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Oxygen-Helium Gas Mixture "Heliox" for the Treatment of Respiratory Failure in Patients with New Coronavirus Infection Covid-19 (Randomized Single-Center Controlled Trial)

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INTRODUCTION Treatment of respiratory failure in pneumonia caused by coronavirus infection (COVID-19) is still an unsolved problem that requires a comprehensive approach and the development of new methods that expand the range of possibilities of modern therapy. There is evidence that the heated oxygen-helium mixture has a positive effect on gas exchange in the infiltration zone by improving both ventilation and diffusion.

AIM OF STUDY To evaluate the effectiveness of the inclusion of a heated oxygen-helium mixture HELIOX (70% Helium/ 30% Oxygen) in the complex intensive care of respiratory failure of pneumonia caused by SARS-CoV-2 infection.

MATERIAL AND METHODS The study included 60 patients with confirmed viral pneumonia caused by COVID-19. The patients were randomized into two groups: group 1 (n=30) — patients who were treated with the standard COVID-19 treatment protocol with the heated oxygen-helium mixture HELIOX, and group 2 (control) (n=30) — patients who received standard therapy. Lethality was studied for 28 days, the time in days until a steady increase in SpO_2>96% was achieved when breathing atmospheric air; the time until the patient is transferred from the intensive care unit (ICU) to the general department.

RESULTS Inhalation of the HELIOX mixture (70% Helium / 30% Oxygen) resulted in a faster recovery of the hemoglobin oxygen saturation index (SpO_2). Starting from day 3, these differences became statistically significant. The time in days from inclusion in the study to a persistent increase in the degree of oxygen saturation of hemoglobin (SpO_2>96%) when breathing atmospheric air in the group with inhalation of the HELIOX mixture was less — 8 (7; 10), compared to 10 (8;13) in the control group (p=0.006). In the group with inhaled HELIOX mixture, the median treatment time in the ICU was 8 (7; 9.5) days vs 13 (8; 17) days (p<0.001) in the comparison group.

CONCLUSIONS Inhalation of the HELIOX mixture (70% Helium / 30% Oxygen) led to a faster recovery of the hemoglobin oxygen saturation index SpO_2, which contributed to reduction in the duration of oxygen therapy and a decrease in mortality.

Keywords: Heliox, Helium, COVID-19, SARS-CoV-2, Respiratory Insufficiency, Oxygen Inhalation Therapy

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CT — computed tomography
AVL — artificial ventilation of the lungs
ARDS — acute respiratory distress syndrome
ICU — department of reanimation and intensive care
PCR — polymerase chain reaction
NIV — non-invasive ventilation of the lungs
RR — respiratory rate
CRP — C-reactive protein

INTRODUCTION

A feature of the new pathogen *SARS-CoV-2* is the development of a serious illness (coronavirus infection 2019 (*COVID*-19)), characterized by high mortality [1–4]. As of June 1, 2021, more than 5,000,000 cases of *COVID*-19 coronavirus infection were recorded in Russia. The total number of deaths from a new coronavirus infection in Russia as of this date amounted to more than 120,000 people [5]. Worldwide, according to the World Health Organization, more than 170 million people were infected, more than 3.5 million people died [6].

Clinically, *COVID*-19 can be either asymptomatic or cause a wide range of symptoms such as fever, cough, runny nose, sore throat, and shortness of breath. Reproduction of the pathogen *SARS-CoV-2* in the lower respiratory tract causes severe pneumonia, which becomes the main cause of the severe course of the disease and poor outcome [2, 6–9]. Treatment of respiratory failure in pneumonia caused by *COVID*-19 is still an unsolved problem that requires an integrated approach and the development of new methods that expand the range of possibilities of modern therapy.

There is evidence that the heated oxygen-helium mixture has a positive effect on gas exchange in the infiltration zone by improving both ventilation and diffusion [11–13]. The low density and high diffusion capacity of helium allow it to penetrate through narrowed bronchi, as well as through Lambert's canals and Cohn's pores through unaffected adjacent areas of the lung into the inflammation focus, where, due to low solubility in the blood, a mixture of helium with oxygen (Heliox) remains in poorly ventilated alveoli prevents the development of atelectasis [14–16]. In addition, it improves the transport of oxygen through the alveolocapillary membrane, and the high diffusion coefficient of carbon dioxide (CO_2) in helium contributes to its elimination, which ensures the maintenance of gas exchange in the infiltration focus. The heated oxygen-helium mixture, reaching the respiratory part of the lungs, causes persistent, deep, prolonged hyperemia of the alveolar tissue with an increase in the diameter of the lung capillaries by 3-10 times [13, 14, 16–18]. Improvement of microcirculation with an increase in the number of leukocytes leads to dehydration and resorption of the inflammatory focus. Improved blood flow also contributes to more active delivery of antibacterial and antiviral drugs to the affected areas. It should be noted that a number of studies have shown the anti-inflammatory effect of Heliox, a decrease in oxidative stress and damage to lung tissue [17, 19]. Systematic review by *C. Beurskens et al.* (2015) showed that in both pediatric and adult animal models, the oxygen-helium mixture improved gas exchange, allowing for less invasive ventilation in a wide range of models using different ventilation modes. Clinical studies have shown a decrease in the work of breathing during heliox ventilation with a concomitant increase in pH and a decrease in PaCO2 level compared with ventilation with an oxygen-air mixture [16].

Pathological changes inherent in pneumonia caused by the *SARS-COV*-2 virus (from early signs: edema of the affected parts of the lung, protein exudate and reactive hyperplasia of pneumocytes with the development of inflammatory infiltrates to the formation of hyaline membranes, bronchial obstruction and atelectasis in severe acute respiratory distress syndrome - ARDS), suggest the effectiveness of the heated oxygen-helium mixture in the complex intensive care of patients with acute respiratory failure, including against the background of pneumonia in patients with *COVID*-19.

Purpose of the study: to evaluate the effectiveness of the inclusion of the heated oxygen-helium mixture "HeliOx" (70% helium / 30% oxygen) in the complex intensive therapy of respiratory failure pneumonia caused by *SARS-CoV*-2 infection.

MATERIAL AND METHODS

Single-center randomized prospective study conducted at the Military Medical Academy named after SM. Kirov Ministry of Defense of the Russian Federation. The study was approved by the Independent Ethics Committee (protocol No. 236 dated May 21, 2020). The inclusion criteria for the study were: men and women aged 18 to 75; pneumonia, confirmed by the results of computed tomography (CT) of the chest; respiratory failure (the ratio of the partial pressure of oxygen in arterial blood and the fraction of inhaled oxygen (PaO_2 / FiO_2) in the range of 200-300 mm Hg or blood oxygen saturation (SpO_2) 80-93% when breathing in atmospheric air) on the day of inclusion in the study. The exclusion criteria were: pregnant and breastfeeding women; disturbances of consciousness of any degree; pneumothorax; inability of the patient to cooperate with the medical staff; obesity III degree (body mass index not less than 40 kg / m^2); bronchorrhea; damage to the upper respiratory tract; trauma to the facial skeleton; burns to the face; multiple organ failure; sepsis; a history of face, esophagus, or stomach surgery; decompensated respiratory or metabolic acidosis or alkalosis; previous invasive ventilation or respiratory support for 6 months before the screening period; instability of hemodynamics (the need for vasopressor support); chronic heart failure III – IV functional class; acute disorders of cerebral or coronary circulation (transient ischemic attack, ischemic or hemorrhagic stroke, acute coronary syndrome, acute myocardial infarction) within 6 months before the screening period; known (according to the history) or suspected abuse of alcohol, psychotropic drugs, drug dependence, drug addiction; the presence of mental illness, including a history. The exclusion criteria from the study were: the patient's desire to discontinue participation in the study (withdrawal of informed consent); the research physician's decision that the patient should be excluded for the benefit of the patient; the patient refused to cooperate with the researcher or was undisciplined; hypoxemia with impaired gas exchange, aggravation of shortness of breath (decrease in SpO_2 to less than 80% during the procedure).

All patients were diagnosed using the determination of RNA (DNA) pathogens of acute respiratory viral infections in scraping of epithelial cells of the oropharynx and nasopharynx by polymerase chain reaction (PCR), CT scan of the chest organs was performed. The study included 60 patients. The study design is presented in Fig. 1.

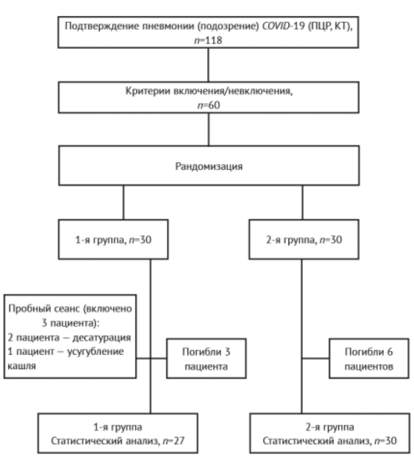

Fig. 1. Research design

Notes: CT — computed tomography; PCR — polymerase chain reaction

Simple tabular randomization was done by generating random numbers using a resource *Research Randomizer (https://www.randomizer.org)*. The patients were randomized into 2 groups: group 1 (main, n = 30: 23 men, 7 women) consisted of persons who were included in the standard *COVID*-19 treatment protocol with HeliOx heated oxygen-helium mixture (70% helium / 30% oxygen), in the 2nd group (comparison) (n = 30: 24 men, 6 women) - patients who received standard therapy according to the Interim Guidelines "Prevention, Diagnosis and Treatment of New Coronavirus Infection (*COVID*-19)" (versions 5-9, approved by the Ministry of Health of the Russian Federation) and temporary algorithms for the management of patients with infection caused by *SARS*-*CoV*-2 in the clinics of the Military Medical Academy version 2.0-3.0. In the 1st group, inhalation of an oxygen-helium mixture heated to 80 ° C (HeliOx (70% helium / 30% oxygen)) was performed using the Ingalit-B2-01 apparatus (ZAO "Specialized Design Bureau of Experimental Equipment at the Institute of Medical biological problems of the Russian Academy of Sciences", RF), 10 minutes 4 times a day for 7 days, which was fed through a mask at normal barometric pressure (Fig. 2).

Fig. 2. Inhalation of heated oxygen-helium mixture (HeliOx (70% Helium/30% Oxygen)) with "Ingalit-B2-01"device

The primary endpoint of the study was all-cause mortality within 28 days. The secondary endpoints were: the time in days from the start of treatment with the study drug until the persistent achievement of an increase in SpO_2 of more than 96% when breathing in atmospheric air; respiratory rate (RR); the frequency of transferring patients to non-invasive ventilation (NIV) and mechanical ventilation with tracheal intubation (ALV); relief of fever (which was defined as a decrease in axillary temperature less than 37 ° C without the use of antipyretics); the severity of cough was not more than 1 point on a 6-point scale (from 0 to 5); time before the transfer of the patient from the intensive care unit (ICU) to the general department. The groups were comparable in terms of age, sex, degree and volume of lung damage, RR, SpO_2, severity of cough, blood ferritin and *C*-reactive protein (*C*RP) values. General characteristics of patients are presented in table 1.

Table 1

General characteristics of patients upon inclusion in the study

	1st group (*n*=30)	2nd group (*n*=30)	Statistical differences, *p*
Men, *n* (%)	26 (81,3%)	27 (84,4%)	0,756*
Women, *n* (%)	6 (18,8%)	5 (15,6%)	
Age, years; Me (Q1; Q3)	51 (43,75; 57,25)	55,5 (45,0; 65,0)	0,145*
Duration from the first symptoms to hospitalization, days; Me (Q1; Q3)	7,2 (2,6; 11,8)	6,3 (3,9; 9,6)	0,743*
CT scan of the lungs, degree of defeat Me (Q1; Q3)	3,0 (2,25;4,00)	3,0 (3,00;4,00)	0,733*
Percentage of lung lesions CT, %; Me (Q1; Q3)	60,00 (50,0;78,75)	64,00 (45,0;75,0)	0,898*
Body temperature, °C; M±SD	37,15±0,95	37,21±0,87	0,797**
Respiratory rate, per minute, Me (Q1; Q3)	22,0 (18,5; 22,0)	20,0 (18,0;23,5)	0,985*
SpO_2 when breathing atmospheric air; Me (Q1; Q3)	90,0 (88,0; 92,0)	90,0 (87,75; 92,0)	0,928*

The content of ferritin in the blood (norm 20-250 mcg / l) M±SD	714,21±80,71	746,24±94,34	0,788**
The content of CRP in the blood (the norm is 0-5 mg / l) M±SD	84,04±9,1	73,90±10,29	0,464**
The severity of cough, score; Me (Q1; Q3)	4 (4; 4)	4 (4; 4)	0,175*

Notes: * — Mann-Whitney comparison; ** — t-test. CT — computed tomography; CRP— C- reactive protein

STATISTICAL PROCESSING

Data analysis was carried out using the program *SPSS*-26 для *Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA)*. The variables were examined using visual (histogram, probabilistic plot) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk tests) to determine if they are normally distributed. With a normal distribution, the data were represented by the mean and standard deviation $M \pm SD$; quantitative data that do not obey the law of normal distribution were presented as a median and 25th and 75th percentiles - *Me* (*Q*1; *Q*3). An analysis was carried out to describe and generalize the distributions of the variables. The description of the frequencies of the values in the sample under study was presented with a mandatory indication of the given characteristic of the sample (*n,* %). Intergroup comparisons with respect to parametric data were performed using the *t*-test, and nonparametric comparisons using the Mann – Whitney *U*-test. Tests were considered statistically significant at $p < 0.05$.

RESULTS

One of the inclusion criteria was the development of respiratory failure against the background of the development of pneumonia caused by *COVID*-19 (PaO_2 / FiO_2 in the range of 200-300 mm Hg or SpO_2 80-93% when breathing in atmospheric air) on the day of inclusion in the study. The studied groups at the time of inclusion in the study were comparable in terms of the SpO_2 level (group 1 - 90 (88; 92)%, group 2 — 90 (87,75;92)%, *p*=0,928). Also, the groups were comparable in terms of the volume and degree of lung damage according to CT data. The degree of lung damage according to CT data at admission in the 1st group was 3 (3; 4), in the 2nd group — 3 (2,75; 4) (*p*=0,981). The volume of lung lesions on CT in the 1st group was 60% (52.5; 80), in the 2nd group — 62% (43,25; 76,25) (*p*=0,795). A significant amount of lung damage and the development of respiratory failure required oxygen therapy in all patients included in the study. The severity of respiratory failure in the first group in two cases required a high concentration of oxygen in the inhaled mixture, therefore, during a test session of inhalation of the HeliOx mixture (70% helium / 30% oxygen) due to the development of hypoxia (decrease in SpO_2 to less than 80%, aggravation of shortness of breath feeling short of breath) 2 patients were excluded from the study. Another patient was excluded from the study in group 1, who, when trying to inhale a heated mixture, developed coughing fits with the development of desaturation and a feeling of lack of air.

Both patients of the 1st group excluded from the study, who showed desaturation during the trial session, died despite the treatment. In the 1st group, after the end of the course of inhalation of the "HeliOx" mixture (70% helium / 30% oxygen), one more patient died; total mortality in the 1st group was 3 patients (10%), while in the 2nd group - 6 (20%). The differences in mortality were statistically significant (*p*=0,049).

The deterioration of the condition of the patients of the 2nd group also required a more frequent transfer of patients to NIV and mechanical ventilation. In the group with inhalation of the HeliOx mixture (70% helium / 30% oxygen), the frequency of switching to NIV and ILV was 16.7% (5 patients - 3 IVL), in group 2 - 26.7% (8 patients - 6 ILV).

Inhalation of the HeliOx mixture (70% helium / 30% oxygen) led to a faster recovery of the hemoglobin oxygen saturation (SpO_2) index. Starting from day 3, these differences became statistically significant (Fig. 3). Accordingly, the time in days from the start of treatment with the study drug until the persistent achievement of an increase in the degree of saturation of hemoglobin with oxygen (SpO_2 more than 96%) when breathing atmospheric air in the group with inhalation of the HeliOx mixture (70% helium / 30% oxygen) was less - 8 (7 ; 10) when using the mixture "HeliOx", and in the comparison group 10 (8; 13) (*p*=0,006). A decrease in the need for oxygen therapy in patients in group 1 led to a reduction in the time spent by patients in the ICU. In the group with inhalation of the HeliOx mixture (70% helium / 30% oxygen), the median treatment time in the ICU was 8 (7; 9.5) days, and in the comparison group, 13 (8; 17) days ($p < 0.001$, statistically meaningfully).

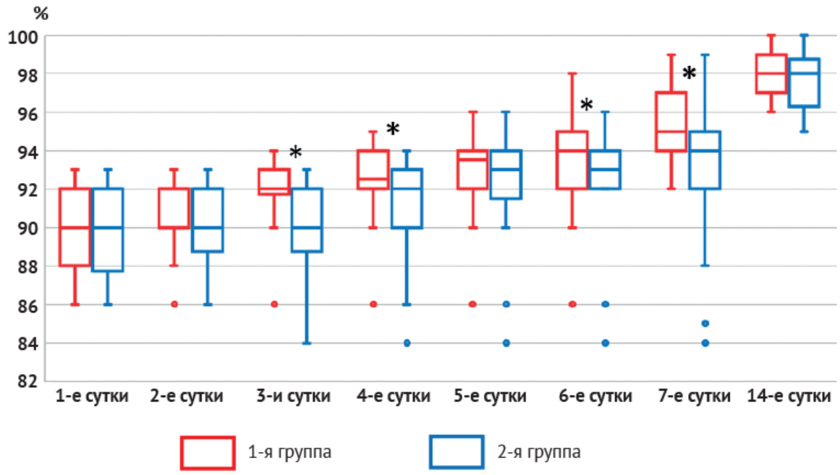

Fig. 3. SpO_2 dynamics in groups

Oxygen therapy in the group with inhalation of the HeliOx mixture (70% helium / 30% oxygen) was statistically significantly shorter: in the 1st group - 5 (4-7) days, and in the 2nd group - 8.5 (6-12) days (p <0.001). Since in the 1st group the SpO_2 level recovered faster, the respiratory rate in this group, starting from the 3rd day, was lower.

Inhalation of the "HeliOx" mixture (70% helium / 30% oxygen) influenced the severity of the cough. In the 1st group, the discomfort from coughing in patients decreased faster than in the comparison group, statistically significant differences were formed by the 4th day and only by the 5th day the difference in the severity of cough leveled off (Table 2). After a session of inhalation "HeliOx", most patients noted a subjective improvement and easier breathing.

Table 2

Respiratory rate and cough severity indicators on a 6-score scale

Day	Indicators of the severity of cough on a 6-point scale, points			Respiratory rate per min.		
	Group 1 (n=27)	Group 2 (n=30)	p*	Group 1 (n=27)	Group 2 (n=30)	p*
1st	4 (4; 4)	4 (4; 4)	0,175	22,0 (18,5; 22,0)	20,0 (18,0; 23,5)	0,985
2nd	3 (3; 3)	3 (3; 3)	0,238	20,5 (18,25; 22,0)	22,0 (20,0; 24,0)	0,056
3rd	2 (2; 3)	3 (2; 3)	0,085	20,0 (18,0; 22,0)	22,0 (20,0; 24,0)	0,017
4th	2 (1; 2)	2 (2; 3)	0,02	19,0 (18,0; 21,5)	22,0 (20,0; 24,0)	0,001
5th	1 (1; 1)	1,5 (1; 2)	0,189	18,0 (17,0; 21,5)	22,0 (20,0; 23,75)	0,000
6th	1 (0; 1)	1 (0; 1)	0,236	18,0 (16,25; 20,0)	22,0 (20,0; 23,75)	0,000
7th	0 (0; 1)	0 (0; 1)	0,269	18,0 (16,0; 20,75)	22,0 (18,0; 24,75)	0,009
14th	0 (0; 0)	0 (0; 1)	1	16,5 (16,0; 20,0)	20,0 (18,0; 23,5)	0,024

There were no statistically significant differences in the study groups in the relief of fever (which was defined as a decrease in axillary temperature to less than 37 ° C, was not identified).

DISCUSSION

The study showed that inhalation of the HeliOx mixture (70% helium / 30% oxygen) led to a faster recovery of the hemoglobin oxygen saturation index SpO_2 and reduced the duration of oxygen therapy. Similar results were obtained by other researchers. *Beurskens et al.* (2014) studied the effect of Heliox (50% helium, 50% oxygen) on gas exchange in patients on protective mechanical ventilation. After switching patients with mechanical ventilation with oxygen-air mixture to heliox, in order to maintain the target pH and $PaCO_2$, it was possible to reduce the respiratory rate statistically significantly (p <0.02). A tendency towards a decrease in the minute volume of ventilation also was noted. After the cessation of ventilation with heliox, these parameters did not change. In addition, a trend towards a decrease in peak pressure was revealed. Resistance of the airways and lung compliance did not change against the background of mechanical ventilation with Heliox. At the same time, the change of gas from the oxygen-air mixture to heliox led to a rapid decrease in $PaCO_2$, which then remained at the same level during the entire period of application of Heliox and returned to the initial value immediately after its cancellation [13].

Morgan et al. (2014) described a clinical case of successful treatment of respiratory failure with Heliox in a 10-month-old boy with coronavirus respiratory tract infection. In addition to the already ongoing treatment, the boy was prescribed additional inhalations of Heliox (80% helium, 20% oxygen) through a nasal cannula at a rate of 8 l / min, after which SpO_2 immediately increased to 84% (while oxygen therapy was continued). One minute after the start of Heliox inhalation, the NPV dropped to 31–36 per minute, but SpO_2 remained below 90%. Then the concentration of helium was reduced to 60%, and the gas flow rate to 7 L / min, while the secondary oxygen flow rate was increased from 1 to 3 L / min. As a result, SpO_2 increased to 96% and the patient's condition stabilized. Heliox therapy was discontinued on the 3rd day, the patient was transferred from the ICU to the therapeutic unit on the 10th day, and 7 days later the boy was discharged home [20].

Kneyber et al. (2009) in a prospective double-blind crossover study proved the effectiveness of Heliox (60% helium, 40% oxygen) in ventilated children with respiratory syncytial virus. The aim of mechanical ventilation was to maintain $SpPO_2$ and $PaCO_2$ in arterial blood, measured percutaneously, at levels of 88–92% and 45–65 mm Hg respectively. Mechanical ventilation with Heliox was accompanied by a statistically significant (p <0.001) decrease in the resistance of the respiratory system, however, no statistical changes in oxygenation were found [21].

A.L. Krasnovsky (2013) studied the effectiveness of inhalation of a heated oxygen-helium mixture in the complex therapy of patients with pneumonia. In the group of complex therapy with the use of thermogeliox inhalations, complete X-ray resolution of pneumonia (disappearance of infiltrative changes) occurred more often, which was observed during all periods of X-ray imaging. By the 12th day, the infiltration was resolved in 57% of the examined patients from the main group (4 out of 7) and none of the comparison group (0 out of 2), by the 13th day - in 66% and 50% of patients, respectively, by on the 14th day - in 80% and 64% and by the 15th day - in 80% and 55%, respectively. In the group with inhalation of oxygen-helium mixture, the disappearance of cough was faster. At the same time, the inclusion of a course of inhalations of Thermogeliox into the complex therapy of patients with pneumonia did not affect the rate of relief of the systemic inflammatory response, assessed by the dynamics of blood levels of *C*RP, fibrinogen, leukocytes and neutrophils [17].

In a study by *W. Seliem* and *A. Sultan* (2017), associated with the use of 50% oxygen-helium mixture in children with acute respiratory syncytial viral bronchiolitis, after 2 hours of treatment with Heliox, oxygen saturation and PaO_2 significantly improved compared to the air-oxygen group. 98.3% versus 92.9%, 62.0 mm Hg versus 43.6 mm Hg (p = 0.04 and 0.01, statistically significant), respectively. In addition, the PaO_2 / FiO_2 ratio was significantly higher in the Heliox group compared to the air-oxygen group - 206.7 versus 145.3 [22].

This study has some limitations. First of all, this is a well-defined group of patients who received oxygen therapy using oxygen inhalation through a face mask. This study did not include patients who could be included in it according to the degree of gas exchange disturbance, but at the initiation of the study, they received respiratory therapy in the form of high-flow oxygenation or NIV.

CONCLUSION

The experience of using the Heliox mixture (70% helium / 30% oxygen) has demonstrated its effectiveness in the complex intensive therapy of respiratory failure of pneumonia caused by *COVID*-19. Inhalation of the Heliox mixture (70% helium / 30% oxygen) led to a faster recovery of the hemoglobin oxygen saturation index SpO_2, which contributed to a reduction in the duration of oxygen therapy and a decrease in mortality.

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