Physical activity in the post-COVID-19: AEROBICOVID project design and perspectives

Atividade física no pós-COVID-19: escopo do projeto AEROBICOVID e suas perspectivas

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ABSTRACT

During the COVID-19 pandemic, several late-onset impairments have been observed, affecting the health and functionality of those involved. On the other hand, lower SARS-CoV-2 infection rates and severity of symptoms were observed in high-altitude cities. In this sense, the AEROBICOVID project was developed with the hypothesis that exercise would be an important opportunity for health improvement and that hypoxia would promote additional benefits in the recovery process. The cohort was about 84 participants with approximately 30 days since the COVID-19 symptoms recovery, 25 in the control group, and 59 divided into three moderate physical training groups. The project had good results in teaching, research, and extension, but also faced difficulties in operationalization. This experience is the basis for future proposals through an extension project at the University of São Paulo and in a Family Health Unit, besides a research project that will develop a new low-cost hypoxia technology.

Keywords: COVID-19, Altitude, Hypoxia, Exercise, Clinical trial.

RESUMO

Durante a pandemia de COVID-19 estão sendo observados vários efeitos tardios, afetando a saúde e a funcionalidade dos acometidos. Por outro lado, foram observadas menores taxas de infecção pelo SARS-CoV-2 e gravidade dos sintomas em cidades de elevada altitude. Neste sentido, o projeto AEROBICOVID foi desenvolvido com a hipótese de que o exercício seria uma proposta importante para a melhoria da saúde e que a hipóxia promoveria benefícios adicionais no processo de recuperação. Participaram 84 pessoas com aproximadamente 30 dias desde a recuperação dos sintomas da COVID-19, 25 no grupo de controle e 59 divididos em três grupos de treinamento físico moderado. O projeto teve bons resultados no ensino, pesquisa e extensão, mas também enfrentou dificuldades na operacionalização. Estas experiências são a base para propostas futuras através de um projeto de extensão na Universidade de São Paulo e em uma Unidade de Saúde da Família, além de um projeto de pesquisa que desenvolverá uma nova tecnologia de hipóxia de baixo custo.

Palavras-chave: COVID-19, Altitude, Hipóxia, Exercício, Estudo clínico.

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INTRODUCTION

The spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing COVID-19, began in November 2019. In March 2020, the World Health Organization (WHO) elevated the contamination's status to a pandemic. The proportion of deaths among the infected ranges from 2 to 3%, and the recovery rate is high[1]. In this regard, a new demand arises in the post-COVID-19 context, as some symptoms may persist and limit convalescents, leading to long-term complications, such as cardiorespiratory, pulmonary, endocrine, renal, functional, and psychological disorders[2].

Physical exercises can reduce chronic inflammation, strengthen the immune system, and improve physical fitness and mental health[3]. In addition, higher levels of aerobic capacity can produce short-term improvements in the immune and cardiorespiratory systems[4]. Thus, exercise interventions are considered an alternative in the post-COVID-19 context.

Since the beginning of the pandemic, several studies pointed out that people living at high-altitude, with lower levels of oxygen (O_2), showed a lower prevalence of COVID-19 and reduced severity in cases of infection[5,6]. In Brazil, a study described that the cities with high altitudes and low relative humidity showed decreased relative incidence and mortality rates related to COVID-19[7]. These findings are probably due to physiological and anatomical adaptations in the lungs, improved perfusion, and mainly due to activation of hypoxia-inducible factor 1α (HIF-1α)[5]. Studies related to HIF-1α present recent scientific relevance, highlighted in the innovative research that won the Nobel Prize in Medicine and Physiology in 2019[8].

Additionally, recent studies have demonstrated the possibility of using erythropoietin (EPO) as an auxiliary approach in the treatment of COVID-19[9]. In this sense, the proposal of the AEROBICOVID project developed the hypothesis that physical exercise could be an important health improvement in the post-COVID-19 recovery process, and that hypoxia exposure could promote additional effects through HIF-1α and EPO. These benefits contribute to establishing new time-efficient and non-pharmacological protocols to treat people recovering from COVID-19. Therefore, this study aimed to describe the AEROBICOVID project design and present future perspectives from successful experiences and operational difficulties.

METHODS

The study was approved by the Research Ethics Committees from the School of Physical Education and Sport of Ribeirao Preto, University of Sao Paulo (USP) (CAAE: 33783620.6.0000.5659) and the School of Pharmaceutical Sciences of Ribeirao Preto - USP (CAAE: 33783620.6.3001.5403).

The inclusion criteria were (1) participants aged between 30 and 69 years old and recovered from COVID-19, (2) reported mild to severe symptoms, and (3) from 15 to 60 days after recovery from clinical signs or medical discharge (if they had been hospitalized). The exclusion criteria were (1) exposure to high-altitude places > 1500 m in the last three months, (2) significant physical limitations to carry out evaluations or intervention, (3) acute or chronic clinical illnesses without medical supervision, (4) anemia, (5) use of immunosuppressive drugs, (6) pregnant women, (7) hormone replacement, (8) smokers, (9) excessive use of alcohol or drugs, (10) three absences in a row during the intervention, and (11) taking part in less than 75% of the total sessions planned.

The evaluations and intervention took place at the School of Physical Education and Sport of Ribeirao Preto - USP. The controlled clinical trial was randomized, double-blind, and composed of four groups. The control group (CG) was formed by the participants who could not participate in the physical training intervention and agreed to conduct a follow-up through the evaluations. The physical training groups were randomly divided into: effort and pause in normoxia (G_N); effort in normoxia and pause in hypoxia (G_{HR}); and, effort and pause in hypoxia (G_H). The eight-week moderate training sessions in the cycle ergometer were executed three times a week and consisted of three parts (warm-up, main part, and cool-down) with a total duration of up to 50.5 min. The warm-up and the cool-down were performed at "easy" intensity in the rate of perceived exertion (RPE), lasting 5 and 3 min, respectively. The main part was carried out in sets of efforts lasting 5 min with an intensity of 90–100% of the anaerobic threshold (second metabolic threshold) with a passive pause of 2.5 min between efforts. Training loads were increased during the first four weeks by volume, from three to six sets.

The experimental protocol was composed of 13 weeks, and the physical training intervention was performed for eight weeks. In weeks 0, 9 (after the

intervention), and 13 (four weeks after the end of the intervention), the following evaluations were performed: application of Physical Activity Readiness Questionnaire (PAR-Q), anamnesis, International Physical Activity Questionnaire (IPAQ), 12-item health survey (SF-12), and Depression, Anxiety, and Stress Scale (DASS-21); blood collection for the analysis of genotyping, hematological parameters, and inflammatory mediators; blood pressure; anthropometric measurements; body composition; autonomic parameters; pulmonary function assessments; graded exercise test to determine VO_{2PEAK} and anaerobic threshold; and, motor tests to assess strength, aerobic fitness, agility and balance (Figure 1).

Blood lactate concentration, target heart rate, blood oxygen saturation, and RPE were used to control the load. In addition, Lake Louise Score was applied to observe possible adverse effects of hypoxia exposure. Finally, between weeks 4 and 5, the graded exercise test was performed to adjust the prescribed intensity.

An approximately 3000 m, ≅13.5% FiO_2 (inspired fraction) was simulated using a hypoxia generator (Colorado Altitude Tents, Colorado, USA) that fed the air in a tent. The tent stored and distributed the air through hoses to individual one-way masks (Figure 2).

To have information related to sample size estimation, statistical analysis, and other methodological details, please access the published study protocol[10].

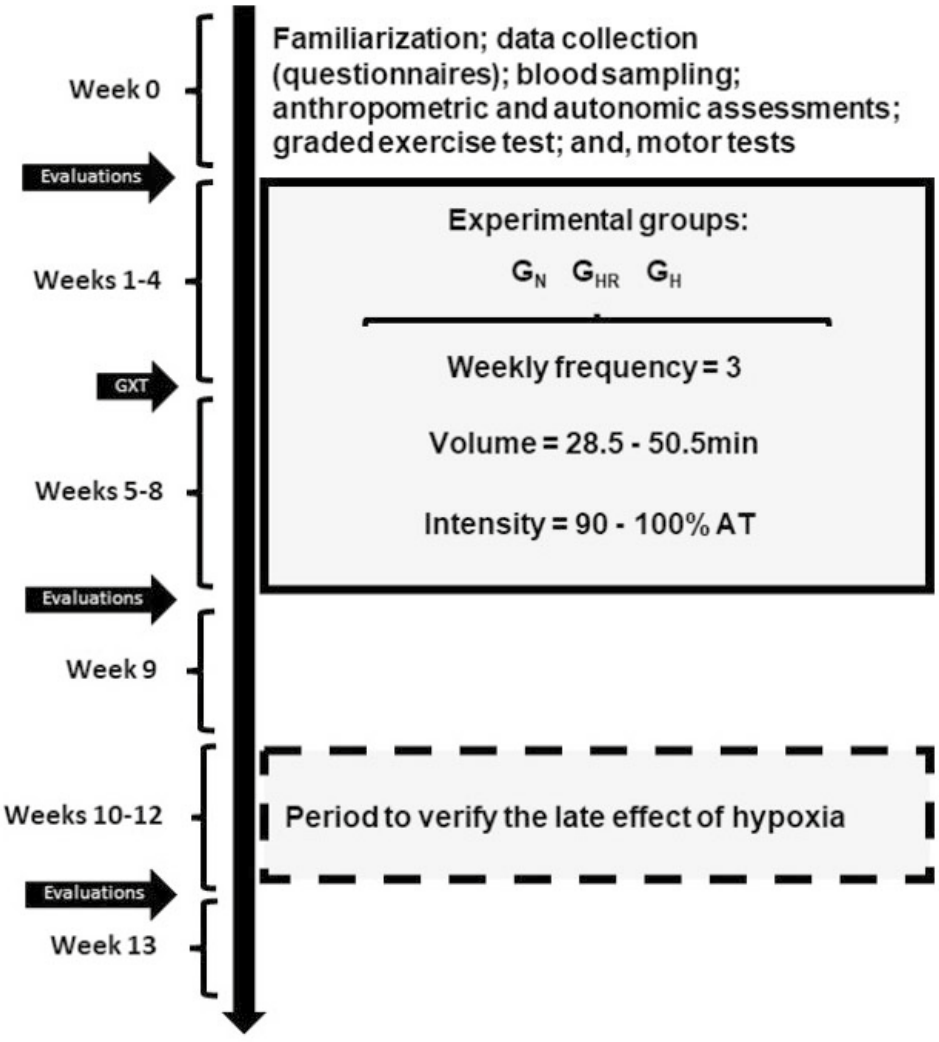

Figure 1 - Experimental design. G_N = effort and pause in normoxia. G_{HR} = effort in normoxia and pause in hypoxia. G_H = effort and pause in hypoxia. AT = anaerobic threshold. GXT = graded exercise test.

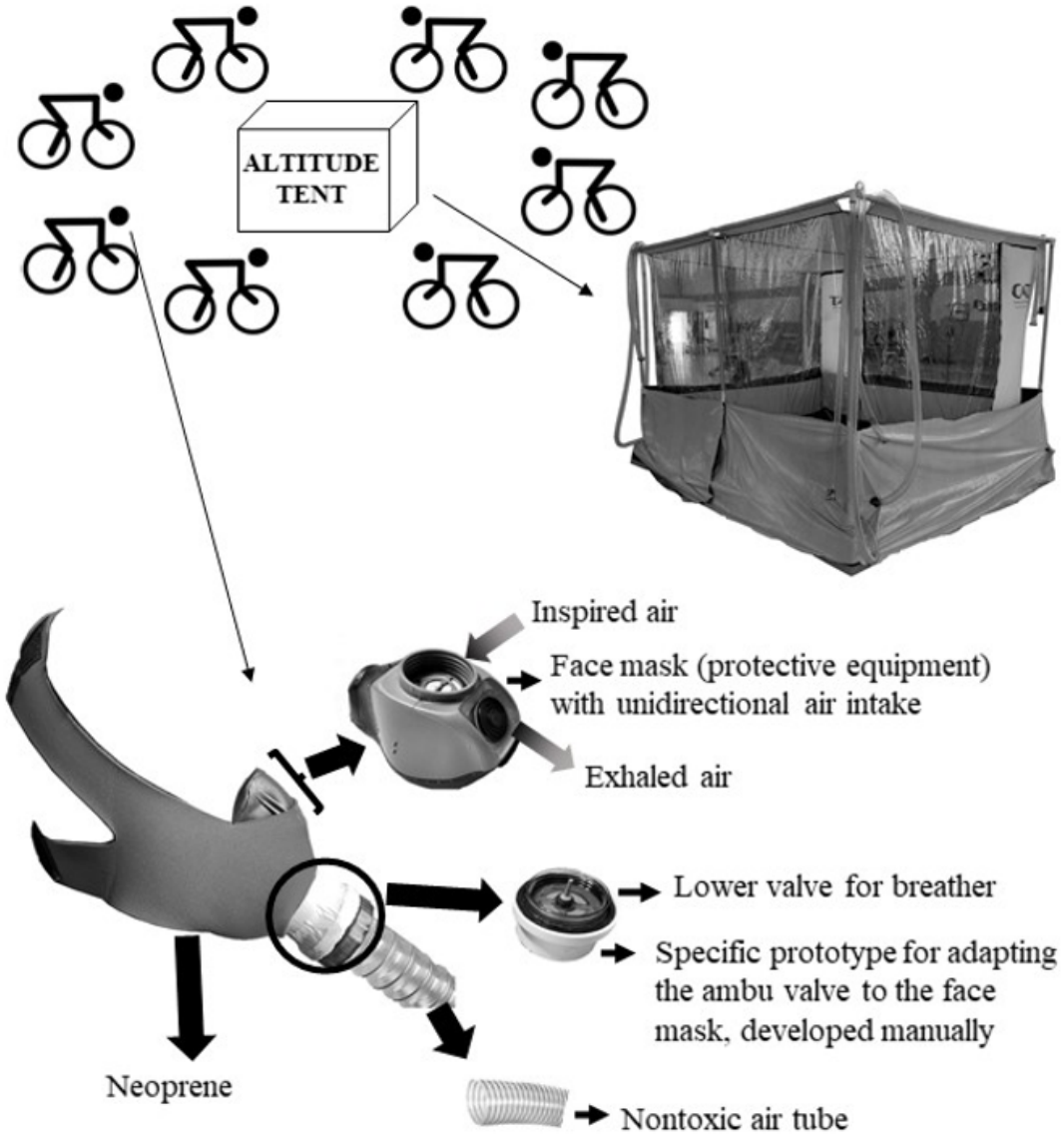

Figure 2 - Strategy for training participants and individual mask.

RESULTS

The AEROBICOVID project was funded by the USP Vida Project, which was created to advance research and overcome COVID-19 with voluntary donations from individuals and companies. The project was carried out from September 2020 to February 2021 and offered health monitoring and physical training associated with hypoxia to 84 individuals who recovered from COVID-19 with functional impairment. Graded exercise test results showed that, from the 84 people evaluated, 78 had a VO_{2PEAK} below the expected for their age[11]; on average, 30,2% below the expected. In addition, the classification according to the disease severity during COVID-19 was: the participants who presented symptoms, but no dyspnea (n = 16) were considered 'mild'; those who showed symptoms, including dyspnea (n = 51), were considered 'moderate'; those who required hospitalization care (n = 9) were considered 'severe'; and, those who needed mechanical respiration (n = 8) were considered 'critical'.

Based on the RPE throughout the training sessions, we observed that the training model

adopted did not generate a high perception of effort, staying around '3', referring to the description of 'easy' intensity. This result indicates that besides being a safe and effective model, it does not generate significant discomfort.

After the training period, the participants were asked about their perception of the training group protocol, with two possible answers – 'hypoxia group' or 'normoxia group'. It was observed that the blind methodology was satisfactory since less than half of the participants (47.8%) got the training condition right.

Of the 59 who started, 45 finished the 8-week physical training intervention, representing a waiver of participation for about 24% of participants who trained, a value below average compared to clinical studies involving physical exercise and with similar intervention durations[12,13]. Also, a health status follow-up was provided, with a new evaluation scheduled four weeks after the end of the intervention to investigate the late effect of hypoxia on health parameters, as previously identified by Camacho-Cardenosa *et al.*[14]. Participants were encouraged to maintain their exercise routine spontaneously for this objective. Bicycles and treadmills were available at the university for such practice. However, of the 45 who completed the physical training intervention, 34 returned for the late-moment evaluation, and of these, only 16 claimed to maintain a physical exercise routine after the intervention. Thus, this evaluation eventually became about the effect of detraining rather than the late effect of hypoxia. Furthermore, the participants who did not maintain their exercise routine showed worsening in several health parameters.

The social intervention was articulated for the visibility of this project on TV to attract participants, disseminate the preliminary results, and encourage the population to practice physical activities in the post-COVID-19 context (https://globoplay.globo.com/v/8957251/programa/; https://globoplay.globo.com/v/9434555/).

In this way, the AEROBICOVID project provided successful experiences of study and obtained important results for teaching by providing a field of practice for undergraduate and graduate students from the university; research, through the development of new insights on health improvement, participation in academic events, and production of manuscripts for scientific journals; and extension, by offering a physical activity program for the community.

PERSPECTIVES

These promising results are the basis for future projects; however, some difficulties promote reflections and proposals for adjustments. To make this idea operational, the project demanded investment in individual safety materials for the participants and the research team, the preparation and maintenance of structure and strategy to induce hypoxia, and simulation of altitude.

In order to take advantage of the experience initially obtained and expand this proposal, the following resources will be carried out: I) a university extension project with the formation of a new research team from the Unified Scholarship Program of USP. The new proposal is to promote bodily practices and physical activities in the post-COVID-19 context, forming a group at the university and another in the Paulo Gomes Romeo Family Health Unit, in the western district of Ribeirao Preto; II) a research project with the development of new technology. The results of AEROBICOVID were so promising that they motivated us to invest efforts in scientific/technological development to induce hypoxia with a portable, wearable, and low-cost device. This new research will be performed using a model of combined training, supported by grants on the call for Integrated Research Projects in Strategic Areas (PIPAE) from the Dean of Research-USP; III) approach with the Health and Sport Secretaries of the Ribeirao Preto City Hall, for future implementations in other Units of Primary Health Care.

FINAL CONSIDERATIONS

Exercise alone showed benefits in health parameters, and hypoxia exposure promises a new strategy for performing health care. In preliminary results, similar effects on cardiorespiratory capacity, physical fitness, metabolic variables, and heart rate variability were observed in groups trained in normoxia and hypoxia. Moreover, it was observed that hypoxia generates additional effects on hematological variables and peripheral saturation at rest when combined with exercise. It is worth mentioning a significant positive effect that indicates that training associated with hypoxia may promote similar adaptations, with reduced stress in muscle, tendon, ligament, and cartilage tissues[15]. This possibility could positively impact populations with joint involvement or in overweight and obese

conditions. These findings are the basis for future actions, generating greater accessibility and expanding the field of activity, besides offering more significant benefits to the community.

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Conflict of interest:
The authors declare no conflict of interest.

Authors' contributions:
GPC participated in the organization and operationalization of the research, data collection of the training monitoring, and the writing the text. EW and YFF participated in the data collection of the training monitoring and critical revision of the text. CAS is one of the consortium's collaborators, operationalized the blood draws, and critically reviewed the text. MP is one of the consortium collaborators and provided the hypoxia generators, tents, manufactured the individual and one-way mask system, and critically revised the text. Finally, AAT is the consortium coordinator, organized and managed the intervention in all instances, and critically reviewed the text.

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Clinical trials:
This study is registered on the Brazilian Registry of Clinical Trials (https://ensaiosclinicos.gov.br/) - identifier RBR-5d7hkv

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