δ Number of steps $_{(before-after)}$	28		2		37		15	

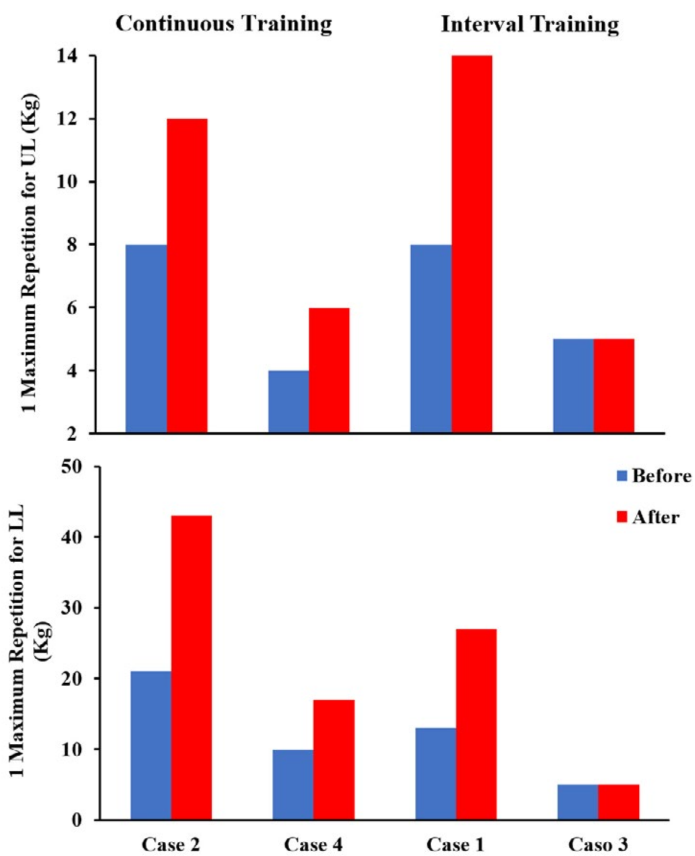
FVC: forced vital capacity; FEV1: forced volume in one second; FEF25-75%: forced expiratory flow between 25-75% of forced vital capacity; SVC: slow vital capacity; CI: inspiratory capacity and SpO2: oxygen pulse saturation.
Source: The authors (2023).

Figure 1. Step and 6-minute walk test before and after cardiopulmonary and metabolic rehabilitationprotocol.



Source: The authors (2023).

Figure 2. 1 maximum repetition test for upper and lower limbs before and after cardiopulmonary and metabolic rehabilitation protocol



Source: The authors (2023).

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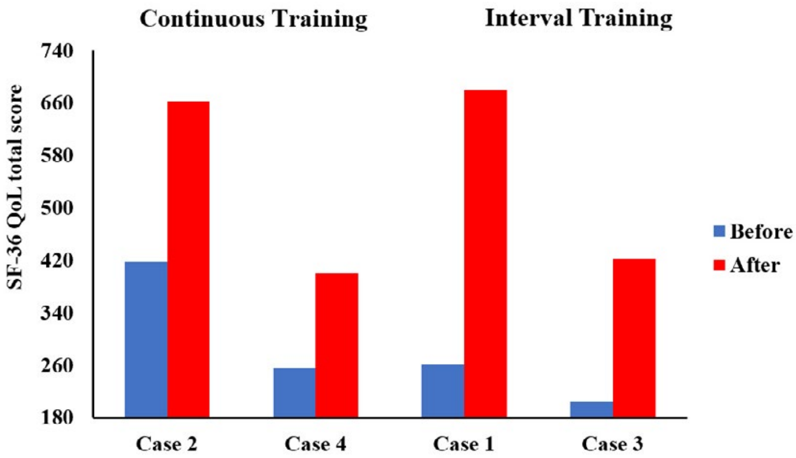
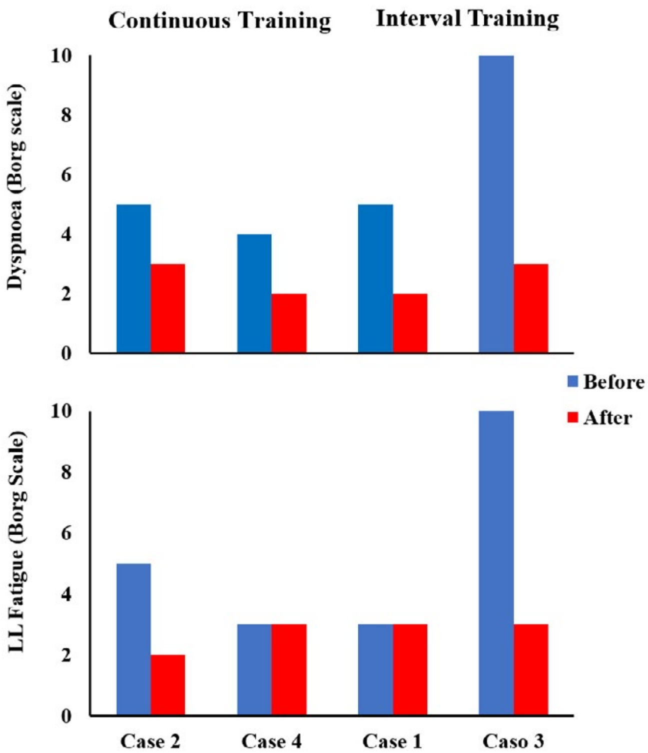
Figure 3. Total score of the SF-36 quality of life questionnaire before and after cardiopulmonary and metabolic rehabilitation protocol



Source: The authors (2023).

Figure 4. Sensory responses at the end of the 6-minute step test before and after cardiopulmonary and metabolic rehabilitation protocol



Source: The authors (2023).

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Discussion

This series of cases with 4 patients after hospital discharge due to COVID-19 who presented oxyhemoglobin desaturation during exertion showed that 3 months of CPMR resulted in considerable functional gains, with increased tolerance to exertion, functional capacity, peripheral muscle strength and inspiration, associated with lower symptoms of dyspnea and lower limb fatigue during exercise and better QoL, particularly in those submitted to HIIT. In addition, there was no oxyhemoglobin desaturation during 6MST and normalization of lung function at reassessment in 3 out of 4 cases.

The long-term consequences of changes in lung function and functional capacity in post-COVID-19 patients are still poorly established, but some studies have shown that at least 50% of patients who progressed to severe infection had a reduction in lung functionality and effort capacity.[2,20-21]

These complications are probably caused by the exacerbated inflammatory response associated with a pro-inflammatory "cytokine storm" and other factors such as the use of high concentrations of O2, prolonged mechanical ventilation, and these reasons lead to damage to various organs such as the lungs, heart, brain, kidneys, blood vessels, liver, muscles, nerves, among others.[22]

O2 is the most used therapy in patients hospitalized with COVID-19. In the most severe cases, there may be a need to use high concentrations and prolonged administration time. Hyperoxia is essential to maintain adequate oxygenation in the short term, however there may be long-term adverse consequences on the lung parenchyma, such as changes in immunological, metabolic, hemodynamic responses and in the function of the alveolar-capillary barrier, which consequently lead to remodeling and pulmonary fibrosis. Significant exposure to hyperoxia in patients with COVID-19 may be unavoidable to preserve life, therefore these sequelae superimposed on the cytopathic effects of the SARS-CoV-2 virus negatively impact the pathogenesis of COVID-19-induced lung injury.[23]

All patients in this case series used high concentrations of O2 (>7L/min or FIO2 >50%), 3 underwent NIV, and 2 failed NIV and required OTI. Another severity factor for COVID-19 is obesity and in this series of cases, 3 out of 4 patients were obese and all evolved into a severe case and consequent greater functional limitation after hospital discharge.[1]

The desaturation of oxyhemoglobin during exertion in the post-COVID-19 period seems to be associated with impairment of lung function, such as, for example, pulmonary fibrosis and reduced diffusion capacity[3,20], such changes cause ventilation/perfusion disorders such as increase in wasted ventilation in dead space, leading to ventilatory inefficiency[5], therefore the early identification of this patient profile can help in the indication of CPMR and supplemental use of O2 during exercise[20], making physical therapy more tolerant and safe, since hypoxemia leads to considerable organic damage and is associated with higher mortality and worse prognosis.[4]

The drop in SpO2 during exercise, presented in the 4 patients evaluated in this case series, has a negative effect on the effort tolerance resulting in a reduction in exercise capacity and physical deconditioning.[20] It is noteworthy that all our patients had a performance ≤ 80% of the predicted performance in the 6MST and 6MWT in the before CPMR.

Low exercise capacity and greater physical deconditioning in the post-COVID-19 period are probably not only related to direct pulmonary, cardiac and muscular changes, but also to autonomic and endothelial dysfunction due to exaggerated infection and autoimmune mechanisms that affect neurons and the endothelium. These dysfunctions lead to ventilatory inefficiency, tachypneic pattern, peripheral vasomotor tonus disorder that explain impaired O2 supply/extraction, in addition to cardiac preload failure and postural tachycardia. Additionally changes in metabolism and lactate production are also present.[24]

In view of the above, CPMR programs with an emphasis on physical exercises are essential in the functional recovery process of post-COVID-19 patients. So far, there is evidence suggesting that individualized and comprehensive training should be prescribed according to the physical condition, limitations and symptomatology of each patient. Factors such as intensity and duration of effort are necessary determinants for the physiological adaptations of training and the greater the intensity, the greater the physiological benefits.[7]

Comparing training in this case series, HIIT generated greater gains compared to CMIT, which corroborates Turri-Silva et al.[25] who found a superior effect of high-intensity training, compared to lower-intensity training, on cardiorespiratory conditioning, muscle strength and physical performance in patients with heart failure. In post-COVID-19 patients, HIIT may generate better physiological gains by preventing high lactate accumulation and allowing more intense exercise stimuli for peripheral muscles with less cardiac work and less exercise-induced hyperventilation.[7]

Case 2, who underwent CMIT, was the only patient who continued with oxyhemoglobin desaturation in 6MST after 3 months of CPMR, it is worth noting that he had the longest hospital stay (68 days), difficult O2 weaning and values below 80% of predicted forced vital capacity (FVC), SVC and IC at reassessment.

Finally, CPMR is a fundamental intervention for the management of patients with chronic cardiopulmonary diseases who present severe and persistent symptoms of exertion intolerance.[7] This fact is substantiated by the evidence that points to improvements in exercise capacity and functional capacity, moreover, in recent years there has been strong evidence that CPMR results in a reduction in the number of exacerbations/decompensations, and consequently in hospitalizations.[26]

This study has some limitations. The carbon monoacid diffusion capacity was not measured, an exam that could prove the association between low diffusion and oxyhemoglobin desaturation during exertion, in addition, the cardiopulmonary exercise test, which is the gold standard for assessing the limiting factors of exertion and for better prescription of aerobic training, were not performed. Finally, as this is a series of cases, there is low representativeness and possibility of generalization of the data, therefore, randomized clinical studies are necessary to elucidate the effects and benefits of RCPM, as well as what is the best or most indicated type of training for patients after the acute phase of COVID-19.

Conclusion

CPMR promoted important functional gains with an increase in functional capacity and improvement in QoL, in addition to the reduction of symptoms during exertion. Additionally, there were greater benefits in patients undergoing HIIT.

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Author contributions

Souza AS planned, conducted the evaluations, analyzed the data and wrote the manuscript. Macedo JB collected the data and participated in the study planning. Pinto TF analyzed the data and revised the manuscript. Gonzaga LRA conducted the assessments and analyzed the data. Pereira MAN participated in the planning of the study and revised the manuscript. Bittencourt MI designed the study and revised the manuscript. All authors had full access to the study data and supported the publication, as well as read the final version of this manuscript and agreed to be submitted to this journal for possible publication.

Conflicts of interest

No financial, legal or political interest in competing with any third party (government, commercial, private foundation, etc.) was disclosed for any aspect of the submitted work (including, but not limited to, donations, data monitoring advice, study design, manuscript preparation, statistical analysis, etc.)

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