Effects of Moderate-Intensity Training Under Cyclic Hypoxia on Cardiorespiratory Fitness and Hematological Parameters in People Recovered From COVID-19: The AEROBICOVID Study

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Background: Recent studies have indicated that people who live at altitude have a lower incidence of coronavirus disease (COVID-19) and lesser severity in infection cases.

Hypothesis: Hypoxia exposure could lead to health benefits, and it could be used in the recovery process as an additional stimulus to physical training to improve cardiorespiratory fitness (CRF).

Study Design: Randomized controlled clinical trial.

Level of Evidence: Level 2.

Methods: The 43 participants, aged 30 to 69 years, were divided into control group (CG, n = 18) and 2 training groups: normoxia (NG, n = 9) and hypoxia (HG, n = 16). Before and after the intervention were evaluated the lactate threshold 2 (L2), peak oxygen uptake (VO_{2peak}), and a blood sample was collected at rest to evaluate hematological adaptation. Both groups performed an 8-week moderate-intensity physical training on a bike. The HG were trained under normobaric hypoxic conditions (fractional inspired oxygen [FiO_2] = 13.5%).

Results: The 8-week intervention promoted a similar improvement in CRF of people recovered from COVID-19 in the HG (L2 = 34.6%; VO_{2peak} = 16.3%; VO_{2peak} intensity = 24.6%) and NG (L2 = 42.6%; VO_{2peak} = 16.7%; VO_{2peak} intensity = 36.9%). Only the HG presented differences in hematological variables (erythropoietin = 191.7%; reticulocytes = -32.4%; off-score = 28.2%) in comparison with the baseline.

Conclusion: The results of the present study provide evidence that moderate-intensity training in normoxia or hypoxia promoted similar benefits in CRF of people recovered from COVID-19. Furthermore, the hypoxia offered an additional stimulus to training promoting erythropoietin increase and hematological stimulation.

Clinical Relevance: The present exercise protocol can be used for the rehabilitation of people recovered from COVID-19, with persistent low CRF. In addition, this is the first study demonstrating that physical training combined with hypoxia, as well as improving CRF, promotes greater hematological stimulation in people recovered from COVID-19.

Keywords: altitude; erythropoietin; aerobic power; aerobic capacity; coronavirus

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In March 2020, the World Health Organization classified the coronavirus disease (COVID-19) caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2) as a pandemic.[52] News related to COVID-19 is commented on in daily media and has great concern and impact on Global Public Health.[23] The COVID-19 pandemic is an unprecedented health emergency of our era, causing mortality and disease worldwide. The clinical condition is diverse, ranging from asymptomatic infection to acute respiratory syndrome and damage to various body systems, increasing inflammatory markers, cardiovascular disorders, lung injuries, and kidney damage.[23]

However, a new demand arises in the post-COVID context because some symptoms can last and limit people recovered from COVID-19. After recovery, it is possible to identify people with alterations in cardiovascular and pulmonary systems, in addition to the hematological parameters.[5,23,28] Pulmonary injuries and cardiovascular disorders that impair cardiorespiratory fitness (CRF) have been described predominantly for hospitalized people with COVID-19 but also in asymptomatically infected individuals.[2] The persistent symptoms related to this context are associated with a measurable functional deficit in physical fitness, highlighting the reduced CRF.[14,27]

Clavario et al[12] determined the functional capacity of COVID-19 survivors in addition to the safety and tolerability of using cardiopulmonary exercise testing (CPET) in 225 patients with confirmation of COVID-19 3 months after hospital discharge. It was verified that 88% of the patients had peak oxygen consumption (VO_{2peak}) below the predicted. The authors highlighted that 80% of patients experienced at least 1 disabling symptom, an unrelated decrease of VO_{2peak} and functional capacity. They concluded that approximately 33% of COVID-19 survivors have functional limitations 3 months after discharge, associated with muscle impairment.

Recent studies indicate that people who live at high altitudes (above 3000 m) have a lower incidence of COVID-19 and less severity in cases of infection.[1,3,11,30,32,48] In addition, Brazilian cities with high altitude and low relative humidity have a reduced relative incidence and mortality rate of COVID-19.[21] The factors involved in this lower susceptibility to COVID-19 are related to physiological and anatomical adaptations in the lungs, improving perfusion and capacity. Furthermore, the increase in erythropoietin (EPO) concentrations generates a cytoprotective effect with a broad function that reduces inflammatory conditions and microvascular lesions.[1] In addition, recent studies have demonstrated the possibility of using EPO as an auxiliary approach in treating COVID-19.[16,35,46,53]

On the other hand, moderate-intensity interval exercise itself can reduce chronic inflammation and strengthen the immune system,[8,42,51,59] reducing the severity and mortality of viral diseases.[34] In addition, higher levels of CRF can produce short-term improvements in the immune and respiratory systems,[40] both affected by COVID-19.[61] Training methods using hypoxia as an ergogenic resource (cyclic hypoxia) have existed since the 1960s.[17,18,25,44,50] The most recent studies have determined that this type of intervention can present favorable results in health parameters and that the physical training associated with the normobaric hypoxia condition is safe and can be performed with different populations, for example, in the reduction of the fat mass with a concomitant increase of lean mass,[10] and increased CRF.[9]

Thus, we speculated that an interval training program of moderate-intensity performed in cyclic normobaric hypoxia could be an efficient proposal in rehabilitating people recovered from COVID-19 to improve their damaged CRF and increase the hematological stimulation. For this, we aimed to study the effects of 8 weeks of moderate-intensity cyclic hypoxic training on the cardiorespiratory capacity and hematological responses of people recovered from COVID-19.

METHODS

Ethical Review

This study was approved by an institutional review board. All participants gave written informed consent.

Participants

Sixty-nine participants were recruited, of which 43 completed all assessments and were therefore included in the study according to the following inclusion criteria: men and women aged between 30 and 69 years, approximately 30 days since the recovery of clinical signs or medical discharge (in case of hospitalization); and having previous experience in aerobic exercise. The exclusion criteria were as follows: exposure to an altitude higher than 1500 m in the last 3 months; significant physical limitations to carry out the evaluations and intervention; acute or chronic clinical illnesses without medical supervision; anemias; use of immunosuppressive drugs; pregnant women; hormone replacement; smokers; and excessive use of alcohol or drugs. In addition, an evaluation of the health status was carried out. The participants who did not present limitations or discomfort that could prevent the performance of the evaluations or the intervention were enrolled in the proposed intervention.

Experimental Design

The study design is a randomized controlled clinical trial composed of 3 groups: the control group (CG, n = 18), participants who were not available to join the intervention and accepted to carry out a follow-up through the evaluations; and the physical training groups, which were randomly divided according to the association of training with hypoxia (HG, n = 16) or normoxia (NG, n = 9).

The experimental protocol of the AEROBICOVID study (Figure 1) consisted of (1) familiarization and carrying out the initial evaluation (baseline [BSLN]) in the 3 sessions of week 0, with CPET on a bike and blood collection, (2) an 8-week intervention with a partial evaluation developing a CPET to adjust the training load between weeks 4 and 5 (half of the intervention), (3) reevaluation at week 9 with the same

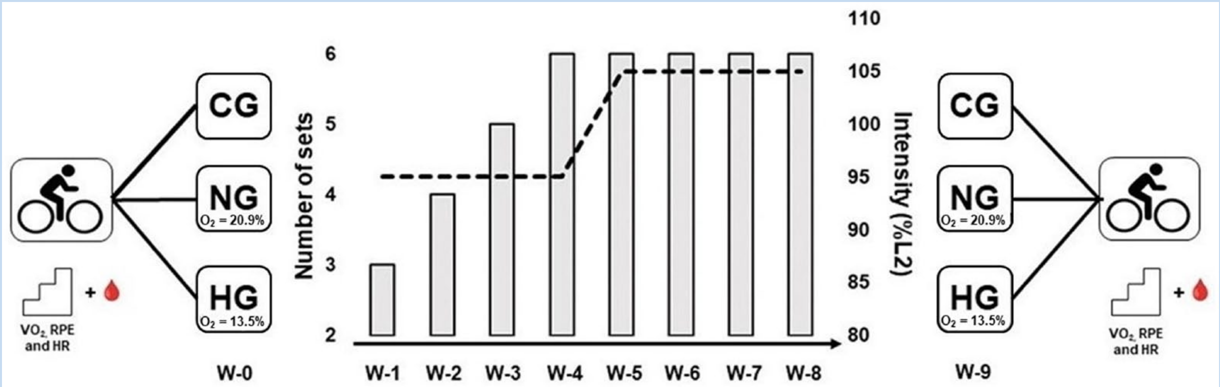

Figure 1. Experimental design illustration. Blood drop, blood collection; CG, control group; HG, hypoxia group; HR, heart rate; NG, normoxia group; RPE, rate of perceived exertion; VO_2, oxygen uptake; W, week.

evaluations of week 0, following the end of the intervention (post), all biological concerns were described elsewhere.[56]

Assessments

Anthropometric Variables

Body mass and height were measured by a 200 kg capacity electronic weighing scale (Mic-Pp, Micheletti), enabling calculation of the body mass index (BMI) using the equation body mass/height^2.

Questionnaires

As control variables, the International Physical Activity Questionnaire (IPAQ) short version, validated in Brazil[37] measured the usual level of physical activity. In addition, the Food Consumption Markers Form of the Ministry of Health[39] was used to assess the frequency of food consumption. Participants were instructed to maintain similar physical activity and eating habits during the study.

Hematological Parameters

Blood collection was performed by peripheral venous access after 8 hours overnight fasting, carried out by a trained and specialized professional. The hemogram parameters, such as total red blood cell count, hematocrit, and hemoglobin concentration, were evaluated at the Clinical Analysis Laboratory, Faculty of Pharmaceutical Sciences of Ribeirão Preto according to the technical service's standard routine and methodology. The hematologic stimulation index (off-score) was obtained from hemoglobin (Hb in g/L) and reticulocytes (Ret %): off-score = Hb (in g/L) $60\sqrt{\text{Ret}(\%)}$.[26,47] The EPO plasma concentration was determined by immunoassay according to the fabricant (EPO ELISA Kit R&D Systems).

Peak Aerobic Power (VO_{2peak})

A CPET was used to estimate lactate thresholds 1 (L1) and 2 (L2), VO_{2peak} and iVO_{2peak}. The CPET was performed in a pendular cycle ergometer with mechanical braking (Ergométrica, Monark). First, the participants started a 5 minute warm-up without any additional load; after that, the intensity was increased by 15 watts every 2 min until the participant did not maintain the 60 rpm cadence or volitional exhaustio

Oxygen uptake was measured breath by breath by the gas analyzer (K4b2, COSMED), calibrated according to the manufacturer's specifications. The VO_{2peak} was defined as the highest VO_2 average in the last 60 seconds in the test. The iVO_{2peak} was the lowest intensity at which the individual reached VO_{2peak} during the test. If the participant did not complete the last stage of the incremental test, the iVO_{2peak} is estimated by the equation proposed by Kuipers et al.[33]

Blood samples (25 µL) were collected from the earlobe at the end of each stage, using previously calibrated heparinized capillaries. Blood samples were immediately dispensed and homogenized in microtubes containing 1% sodium fluoride for blood lactate concentration [La] analysis using the YSI 2300 STAT analyzer (YSI, Yellow Springs, OH). The bisegmented method was used, in which the points obtained between [La] and the intensities were subjected to 3 linear adjustments so that the 2 intersections obtained will be assumed as L1 and L2 intensities.[41] Concomitantly, heart rate (HR) and rate of perceived exertion (RPE) were monitored at the end of each stage.

Intervention

Hypoxia Instrumentation

A unidirectional mask (Air Safety) was connected to a 3 m long flexible hose (IVPU, vacuum air PU 1.1/2 cm), and the opposite end was connected to a tent (2 m wide, 3m long, and 2 m high; Colorado Altitude Training Tent), with 12,000 L of air capacity, connected to a hypoxia generator (CAT 430, Altitude Control Technologies). The system was turned on throughout the experiment because the air outlet in the hypoxia generator is approximately 50 L/min. Therefore, the participants' average ventilation after each effort could, in some cases, be greater than 120 L/min. Thus, it was possible to guarantee air safety with a low inspired fraction of oxygen (FiO_2 = 13.5%) for the entire training session. The oxygen concentration monitoring inside the tent was made through an oxygen sensor (Oxygen Sensor R-17MED, Teledyne Analytical Instruments). The detailed strategy for hypoxia instrumentation is available in the published protocol of this study.[56]

For the NG, the participants performed the same procedures; however, the opposite hose end received ambient air (FiO_2 = 20.9%) without the participant's knowledge (blind procedure). The altitude where the experiment occurred was 540 m above sea level.

Hypoxic Dose Calculation and SpO_2 by FiO_2 index

The hypoxic dose was initially defined in km·h = (m/1000)·h,[22] considering that participants may show different peripheral oxygen saturation (SpO_2) reductions for the same FiO_2, leading to lower oxygen availability in hypoxia conditions concomitantly with an oxygen demand increase resulting from exercise. Then, each participant's hypoxic dose was estimated using 2 distinct methods assumed from the product between exposure time in hours (t) by the SpO_2 average reduction in the training session, considering a resting SpO_2 value corresponding to 98%. Thus, hypoxic dose = (98 SpO_2 average) · t, adapted from Millet et al.[38] It was also calculated by the product between SpO_2 by FiO_2, the index (SF) proposed by Soo et al.[54]

Training Program

The training sessions were performed thrice a week, with a total duration of up to 50.5 min. The initial part (warm up) and the final stage (cool down) lasted for 5 and 3 min, respectively, and were performed in low intensity, corresponding to "easy" by the RPE. In the main part, the intensity was based on L2 values obtained in the initial and partial evaluation (90-100% L2 from first to the fourth week, and 100-110% L2 from fifth to the eighth week). Each training set consisted of efforts lasting 5 min in the intensity of L2 with a break of 2.5 min between efforts. According to the week of training, the number of sets variated from 3 to 6 sets (Figure 1). HR and RPE were used to control the intensity during all training periods. Furthermore, blood oxygen saturation was monitored to evaluate the hypoxia and training responses using a pulse oximeter (D300C1, Dellamed). The measurements were recorded in 3 moments: rest, end of each effort, and end of the break.

Statistical Analyses

The data normality was checked using the Shapiro-Wilk test. After the normality confirmation, data were expressed in means (SD). Then data were analyzed using a 2 × 3 (time [BSLN × 8-W] × group [CG × HG × NG]) repeated-measures analysis of variance (ANOVA) to verify the possible variations in statistics. Additionally, the effect size (η^2) was calculated for the comparisons between groups and interpreted according to Cohen.[13] Statistical difference was defined as $P < 0.05$, and the Bonferroni post hoc test was used if necessary. The statistical tests were performed with the software JASP (Version 0.13.1.0).

Responsiveness to intervention was computed by comparing typical error (TE) and the smallest worthwhile change (SWC).[29] TE was calculated by dividing the SD of the trial-to-trial difference score by $\sqrt{2}$.[29] The SWC was derived from between-subject SD multiplied by either 0.2,[6,29] representing the typical small effect. The option to present the "thresholds" (SWC and 2 × TE) is due to their relevance in clinical application, ie, changes greater than SWC and especially 2 × TE, regardless of statistical significance, may indicate clinical significance.

It was considered responsive for those who, for each variable, present values higher than 2 times TE.[6,29,57] Those analyses were performed on Microsoft Office Excel spreadsheets.

RESULTS

Control Variables

No differences were observed between groups in food records between baseline and 8 weeks (Appendix Tables A1 and A2, available in the online version of this article). In addition, no alterations were observed in walking and sitting times. Still, an increase in physical activity levels (moderate and vigorous) related to participation in the intervention program was observed (Appendix Table A3, available online).

Anthropometric Variables

No statistics differences were observed between groups in age (years), CG 47.3 (10.5), NG 50.1 (10.5) and HG 49.0 (9.7), P = 0.78, and effect size (η^2 = 0.012).

The participant's body mass and BMI are listed in Table 1, and no statistical alterations were observed; therefore, the differences in body mass and BMI were lower than the smallest worthwhile change.

Internal Training Load and Hypoxic Dose

Internal training loads, obtained from exercise time and RPE average, were similar between groups (NG = 3071 ± 742 a.u., and HG = 2954 ± 1032 a.u.).

The hypoxic dose, calculated during the training sessions from FiO_2, was 9.97 for NG and 64.6 km/h for HG. At the same time, the hypoxic dose calculated by peripherical oxygen saturation was 160.5 (93.2) for NG and 1471.3 (354.6) %·h for HG. Thus, in each session, the SF index means calculated from FiO_2 and SpO_2 were 464.0 (3.1) and 657.2 (17.5) $SpO_2 \cdot FiO_2^{-1}$ for the NG and HG, respectively.

Maximum Parameters of CPET

Table 2 describes the results obtained at the maximum intensity reached by the participants in the CPET at baseline and 8 weeks. Statistical improvements were observed in VO_{2peak} (L/min) and iVO_{2peak} in both trained groups (NG and HG) compared with the baseline. However, no difference was observed between them. No differences were found in the CG. Regarding the relation to body mass VO_{2peak} (mL/kg/min),

Table 1. Anthropometric variables for the 3 experimental groups

				Time		Group		Time × Group	
	BSLN	8W	Diff	*P* Value	η^2	*P* Value	η^2	*P* Value	η^2
Body mass (kg)									
CG	85.28 (14.47)	85.86 (15.06)	0.58						
NG	79.78 (16.04)	80.17 (16.56)	0.39	0.94	9.214^{-7}	0.36	0.050	0.13	6.399^{-4}
HG	88.68 (10.08)	87.79 (10.87)	-0.89						
BMI (kg/m^2)									
CG	30.22 (4.33)	30.41 (4.45)	0.19						
NG	29.04 (3.13)	29.16 (2.99)	0.12	0.91	3.009^{-6}	0.58	0.027	0.12	0.001
HG	31.00 (3.88)	30.65 (3.84)	-0.35						

BMI, body mass index; BSLN, baseline; CG, control group; Diff, difference; 8W, 8 weeks; η^2, effect size; HG, hypoxia group; NG, normoxia group; SWC, smallest worthwhile chance.

HR_{peak}, and $[La]_{peak}$ no changes were detected. Statistical changes in RPE were observed only in HG after 8 weeks training ($P = 0.01$).

Submaximum Parameters of the CPET

Tables 3 and 4 describe the values associated with the submaximum parameters of the incremental test, L1 and L2. For L1 analysis, the value of VO_2 (mL/min and mL/kg/min) and power were statistically higher after the 8 weeks of training in the NG. In addition, the HG improved the power associated with L1. For L2, similar improvements were observed in VO_2 (mL/min and mL/kg/min) and power in NG and HG after the intervention compared with baseline.

Figure 2 shows, from the individual changes related to SWC and 2 × TE, that both NG and HG improved the aerobic capacity and power variables compared with CG.

Significant differences were not observed for erythrocyte counts, hemoglobin concentration, and hematocrit percentage, comparing the results after 8 weeks training and baseline (Table 5). Conversely, EPO levels and off-score were found to be higher in all 8-week experimental groups than at baseline ($P < 0.01$), but nondifference between training groups protocols were demonstrated (CG versus NG or HG). On the other hand, a decreased level of reticulocytes was observed for all 8-week groups, which was also statistically different in comparison to baseline ($P < 0.01$), but also nondifference between experimental groups (Table 5). In addition, HG showed an improvement in EPO and off-score and a decrease in reticulocytes after the 8-week intervention.

Figure 3 shows, from the individual changes above SWC and 2 × TE, that both NG and HG improved EPO and off-score, and decreased reticulocytes compared to CG, but not for erythrocytes, hemoglobin, and hematocrit.

DISCUSSION

The main findings of the present study were that 8 weeks of moderate-intensity training improves the CRF of people recovered from COVID-19. In addition, hypoxia promoted advances similar to training in normoxia, with a greater hematological stimulation.

Other studies had systematically reported the relationships between maximal exercise capacity[7] and CRF (ie, VO_{2peak})[45] and survival rate for patients with various pathologies. In the case of symptomatic COVID-19 individuals, as well as other respiratory diseases, a reduction in VO_{2max} has also been observed. Barbagelata et al,[4] in a cross-sectional study, showed that patients with the post-COVID-19 syndrome had significantly lower (~10%) VO_{2peak} (25.8 ± 8.1 mL/kg/min) compared with asymptomatic individuals (28.8 ± 9.6 mL/kg/min).

Debeaumont et al[15] evaluated physical fitness and its relationship with functional dyspnea by performing CPET in COVID-19 survivors 6 months after hospital discharge, those admitted to the general ward had a relatively preserved VO_{2peak} (87%), while those requiring the intensive care unit had a moderately reduced VO_{2peak} to 77%. These authors concluded that persistent dyspnea was associated with reduced physical fitness at 6 months.

In the present study, participants who underwent the experimental training program (NG and HG) showed significant improvements in VO_{2peak} of 3.9 mL/kg/min and 3.5 mL/kg/min, respectively, besides the fact that a clinic change was observed for these groups, because most individuals showed responsiveness (changes greater than SWC and 2 × TE) to the intervention, while the CG does not significantly modify their values. These results suggest that the proposed training model

Table 2. Effects of moderate-intensity cyclic hypoxic training on cardiorespiratory capacity and monitoring variables of the incremental test of patients recovered from COVID-19

				Time		Group		Time × Group	
	BSLN	8W	Diff	*P* Value	η^2	*P* Value	η^2	*P* Value	η^2
VO_{2peak} (mL/min)									
CG	1801.8 (414.7)	1843.6 (479.2)	41.8						
NG	1763.3 (634.2)	2058.6 (713.5)*	295.3	<0.01	0.039	0.85	0.007	0.01	0.015
HG	1764.1 (428.4)	2051.1 (478.2)**	287.0						
VO_{2peak} (mL/kg/min)									
CG	21.6 (5.7)	21.9 (6.4)	0.3						
NG	22.1 (6.5)	26.0 (8.3)	3.9	<0.01	0.481	0.61	0.024	<0.01	0.301
HG	20.1 (5.2)	23.6 (8.3)	3.5						
iVO_{2peak} (watts)									
CG	106.3 (41.2)	113.5 (42.9)	7.2						
NG	95.7 (52.4)	131.0 (57.7)**	35.3	<0.01	0.062	0.79	0.010	<0.01	0.017
HG	106.7 (36.2)	133.0 (37.6)**	26.3						
$[La]_{peak}$ (mM)									
CG	6.8 (1.7)	5.7 (1.6)	-1.1						
NG	6.2 (2.5)	6.9 (1.9)	0.6	0.94	3.556^{-5}	0.55	0.021	0.02	0.049
HG	6.6 (2.2)	7.1 (1.7)	0.6						
HR_{peak} (bpm)									
CG	151.5 (18.1)	149.3 (17.4)	-2.2						
NG	160.2 (17.6)	158.4 (13.2)	-1.8	0.78	3.372^{-4}	0.21	0.062	0.60	0.004
HG	156.6 (13.7)	158.8 (13.2)	2.2						
RPE_{peak}									
CG	8.7 (1.4)	9.2 (1.5)	0.5						
NG	8.6 (1.6)	7.2 (2.3)	-1.4	<0.01	0.044	0.16	0.057	<0.01	0.071
HG	9.6 (0.9)	8.2 (2.4)*	-1.4						

BSLN, baseline; CG, control group; COVID-19, coronavirus disease 2019; Diff, difference; 8W, 8 weeks; η^2, effect size; HG, hypoxia group; HR, heart rate; iVO_2, VO_2 intensity; [La], lactate concentration; NG, normoxia group; *P*, significance level; RPE, rate of perceived exertion; VO_2, oxygen uptake.
Data presented as mean (SD).
$^*P < 0.05$, $^{**}P < 0.01$ between BSLN and 8W in the same group.

effectively improved the aerobic power of people recovered from COVID-19. Compared with NG, HG also showed similar improvements in all physiological responses (L1, L2, and VO_2) and in their respective workloads.

We understand that this is a significant result from a practical point of view, especially for the HG participants, who achieved aerobic and functional gains similar to the NG, with a likely reduction in the external workload during exercise in hypoxia

Table 3. Effects of moderate-intensity cyclic hypoxic training on lactate threshold 1 (L1) reached in the incremental test and monitoring variables of people recovered from COVID-19

				Time		Group		Time × Group	
	BSLN	8W	Diff	*P* Value	η^2	*P* Value	η^2	*P* Value	η^2
VO_{2L1} (mL/min)									
CG	1191.1 (197.5)	1263.8 (301.3)	72.7						
NG	1229.9 (215.7)	1603.8 (397.1)*	373.9	<0.01	0.134	0.27	0.060	0.08	0.039
HG	1198.5 (195.0)	1411.4 (278.8)	212.9						
VO_{2L1} (mL/kg/min)									
CG	13.7 (2.5)	14.5 (3.5)	0.8						
NG	15.0 (1.8)	19.5 (4.7)*	4.5	<0.01	0.128	0.05	0.126	0.07	0.040
HG	13.1 (2.2)	15.6 (3.2)	2.5						
$Intensity_{L1}$ (watts)									
CG	37.5 (17.3)	49.4 (24.6)	11.9						
NG	34.3 (21.1)	63.8 (33.5)*	29.5	<0.01	0.191	0.75	0.014	0.06	0.024
HG	28.0 (13.5)	54.1 (26.5)**	26.1						
$[La]_{L1}$ (mM)									
CG	1.67 (0.5)	1.33 (0.4)	-0.3						
NG	1.87 (0.7)	1.65 (0.6)	-0.2	0.09	0.043	0.24	0.055	0.79	0.007
HG	1.82 (0.5)	1.68 (0.5)	-0.1						
HR_{L1} (bpm)									
CG	109.4 (15.3)	108.7 (8.8)	-0.7						
NG	121.4 (16.5)	123.4 (8.2)	2.0	0.42	0.008	0.04	0.148	0.56	0.014
HG	109.6 (6.9)	115.2 (12.4)	5.6						
RPE_{L1}									
CG	2.3 (0.5)	2.6 (1.02)	0.3						
NG	2.6 (1.3)	2.1 (0.7)	-0.5	0.22	0.020	0.39	0.040	0.17	0.020
HG	3.1 (1.2)	2.5 (0.51)	-0.6						

BSLN, baseline; CG, control group; COVID-19, coronavirus disease 2019; Diff, difference; 8W, 8 weeks; η^2, effect size; HG, hypoxia group; HR, heart rate; iVO_2, VO_2 intensity; [La], lactate concentration; NG, normoxia group; RPE, rate of perceived exertion; VO_2, oxygen uptake.
Data presented as mean (SD).
*$P < 0.05$, **$P < 0.01$ between BSLN and 8W in the same group.

compared with the same training model performed in normoxia. This assumption is made because the evidence[50,60] supports that hypoxic training impairs the capacity to maintain the same intensity as under normoxia conditions. Yano and Asano[60] found 12% and 39% reductions in the lactate threshold (LT) workload determined at 2000 m [(596 mm Hg) (759 ± 81 kpm/min)] and 4000 m [(462 mm Hg) (591 ± 60 kpm/min)] hypobaric hypoxia compared with LT obtained at sea level

Table 4. Effects of moderate-intensity cyclic hypoxic training on lactate threshold 2 (L2) reached in the incremental test and monitoring variables of people recovered from COVID-19

				Time		Group		Time × Group	
	BSLN	8W	Diff	*P* Value	η^2	*P* Value	η^2	*P* Value	η^2
VO_{2L2} (mL/min)									
CG	1559.3 (321.9)	1644.7 (468.4)	85.4						
NG	1508.8 (509.3)	1828.9 (577.4)*	320.1	<0.01	0.060	0.92	0.004	0.10	0.01
HG	1511.5 (327.5)	1751.3 (399.0)*	239.8						
VO_{2L2} (mL/kg/min)									
CG	18.63 (4.1)	19.54 (5.6)	0.9						
NG	19.00 (5.8)	23.15 (6.7)*	4.1	<0.01	0.065	0.41	0.037	0.05	0.02
HG	17.11 (3.6)	19.98 (5.6)*	2.9						
$Intensity_{L2}$ (watts)									
CG	73.8 (36.9)	87.8 (42.6)	14.0						
NG	65.8 (42.1)	93.8 (43.6)*	28.0	<0.01	0.078	0.90	0.005	0.16	0.01
HG	73.1 (26.9)	98.4 (38.3)**	25.3						
$[La]_{L2}$ (mM)									
CG	3.5 (1.1)	3.2 (0.9)	-0.3						
NG	3.5 (1.3)	3.8 (1.3)	0.4	0.67	0.002	0.28	0.034	0.50	0.02
HG	3.7 (1.0)	4.0 (1.3)	0.3						
HR_{L2} (bpm)									
CG	136.0 (14.4)	132.3 (15.4)	-3.7						
NG	143.4 (18.5)	144.5 (11.0)	1.1	0.77	4.376^{-4}	0.20	0.063	0.60	0.01
HG	138.8 (11.8)	139.5 (17.0)	0.7						
RPE_{L2}									
CG	4.9 (1.1)	5.2 (2.0)	0.3						
NG	5.1 (2.2)	4.0 (1.3)	-1.1	0.07	0.029	0.52	0.020	0.08	0.04
HG	5.5 (1.3)	4.6 (1.4)	-0.9						

BSLN, baseline; CG, control group; COVID-19, coronavirus disease 2019; Diff, difference; 8W, 8 weeks; η^2, effect size; HG, hypoxia group; HR, heart rate; iVO_2, VO_2 intensity; [La], lactate concentration; NG, normoxia group; RPE, rate of perceived exertion; VO_2, oxygen uptake.
Data presented as mean (SD).
*$P < 0.05$, **$P < 0.01$ between BSLN and 8W in the same group.

(861 ± 45 kpm/min). Sharma et al[50] found reductions of 6% and 4% in the intensity of LT and VO_{2peak}, respectively, of mid distance runners at 2100 m of normobaric hypoxia. Furthermore, these authors concluded that, in general, altitude training at the same intensity seems to correspond to an increase in the difficulty of approximately 30%. In another study, these authors[50] found 5.5% reductions in velocity at VO_{2max} (20.1 ± 1.3 vs 19.0 ± 1.0 km/h) in highly trained runners at 2100 m.

The highest proportion of participants with relevant (higher than SWC) changes in VO_{2peak} was observed in participants who trained in hypoxia, even though both groups showed similar substantial increases in intensity corresponding to VO_{2peak}. NG and HG participants having undergone the same training protocol, the intensity of the stimuli was prescribed based on the internal training load variables (ie, HR and RPE), corresponding to L2.

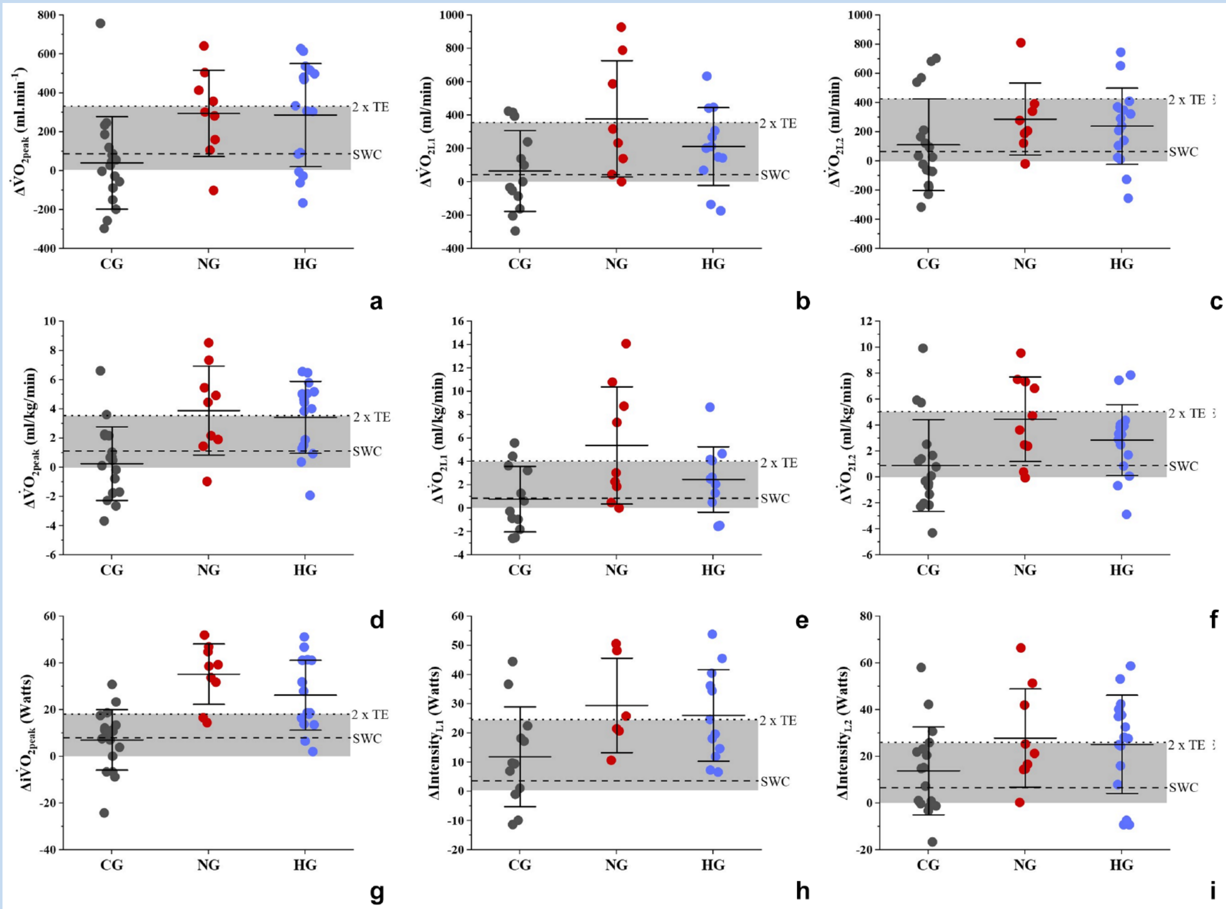

Figure 2. Mean and SD of the difference after 8 weeks of intervention compared to the smallest worthwhile change (SWC), and 2 × typical error (TE) for variables absolute VO_{2peak} (a), VO_{2L1} (b), VO_{2L2} (c), relative VO_{2peak} (d), VO_{2L1} (e), VO_{2L2} (f), iVO_{2peak} (g), $intensity_{L1}$ (h) and $intensity_{L1}$ (i). CG, control group; HG, hypoxia group; NG, normoxia group; L1, lactate threshold 1; L2, lactate threshold 2; VO_2, oxygen uptake; gray circles, CG; red circles, NG; blue circles, HG.

In fact, in the present investigation, the internal training loads were similar, and corroborated our findings, Liu et al[36] reported similar gains from training in hypoxia (FiO_2 = 15.3%) compared with the same program performed in normoxia with exercise intensities based on HR corresponding to 80% of VO_{2peak}, despite the load, the average external work of HG was 25% lower than NG. Collectively, these studies seem to demonstrate that during training performed at altitude, the absolute workload in LT and VO_{2peak} is substantially reduced, and this presents a significant advantage, especially in the health area, because it is possible to achieve the same internal load with less mechanical stress.

A study pointed out that the first adaptations usually observed after sufficient exposure to hypoxia are hematologic, with an increase in the number of erythrocytes and hematocrit leading to more oxygen transport.[49] However, training performed in hypoxia can also affect other genetic factors controlled by HIF-1α that are associated with performance adaptations and muscle adaptations without necessarily increasing oxygen carrying.[20,55] Additionally, our results showed that participants belonging to the HG increased the EPO levels compared to CG and NG. Although EPO and blood parameters were performed before and after 8 weeks, it is still possible to observe positive clinical effects of hypoxia on the reduction of reticulocytes with a concomitant increase in off-score. These last results might be clinically relevant because EPO stimulates the production of erythrocytes and, consequently, red blood cells, which facilitate oxygen transport to the target tissues.[31]

There is still no consensus in the literature regarding the minimum dose needed to produce EPO. Wojan et al.[58] recently investigated the effects of hypoxia exposure itself on EPO production. They found that eight 4 minute passive cycles of intermittent hypoxia, with a target SpO_2 of 80%, represent the shortest protocol to increase serum EPO levels in healthy individuals. Therefore, despite being slightly lower than recommended during passive exposure, the hypoxia doses used

Table 5. Effects of moderate-intensity cyclic hypoxic training on hematological parameters of people recovered from COVID-19

				Time		Group		Time × Group	
	BSLN	8W	Diff	*P* Value	η^2	*P* Value	η^2	*P* Value	η^2
EPO (mIU/mL)									
CG	8.7 (9.4)	14.6 (12.6)	5.9						
NG	3.4 (2.7)	13.4 (8.8)	10.0	<0.01	0.170	0.40	0.033	0.04	0.024
HG	7.2 (7.4)	21.0 (13.8)*	13.8						
Erythrocytes (m/μL)									
CG	4.6 (0.3)	4.7 (0.4)	0.1						
NG	4.5 (0.2)	4.5 (0.2)	-0.1	0.90	3.235^{-5}	0.64	0.020	0.28	0.005
HG	4.7 (0.4)	4.7 (0.4)	-0.0						
Hemoglobin (g/dL)									
CG	14.1 (1.1)	14.2 (1.2)	0.2						
NG	13.9 (0.8)	13.7 (0.7)	-0.1	0.73	1.673^{-4}	0.75	0.013	0.38	0.003
HG	14.1 (1.6)	14.1 (1.6)	0.1						
Hematocrit (%)									
CG	41.8 (2.7)	42.4 (3.1)	0.6						
NG	41.6 (2.1)	40.8 (1.6)	-0.8	0.94	1.388^{-5}	0.36	0.044	0.46	0.044
HG	42.5 (4.8)	42.6 (4.3)	0.1						
Reticulocytes (m/mm^3)									
CG	86.0 (24.1)	78.2 (19.0)	-7.8						
NG	88.2 (26.5)	70.4 (24.8)	-17.8	<0.01	0.088	0.95	0.002	0.01	0.030
HG	99.0 (46.1)	66.9 (30.4)*	-32.1						
Off-Score									
CG	60.3 (18.4)	68.5(19.7)	8.2						
NG	56.5 (18.8)	63.1(18.2)	6.6	<0.01	0.056	0.82	0.008	0.18	0.010
HG	56.4 (25.6)	72.3(20.2)*	15.9						

BSLN, baseline; CG, control group; COVID-19, coronavirus disease 2019; Diff, difference; 8W, 8 weeks; EPO, erythropoietin; η^2, effect size; HG, hypoxia group; NG, normoxia group.
*Considered to $P < 0.05$ between 8W and BSLN in the same group.

in the present investigation were sufficient to stimulate EPO increases, probably due to the combination with moderate-intensity training.

As clinical changes in hematological variables were observed for all groups, this phenomenon could mean a natural process of EPO increase and reticulocyte levels decrease after a long time post-COVID-19 recovery than an effect of training. The increase in EPO, predominantly observed for HG, may represent particular importance for people recovered from COVID-19. Pramsohler et al[43] recently investigated the relationship between COVID-19 and EPO levels in 59 COVID-19 patients hospitalized in the intensive care unit divided according to disease severity into mild, severe, and critical. Reduced hemoglobin levels were found in the critically ill group and the group of deaths. In addition, the coefficient of variation of the red blood cell distribution width and the ferritin values were significantly higher in the intubated and deceased groups. Finally, it was found that the EPO levels of patients who died were substantially lower than the CG and the group of surviving patients.

The other aspect refers to a greater hematological stimulation promoted by hypoxia, which can be seen by the decrease of

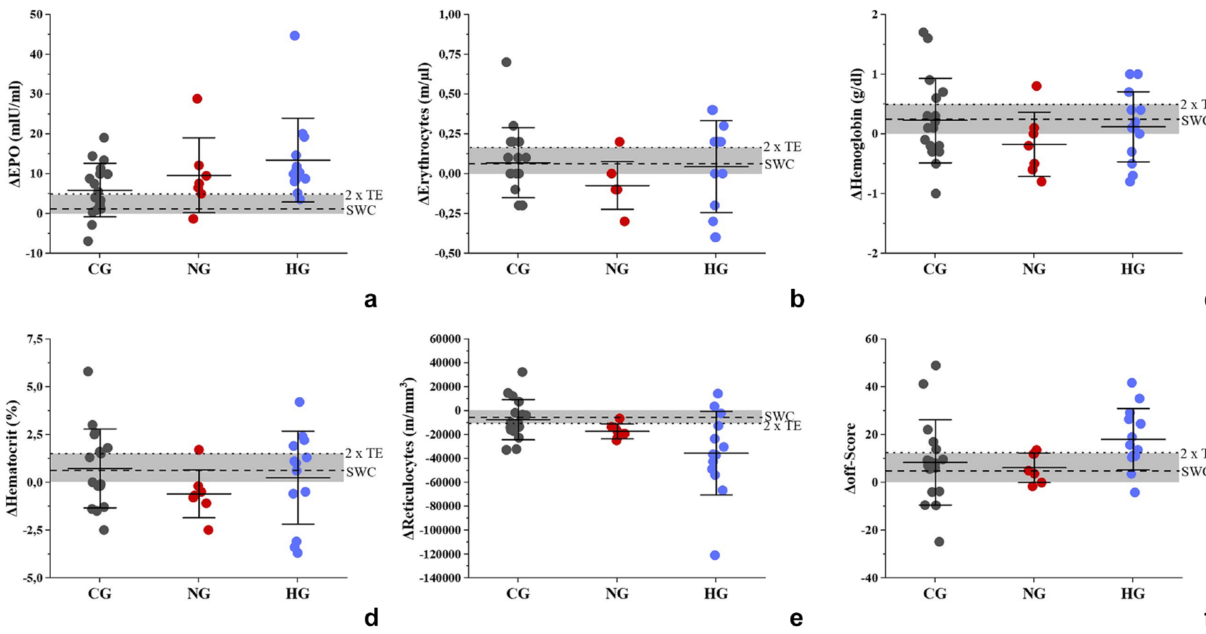

Figure 3. Mean and SD of the difference after 8 weeks of intervention compared to the smallest worthwhile change (SWC), and 2 × typical error (TE) (gray area) for blood variables absolute. (a) EPO (erythropoietin); (b) erythrocytes; (c) hemoglobin; (d) hematocrit; (e) reticulocytes; (f) off-score. CG, control group; HG, hypoxia group; NG, normoxia group; gray circles, CG; red circles, NG; blue circles, HG.

32.5% in reticulocytes, concomitantly with the substantial increase of 28% of the off-score for HG. Faulhaber et al,[19] using a "single-blind" model, compared the effects of exposure to hypoxia (continuous and cyclic) on "key markers" of hematologic adaptation, stress, and cardiac damage in elderly people. Both hypoxia protocols lasted approximately 70 minutes, and SpO_2 severity was 85%. Red cell content increased only on day 5 of exposure to hypoxia, compared with baseline values (+7.7%, $P < 0.01$), whereas hematocrit and off-score increased only at the end of the experiment. The authors concluded that there are differences in responses arising from continuous and cyclic hypoxia protocols when the objective is to stimulate hematological alterations.

Despite discussions about the risks and benefits of using EPO,[16,24,46] clinical and randomized studies are still needed to demonstrate its effectiveness in people recovering from COVID-19. In the present study, the EPO increment was succeeded from the combination of exposure to hypoxia and moderate-intensity aerobic training, which is, therefore, a possible nonpharmacological strategy to improve EPO levels and hematological parameters in individuals recovered from COVID-19.

This study had significant limitations, including the external load during the training sessions that was not controlled, limiting the conclusions regarding the exercise dose performed for each experimental group. In addition, the number of participants allocated to each group is reduced, especially in NG, due to participants' dropout during the project. Therefore, the gravity during the disease and the impairment level after COVID infection were not the same for all participants. Also, age and physical fitness distributions were heterogeneous because diverse populations were enrolled to provide a more generalizable clinical approach.

In conclusion, based on the findings reported in the present study, 8 weeks of moderate-intensity training in normoxia or hypoxia promoted similar benefits in CRF of people recovered from COVID-19. Finally, the hypoxia exposure was an additional stimulus to training, which increased EPO levels and promoted hematological stimulation. Therefore, this type of intervention is suggested as an alternative nonpharmacological treatment for individuals recovering from COVID-19.

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