Application of Hyperbaric Oxygenation in Outpatient Rehabilitation of COVID-19 Survivors
Journal: Issues of balneology, physiotherapy and therapeutic physical culture. 2021;98(6): 16-21
DOI 10.17116/kurort20219806116

Introduction

The novel coronavirus infection pandemic has posed a number of serious challenges for global health, the main of which is the development of therapeutic strategies for COVID-19. Insufficient effectiveness of etiotropic and pathogenetic drugs dictates the need to search for new, including non-drug methods of treating COVID-19 and rehabilitation of patients after the disease.

Hypoxia is one of the main manifestations of the pathological effect of COVID-19 on the human body; In this regard, it seems promising to use non-drug methods based on the use of oxygen in the treatment of a new coronavirus infection. These methods include hyperbaric oxygenation (HBO), or barotherapy, based on the saturation of the body with oxygen under high pressure in a pressure chamber. The method has previously been successfully used to treat decompression sickness, carbon monoxide poisoning, arterial gas embolism, necrotic soft tissue infections, chronic skin ulcers, severe multiple injuries with ischemia, and ischemic ulcers of the diabetic foot [1]. Treatment with oxygen under conditions of high pressure allows you to increase the efficiency of its diffusion through the alveolar barrier,

Studies have been published that confirm the effectiveness of HBOT in the prevention of conditions requiring mechanical ventilation in hospitalized patients with COVID-19 and low saturation [3], a positive result from the use of the method in patients with severe COVID-19-associated pneumonia and hypoxia [4], as well as in acute respiratory distress syndrome [5]. A multicomponent therapeutic effect of HBO on the clinical manifestations of a new coronavirus infection is expected, including correction of hypoxia and tissue hypoperfusion, anti-inflammatory effect by limiting the production of cytokines, effect on stem cell activation, antiplatelet and anticoagulant effects **(Fig. 1)** .

Rice. 1. **Role of hyperbaric oxygen therapy in COVID-19 therapy (adapted from [1]).**

The molecular level of the effect of HBO on the body infected with SARS-CoV-2, taking into account the available experimental data, may include modulation of oxidative stress by influencing reactive oxygen and nitrogen species with implementation through hypoxia-inducible factor 1α (HIF-1α) and transcription factor NK-κB , as well as the normalization of endothelial function, realized through the activity of inducible and endothelial forms of NO-synthases [6]. In addition, *in vitro* experiments suggest a limitation in the production of pro-inflammatory cytokines with a profibrotic effect (interleukin-1β and interleukin-6) and an increase in stem cell mobilization [7].

Since the end of 2020, the term “post-COVID syndrome” (Long COVID) has been entrenched in the medical literature, included in the ICD-10 classifier under the code U09.9 - “condition after COVID-19, unspecified”. It refers to a variety of symptoms in patients who have had COVID-19 and persist for more than 12 weeks after the disease. These include symptoms of chronic fatigue, a number of "small" neurological and cognitive symptoms, as well as a diverse range of disorders from different body systems (cardiovascular, respiratory, nervous, musculoskeletal, etc.) [8]. Treatment guidelines for this condition and its impact on patients' quality of life are under investigation. The potential use of HBO in the recovery of post-COVID-19 patients has also been little explored.

The purpose of the study ***is*** to study the effect of HBO as part of a comprehensive outpatient rehabilitation on a number of clinical and functional indicators of patients who have undergone COVID-19.

Material and methods

A study was made of the effect of HBO on a number of clinical and functional parameters in 45 patients (22 men and 23 women) aged 40 to 60 years who underwent COVID-19 for 1 to 6 months. The patients were divided into 3 equal groups of 15 people: the 1st group included persons who had mild COVID-19 without the presence of viral pneumonia (CT-0); in the 2nd group — persons who had viral pneumonia CT of the 1st stage (CT-1); The 3rd group consisted of patients who underwent the disease with the development of COVID-19-associated pneumonia of the 2nd–3rd stage (CT-2–3). Patients did not have clinically significant decompensated comorbidities, including chronic bronchopulmonary diseases. Patients were not receiving medical therapy for COVID-19 at the time of the study; drug therapy during the rehabilitation period was limited to taking planned drugs for the correction of arterial hypertension and thyroid diseases. The study did not include persons with claustrophobia, epilepsy and episyndrome, acute inflammatory processes.

During a comprehensive examination, the parameters of bioelectrical resistance of body tissues were determined using a bioimpedance analyzer, anthropometric data were evaluated, a 6-minute walk test (6MWT) was performed, electrocardiographic and echocardiographic studies were performed, a general clinical and biochemical blood test was performed, hormonal status and the state of antioxidant protection were assessed based on levels of two main antioxidant enzymes — glutathione peroxidase (GPO) and superoxide dismutase (SOD).

All patients underwent a comprehensive outpatient rehabilitation program, including a basic exercise therapy program with an emphasis on the restoration of the bronchopulmonary system, received psychological consultations according to indications, as well as a course of 10 procedures in the Oxysys 4500 oxygen chamber with a duration of 30 minutes for each procedure: the first 3 procedures with excess pressure 0 ,15 atm., subsequent - at 0.3 atm., with a maximum oxygen concentration of 30%.

Statistical data analysis was performed using the IBM SPSS Statistics 10 software package. Data for analysis were preliminarily prepared and analyzed for outliers. To analyze the normality of data distribution, the Kolmogorov–Smirnov and Shapiro–Wilk tests were used in accordance with the conditions for their application. To assess the characteristics of the spread of values, we used the method of constructing confidence intervals, calculating the error of the mean and median. To compare quantitative nonparametric criteria and search for significant statistical differences in two independent groups, the Mann-Whitney test was used; in the study of differences in two independent samples in terms of quantitative parametric indicators - *T*-Student's criterion; in the study of the reliability of changes in quantitative non-parametric indicators of two related samples, the Wilcoxon rank test was

used. In all statistical studies conducted, the level of significance of differences was assumed to be 0.05.

Results and discussion

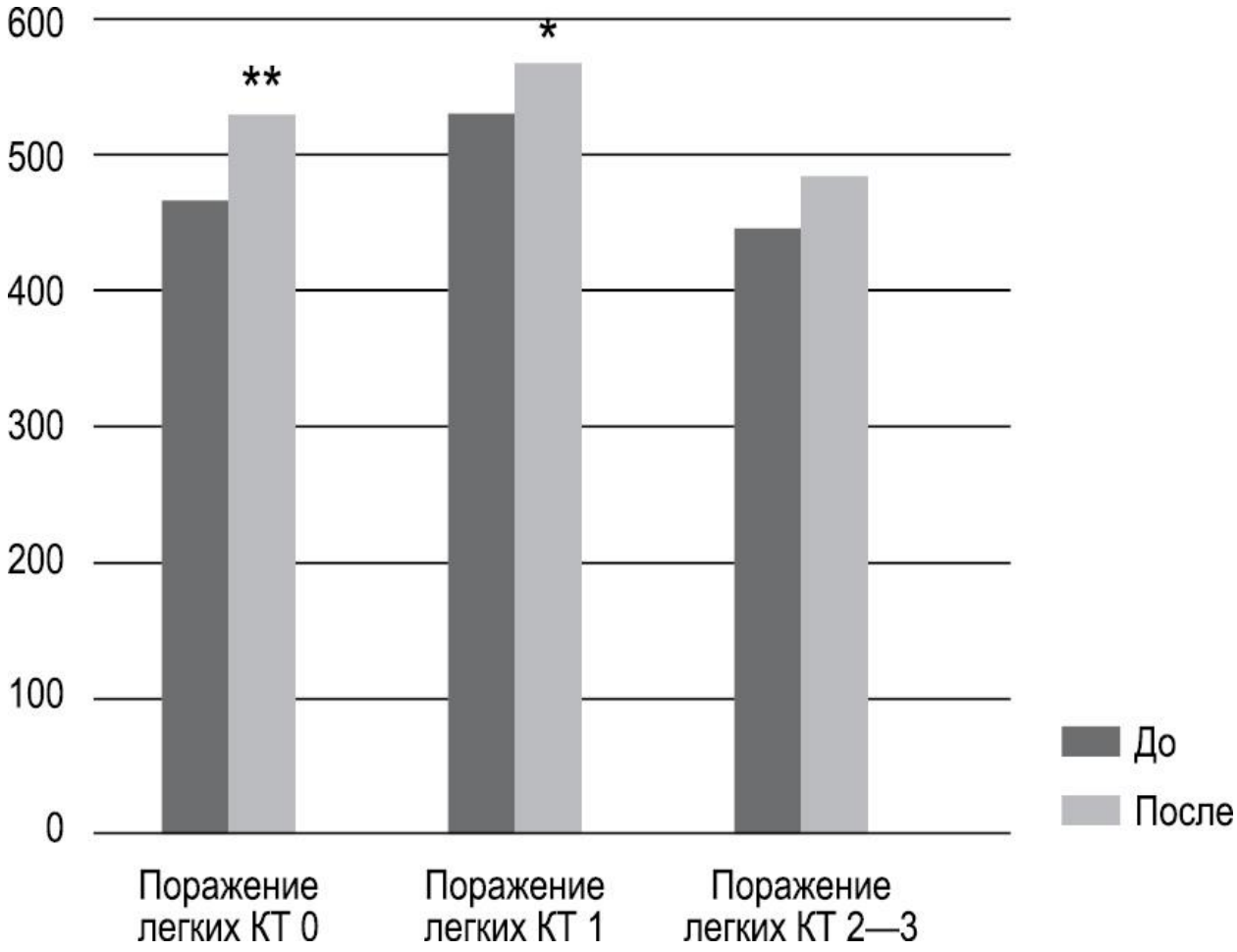
When assessing the spectrum of complaints in patients who underwent COVID-19, complaints of shortness of breath during habitual physical exertion, palpitations, headache, pain and stiffness in the muscles of the back, joints, stiffness of movements, memory loss, sleep disturbances, increased fatigue, impaired sense of smell prevailed. and taste. This generally coincided with the literature data on the most frequently detected symptoms of the Long COVID syndrome [9, 10]. There was no significant correlation between the severity of clinical symptoms and the statute of limitations of COVID-19.

When evaluating anthropometric and physical data, it is important to note that patients of the 3rd group had, on average, the oldest age, higher body weight and a higher percentage of fat mass according to bioimpedansometry. These results confirm data from other studies indicating that age and increased body weight are risk factors for a more severe course of a new coronavirus infection. The mean age of patients in the 1st group was 40.4±9.3 years, in the 2nd group — 45.4±8.6 years, in the 3rd group — 49±6.3 years; the average body weight of patients in the 1st group was 69.2±12.9 kg (fat mass — 22.7±7.9 kg), in the 2nd group — 85.8±22.1 (29.7±9) kg, group 3 — 95.8±22.8 (31.6±14.2) kg **(table)** .

Most of the clinical, functional and laboratory results of a comprehensive examination of patients were within normal or subnormal values. At the same time, slightly higher values of the maximum systolic pressure in the pulmonary artery in the 3rd group should be noted, which in 3 patients reached the degree of slight pulmonary hypertension.

Saturation indicators in patients of all three groups were within normal limits and were comparable, as was the distance traveled according to the results of 6MWT. Only in the 3rd group hypercholesterolemia was detected with an average total cholesterol of 6.5±1.2 mmol/l. Also, patients of the 3rd group had a subnormal level of C-reactive protein with an average value of 9.3 mg/l; the presence of possible residual low-gradient inflammation indirectly confirms the level of fibrinogen, which was also unreliably higher in the group of people who had COVID-19 with more severe CT stages of pneumonia.

Most of the examined patients showed good tolerance to HBOT procedures as part of complex rehabilitation; only one patient of the 2nd group experienced the occurrence of adverse events in the form of stuffy ears and headache, which required the cancellation of the procedure. According to the results of the study, an increase in the distance traveled during the implementation of 6MWT was revealed - significant dynamics was noted in groups with CT stages 0 and 1; in the 3rd group (CT-2-3), against the background of initially lower test scores, it was not possible to achieve significant positive dynamics in the course of the rehabilitation measures carried out **(Fig. 2)** .



Rice. Fig. 2. **Dynamics of the result of the 6-minute walk test during rehabilitation.**

* — p <0.05; ** — p <0.01.

The dynamics of heart ultrasound indicators had positive trends in the form of an increase in ejection fraction and a decrease in maximum systolic pressure in the pulmonary artery, however, the differences were not significant, which does not allow us to draw unambiguous conclusions about the effect of rehabilitation measures on the parameters of central hemodynamics; at the same time, in all 3 cases of minor pulmonary hypertension in group 3, after a course of rehabilitation, systolic pressure in the pulmonary artery returned to normal **(see table)** .

Changes in clinical and laboratory parameters of patients who have undergone COVID-19 during rehabilitation

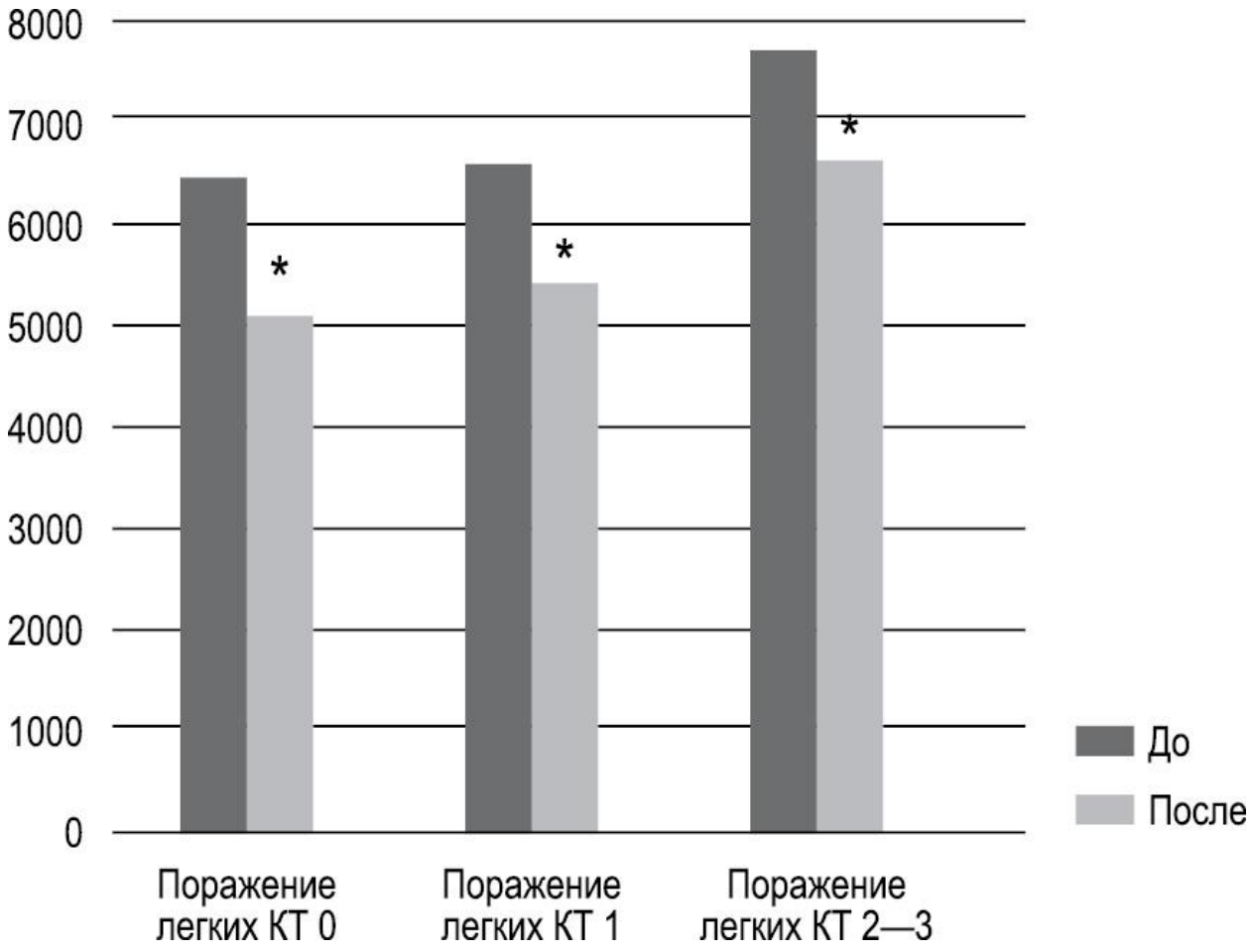
Parameter Parameter	Group 1 (CT-0) (mean age 40.4±9.3 years)	Group 2 (CT-1) (mean age 45.4±8.6 years)	group 3 (CT-2, CT-3) (mean age 49±6.3 years)

	Group 1 (CT-0) (mean age 40.4±9.3 years)		Group 2 (CT-1) (mean age 45.4±8.6 years)		Group 3 (CT-2, CT-3) (mean age 49±6.3 years)	
	before/before	after	before/before	after	before/before	after
Body weight, kg	69.2±12.9	67.2±13.8	85.8±25.1	81.4±24.9	95.8±22.8	96.2±22.2
Fat mass, kg	22.7±7.9	21.0±7.6	29.7±9.0	26.0±8.9	31.6±14.2	31.1±13.4
6MWT, m/6MWT, m	467.9±37.7	531.5±44.3**	533.9±74.3	570.1±57.8*	447.3±85.7	486.7±85.5
EF, %/EF, %	65.5±4.7	67.4±3.2	64.6±3.9	69.3±3.0	63.4±4.3	65.9±4.0
P in LA, mm RS/PAP, mm Hg	15.8±1.6	14.8±1.8	18.7±4.9	16.7±2.5	20.8±6.2	18.4±4.2
O_2 saturation, %/O_2 saturation, %	98.0±0.9	97.8±1.0	97.0±1.0	97.9±0.8	97.6±0.5	97.6±0.5
CRP, mg/L/CRP, mg/L	1.2±0.9	0.8±0.4	3.2±5.2	0.8±0.5	9.3±22.9	7.2±18.7
Fibrinogen, g/l/Fibrinogen, g/L	3.2±0.4	2.9±0.6	3.5±0.8	3.3±0.7	3.6±1.0	3.4±1.1
Norepinephrine, pg/ml Norepinephrine pg/mL	426.2±151.0	348.0±67.8	373.6±120.6	365.1±158.0	481.8±140.9	373.4±177.6**
GPO, units/L/GPO, units/L	6465.0±1637.3	5101.0±1353.3*	6587.8±1919.3	5418.1±1289.7*	7699.5±1747.9	6620.1±1702.1*

Note. 6MXT - 6-minute walk test; EF — left ventricular ejection fraction; P in LA - maximum systolic pressure in the pulmonary artery; GPO, glutathione peroxidase; CRP - C-reactive protein. * — p <0.05; ** — p <0.01.

According to the laboratory examination, a significant decrease in the level of noradrenaline was found in the group of patients who recovered from a new coronavirus infection with CT stage 2-3, with Δ - 13%. In other groups, the decrease in the level of norepinephrine did not reach significant values. The data obtained may indicate a limitation of stress and the activation of the sympathoadrenal system associated with it after the disease, which is probably more pronounced in patients with significant damage

to the lung tissue. A decrease in the level of the antioxidant enzyme GPO was observed - the differences were significant in all three groups of the study **(Fig. 3)** .



Rice. 3. **Dynamics of the level of hyperbaric oxygenation during rehabilitation.**

* — p <0.05.

Such dynamics may indicate a limitation in the level of oxidative stress during rehabilitation and confirm the modulating effect of HBO on oxidation processes. At the same time, there were no significant changes in SOD in all groups.

Conclusion

The experience of using HBO in the process of outpatient rehabilitation of patients who have undergone COVID-19 can be considered successful, given the increase in the functionality of the body during the course of rehabilitation, laboratory signs of limited low-gradient inflammation, sympathoadrenal activity and oxidative stress, with greater positive dynamics in severe COVID-19 groups. CT stages. Of course, the accumulation of

experience and a more detailed study of the use of barotherapy in the complex rehabilitation of patients after COVID-19 is required.

Hyperbaric oxygenation was carried out using an Oxysys 4500 oxygen chamber, provided by INTERFIN LLC under the agreement on scientific and practical cooperation between INTERFIN LLC and MNPC MRVSM DZM. The work had no sponsorship. No financial payments were made to the authors of the article .

Participation of authors: concept and design of the study — E.A. Turova, I.V. Pogonchenkova; collection of material - A.V. Golovach, D.I. Tagirov; statistical data processing - E.A. Turov, A.M. tickling; writing the text - A.M. tickling; editing - E.V. Gusakova, I.V. Pogonchenkov.

The authors declare no conflict of interest.

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How to quote
Turova E.A., Shchikota A.M., Pogonchenkova I.V., Golovach A.V., Tagirova D.I., Gusakova E.V. The use of hyperbaric oxygen therapy in outpatient rehabilitation of post-COVID-19 patients. *Issues of balneology, physiotherapy and therapeutic physical culture.* 2021;98(6):16-21.
Turova EA, Shchikota AM, Pogonchenkova IV, Golovach AV, Tagirova DI, Gusakova EV. Hyperbaric oxygenation in outpatient rehabilitation of COVID-19 convalescents. *Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi culture.*2021;98(6):16-21. (In Russ.).
https://doi.org/10.17116/kurort20219806116
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