

Effect of thermal helium-oxygen mixture on viral load in COVID-19

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Abstract

In this paper, we will discuss the use of t-He/O₂ in the treatment of patients with the viral disease COVID-19. **The aim** of the study is to evaluate the effect of thermal helium-oxygen therapy on viral load, inflammatory markers, and antibody synthesis. **Methods.** A single-center, randomized, prospective study included 60 patients with COVID-19. Patients were divided into two groups: 1 ($n = 30$; 17 male, 13 female) – t-He/O₂ therapy was included in the standard COVID-19 treatment Protocol; 2 ($n = 30$; 16 male, 14 female) – standard therapy in accordance with the clinical recommendations of Healthcare Ministry of Russia for patients with COVID-19. Of the 60 patients included in the study, 28 (46.7%) were medical professionals. The median age of patients in the study was 56.7 (45 – 61) years old. In the group 1 – 58 (45 – 59.5) years old, in the group 2 – 55 (46 – 66) years old. All patients had a positive test of SARS-CoV-2 coronavirus RNA, CT signs of “ground-glass opacity” type lung damage, and areas of air space consolidation. Patients were comparable by gender, age, body mass index (BMI), area of lesion of the pulmonary parenchyma, laboratory data. **Results.** As a result of the use of t-He/O₂, the elimination of the SARS-CoV-2 virus occurred within 48 – 72 hours from the start of inhalation and was confirmed by PCR test. The following changes were found in all patients: synthesis of IgM and IgG antibodies, increase in lymphocytes level, decrease of C-reactive protein, restoration of alanine aminotransferase and aspartate aminotransferase levels, D-dimer, and ferritin. These signs became more pronounced in the 1st group within 72 – 168 hours, compared with the 2nd group, where these results were achieved on the 10th day of therapy. **Conclusion.** The inclusion of thermal inhalation a gas mixture of helium and oxygen (t-He/O₂) in the standard therapy of patients carrying infectious disease caused by SARS-CoV-2 with CT signs of COVID-19 pneumonia (CT1, CT2 grades) reduces the viral load by stimulating antibody synthesis, as the type of immunoglobulin G, and immunoglobulin M causing the effect of “termovaccination”; increases the effectiveness of treatment, reducing the markers of inflammation.

Key words: thermal helium-oxygen mixture, helium, PCR, immunoglobulin G, immunoglobulin M, COVID-19.

Conflict of interests. The authors declare the absence of conflict of interests.

For citation: Shogenova L.V., Varfolomeev S.D., Bykov V.I., Tsybenova S.B., Ryabokon' A.M., Zhuravel S.V., Utkina I.I., Gavrilo P.V., Petrikov S.S., Chuchalin A.G., Panin A.A. Effect of thermal helium-oxygen mixture on viral load in COVID-19. *Pul'monologiya*. 2020; 30 (5): 533–543 (in Russian). DOI: 10.18093/0869-0189-2020-30-5-533-543

Влияние термической гелий-кислородной смеси на вирусную нагрузку при COVID-19

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Резюме

Представлен метод лечения больных COVID-19 при помощи термической гелий-кислородной смеси (t-He/O₂). Целью исследования явилась оценка влияния t-He/O₂ на вирусную нагрузку, маркеры воспаления и синтез антител (АТ). **Материалы и методы.** В одноцентровое рандомизированное проспективное исследование включены больные COVID-19 ($n = 60$; медиана возраста – 56,7 (45–61) года). Пациенты рандомизированы в 2 группы: в стандартный протокол лечения больных COVID-19 1-й группы ($n = 30$: 17 мужчин, 13 женщин; средний возраст – 58 (45–59,5) лет) включена терапия t-He/O₂; у пациентов 2-й группы ($n = 30$: 16 мужчин, 14 женщин; 55 (46–66) лет) проводилась стандартная терапия в соответствии с клиническими рекомендациями Министерства здравоохранения Российской Федерации для больных COVID-19. Из 60 пациентов, включенных в исследование, 28 (46,7 %) являлись медицинскими работниками. У всех больных результат теста РНК коронавируса SARS-CoV-2 был положительным, выявлены компьютерно-томографические (КТ) признаки поражения легких по типу «матового стекла» и участки консолидации. Пациенты были сопоставимы по полу, возрасту, индексу массы тела, площади поражения легочной паренхимы, лабораторным данным. **Результаты.** В результате применения t-He/O₂ элиминация вируса SARS-CoV-2, подтвержденная методом полимеразной цепной реакции, происходила в течение 48–72 ч от момента начала ингаляции. У всех пациентов обнаружены следующие изменения: синтез АТ иммуноглобулина (Ig) М и -G, повышение уровня лимфоцитов, снижение уровня С-реактивного белка, восстановление уровня аланин- и аспаратаминотрансферазы, D-димера, ферритина. Эти признаки становились более выраженными у пациентов 1-й группы в течение 72–168 ч по сравнению с таковыми у больных 2-й группы, где эти результаты достигались на 10-е сутки терапии. **Заключение.** При включении ингаляций t-He/O₂ в стандартную терапию пациентов, переносящих инфекционное заболевание, вызванное SARS-CoV-2, с КТ-признаками пневмонии I и II степени тяжести отмечено снижение вирусной нагрузки и уровня маркеров воспаления, повышение эффективности лечения; происходит также стимуляция синтеза АТ IgG и IgM, вызывая эффект «термовакцинации». В настоящее время изучается ответ на воздействие t-He/O₂ у пациентов с КТ-признаками пневмонии III степени тяжести. Продemonстрирован положительный эффект у тяжелых больных, однако при этом требуются дальнейшее изучение и статистический анализ результатов терапии.

Ключевые слова: термическая гелий-кислородная смесь, гелий, полимеразная цепная реакция, иммуноглобулин G, иммуноглобулин M, COVID-19.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Шогенова Л.В., Варфоломеев С.Д., Быков В.И., Цыбенкова С.Б., Рябоконе А.М., Журавель С.В., Уткина И.И., Гаврилов П.В., Петриков С.С., Чучалин А.Г., Панин А.А. Влияние термической гелий-кислородной смеси на вирусную нагрузку при COVID-19. *Пульмонология*. 2020; 30 (5): 533–543. DOI: 10.18093/0869-0189-2020-30-5-533-543

The first outbreak of the new coronavirus disease 2019 (COVID-19) began in December 2019 in Wuhan, China and has evolved into a major pandemic [1, 2]. A severe acute respiratory syndrome coronavirus (SARS-CoV-2) was later identified as the causative agent. This virus is enveloped in a positive-stranded RNA [3, 4]. About 28,506,254 cases of COVID-2019 and 915,920 deaths (as of) were registered globally by September 11, 2020¹. The fight against the coronavirus infection is an extremely acute issue that requires the development of new methods to expand the therapeutic and preventative options. WHO have not recommended any medicinal product for the treatment of COVID-19 yet. The currently recommended and used therapeutics are supportive. Some repurposed anti-HIV and antiviral drugs are currently in use, including hydroxychloroquine, remdesivir, lopinavir/ritonavir, interleukin 6 (IL-6) receptor inhibitors, and plasma therapy [5–8].

Great hopes are set on the development of synthetic vaccines that affect the antibody synthesis and specifically interact with certain proteins of the virus. The issue of finding new methods for treatment of COVID-19 is pressing.

We have developed a new method based on the use of thermoheliox (inhalation of a high-temperature mixture of helium and oxygen – t-He/O₂).

Helium is an inert gas. It was discovered by *P.Janssen* and *N.Lockyer*, and both reported the discovery independently to the French Academy of Sciences in 1868. Academician *P.L.Kapitsa* played an important role in the study of the physicochemical properties of helium. He began his research during his internship in Rutherford laboratory in London (1938), and continued it in Moscow together with Academician *D.L.Landau* [9–13]. Both scientists were awarded the Nobel Prize for their research on the physical properties of helium.

The authors of this article have more than 20 years of clinical experience with heliox. Initially, we used a thermal helium-oxygen mixture in patients with hypoxemic respiratory failure, and then in patients with hypercapnic respiratory failure^{2,3}.

In the recent years, this experience has been used in a neurological clinic for the treatment of patients with ischemic stroke [14, 15] and in obstetrics to correct the oxygen status of pregnant women in the III trimester⁴.

¹ <https://news.mail.ru/story/incident/koronavirus>

² Kutsenko M.A. [Using an oxygen-helium mixture to treat acute respiratory failure in patients with an exacerbation of chronic obstructive pulmonary disease]: Thesis for a candidate degree in medical sciences. Moscow, 2000 (in Russian).

³ Shogenova L.V. [The efficacy of heliox therapy in patients with acute respiratory failure against an obstructive pulmonary disease]: Thesis for a candidate degree in medical sciences. Moscow, 2003 (in Russian).

⁴ Patent No.RU272750C1 registered in the Russian Federation as of November 08, 2019. Shuginin I.O., Panin A.A., Chuchalin A.G., Petrukhin V.A., Shidlovskaya N.V., Lysenko S.N. [A treatment method for pregnant women with placental insufficiency]. Available at: <https://patenton.ru/patent/RU272750C1> (in Russian).

Our clinical study was preceded by a theoretical analysis of the development of acute viral infection with an assessment of the potential therapeutic effects of t-He/O₂ inhalation. The kinetic model included a description of growth and reproduction of the virus in the human body, the viral damage to the recipient cells, the effects of thermal destruction of viruses, and the antibody response. Theoretical analysis predicted the potential effects of inhalation of t-He/O₂, i.e. the production of antibodies against the proteins of the destroyed viral particles [16]. The analysis of the protein composition of the patient's exhaled air condensate confirmed the safety of thermoheliox [17].

This article discusses the use of t-He/O₂ in the treatment of COVID-19.

Materials and methods

Study group. A single-center, randomized, prospective study included 60 patients with COVID-19. Patients were divided into two groups. Group 1 ($n = 30$) received the standard COVID-19 treatment protocol together with the t-He/O₂. Group 2 ($n = 30$) received the standard treatment in accordance with the clinical recommendations of the Ministry of Health of the Russian Federation "Prevention, diagnostics, and treatment of the novel coronavirus infection COVID-19" [version 5 (approved by the Ministry of Health of the Russian Federation on March 08, 2020), version 6 (approved by the Ministry of Health of the Russian Federation on April 28, 2020), version 7 (approved by the Ministry of Health of the Russian Federation on June 3, 2020)] [18]. Of the 60 patients included in the study, 28 (46.7%) were medical professionals. The male/female ratio was 17/13 in Group 1, and 16/14 in Group 2. The groups were matched by the sex ratio, $p = 0.403$. The median age of the patients was 56.7 years (45 to 61 years). The median age was 58 years (45 years; 59.5 years) in Group 1 and 55 years (46 years; 66 years) in Group 2. The groups were matched by age, $p = 0.537$. The general characteristics of the patients at the enrollment are shown in Table 1.

The clinical symptoms in Groups 1 and 2 are characterized in Table 2. The symptoms included: a loss of smell and taste, runny nose, shortness of breath, dyspnea, weakness, fever, headache, muscle pain, sore throat, and dry cough.

All patients who were enrolled in the study according to the protocol No.11 – 20 dated April 20, 2020, approved by the Ethics Committee on Biomedical Ethics of the N.V.Sklifosovsky Research Institute for Emergency Medicine of Moscow Department of Health received treatment for pneumonia caused by the SARS-CoV-2 virus from April 21 to June 2020 both inclusive.

The diagnostic procedures included specific molecular tests of the respiratory samples (throat and nasopharyngeal swab) (detecting amplifier CFX-96 REAL TIME, Bio-Rad, USA), lung CT scan, express analysis of the gas composition of arterial blood on an automatic analyzer ABL-500 (Radiometer Copenhagen, Denmark), measurement of serum IgM and IgG on an immunoche-

Table 1
General characteristics of patients in groups at the time of inclusion in the study

Таблица 1
Общая характеристика пациентов на момент включения в исследование

| Parameter | Group 1 (n = 30) | Group 2 (n = 30) |
|--|----------------------|---------------------|
| Age, years | 56 [45; 59.5] | 52 [46; 66] |
| Sex, male/female | 17/13 | 16/14 |
| Duration of the disease, days | 2 [1; 4] | 3 [1; 5] |
| Respiratory rate, min ⁻¹ | 25.9 [22; 28] | 24.9 [20; 27] |
| Heart rate, min ⁻¹ | 110.6 [89.3; 122.1] | 115.2 [91.7; 128.4] |
| SpO ₂ , % | 94 [88; 96] | 93 [87; 95] |
| Positive PCR for coronavirus, n | 30 | 30 |
| CT signs of pneumonia (lesion volume in %) | 25.2 [21; 42.5] | 26 [25; 41.7] |
| NIV / high flow oxygen therapy, n | 24 | 23 |
| D dimer, ng/mL | 358 [270; 387] | 354 [294; 432] |
| C-reactive protein, mg/L | 65.1 [45.2; 75.6] | 62.1 [39.1; 67.4] |
| Ferritin, mg/L | 568.8 [423.2; 620.8] | 602.8 [529.4; 75.3] |
| Lymphocytes, % | 15.4 [12.8; 23.2] | 17.2 [14.7; 28.1] |
| AST, U/L | 35.4 [30.2; 49.1] | 34.2 [28.9; 43.5] |
| ALT, U/L | 38.1 [34.1; 42.1] | 36.2 [32.1; 39.2] |
| Immunoglobulin IgM, COI | 0.8 [0.62; 3.21] | 1.2 [0.79; 3.18] |
| Immunoglobulin IgG, U/mL | 16.5 [12.2; 22.1] | 17.1 [15.1; 25.1] |

Note: SpO₂, saturation of hemoglobin with oxygen; PCR, polymerase chain reaction, CT, computed tomography of the lungs; AST, aspartate transaminase; ALT, alanine aminotransferase. The quantitative data are presented as median (lower and upper quartiles).

Примечание: количественные данные представлены как медиана (нижний – верхний квартиль).

miluminescent analyzer (Mindray 6000, USA), complete blood count, analyses of serum markers (D-dimer, C-reactive protein [CRP], ferritin, lymphocytes, aspartate aminotransferase, AST, and alanine aminotransferase, ALT).

All patients had a positive test of SARS-CoV-2 coronavirus RNA, the ground-glass opacities in the lung CT, and the areas of air space consolidation.

The inclusion criteria were:

- Age > 18 years;
- Positive RNA test of SARS-CoV-2 coronavirus
- CT signs of viral pneumonia (CT1, CT2);
- Oxygenation index ≥ 150 according to the Berlin classification;
- Increased CRP and ESR.

Table 2
General characteristics of clinical symptoms in group 1 and 2; n

Таблица 2
Общая характеристика клинических симптомов у пациентов 1-й и 2-й групп; n

| Symptoms | Group 1 (n = 30) | | Group 2 (n = 30) | |
|-------------------------|------------------|----|------------------|----|
| | yes | no | yes | no |
| Loss of smell and taste | 27 | 3 | 25 | 5 |
| Runny nose | 25 | 5 | 24 | 6 |
| Shortness of breath | 28 | 2 | 27 | 3 |
| Dyspnea | 28 | 2 | 27 | 3 |
| Weakness | 26 | 4 | 25 | 5 |
| Fever | 29 | 1 | 30 | 0 |
| Headache | 24 | 6 | 29 | 1 |
| Muscle pain | 25 | 5 | 29 | 1 |
| Sore throat | 27 | 3 | 25 | 5 |
| Dry cough | 28 | 2 | 28 | 2 |

The exclusion criteria were:

- an oxygenation index < 150;
- mechanical ventilation;
- severe impairment of consciousness (score on the Glasgow scale less than 10);
- unstable hemodynamics (systolic blood pressure < 90 mm Hg, heart rate < 50 min or > 160 min);
- hemoglobin < 115;
- profuse sputum secretion;

- vomiting that interfered with the use of masks;
- acute cerebrovascular accident (ACV);
- acute myocardial infarction (AMI) within the last 6 months, and pregnancy.

Study design

All patients underwent swabs from the mucous membrane of the nasal cavity and oropharynx to detect SARS-CoV-2 coronavirus RNA; sampling of venous blood for IgG (semiquantitative) and IgM (semiquantitative) antibodies of SARS-CoV-2 coronavirus by the standard enzyme immunoassay method, for CPB, D-dimer, ferritin, lymphocytes, AST, and ALT levels. Schedule of the examinations is presented in Table 3. The study design is shown in Figure 1.

Treatment with gas mixtures

The t-He/O₂ therapy was performed on the Heliox-Extreme apparatus (LLC Medtekhinnovatsii Russia, medical device code: 944460 (TU 9444-001-0116489960-2915)) through separate oxygen and helium ports. Oxygen was supplied from a centralized hospital oxygen distribution system. Medical helium “A” from a 10-liter metal cylinder under a pressure of 200 atm through a 15 atm pressure regulator (GCE, China). In this work, we used medical helium grade “A” (99.995%; TU 20.11.11-005-45905715-2017, NII KM, RF). The apparatus was mixing two gases (helium and oxygen) in accordance with the specified concentrations. Then the mixture of He and O₂ through the breathing filter Inter-Guard™ (Intersurgical Ltd, UK) and the Flextube hose (Intersurgical Ltd, UK) was fed into the thermistor of the Heliox-Extreme apparatus, which was connected to the exhalation valve (Intersurgical

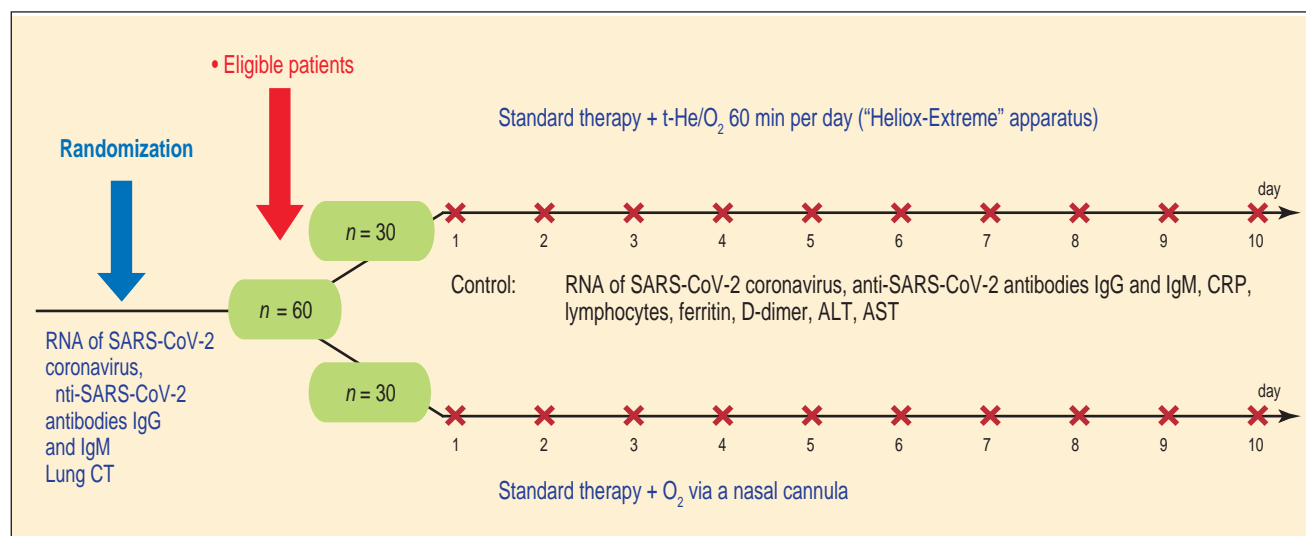


Figure 1. The design of the study (randomized simple comparative) in parallel group (n = 60)
Note: t-He/O₂, thermal helium-oxygen mixture; Ig, immunoglobulin; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CT, computed tomography.

Рис. 1. Дизайн исследования (рандомизированное простое сравнительное) в параллельных группах (n = 60)

Table 3
Monitoring interval by day in the study groups
Таблица 3
Интервал мониторинга по дням в исследуемых группах

| Parameter | Screening/Randomization | Day | | | | | | | | | |
|--------------------------|-------------------------|-----|---|---|---|---|---|---|---|---|----|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| PCR | + | + | + | + | + | + | + | + | + | + | + |
| Immunoglobulin IgG, U/mL | + | | | + | | | | | + | | + |
| Immunoglobulin IgM, COI | + | | | + | | | | | + | | + |
| CRP, mg/L | + | + | + | + | + | + | + | + | + | + | + |
| D dimer, ng/mL | | + | | + | | | | | + | | + |
| CRP, mg/L | | + | | + | | | | | + | | + |
| Ferritin, mg/L | | + | | + | | | | | + | | + |
| Lymphocytes, % | | + | | + | | | | | + | | + |
| AST, U/L | | + | | + | | | | | + | | + |
| ALT, U/L | | + | | + | | | | | + | | + |

Note: PCR, polymerase chain reaction; Ig, immunoglobulin; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Ltd, UK) and the facial anesthetic mask QuadraLite (Intersurgical Ltd, UK).

The patients underwent 4 daily inhalation procedures for 15 minutes with 15-minute intervals. The concentration of He and O₂ was selected individually for each patient in the range from 79 to 50% (He) and from 21 to 50% (O₂) to maintain SpO₂ within 97 – 99% at temperatures from 75 to 96 °C, depending on the saturation index, tidal volume, and the patient comfort.

At SpO₂ ≥ 93%, the inhalation of t-He/O₂ started with 79% He and 21% O₂ at a temperature of 85 – 96 °C with a gradual increase in O₂ fraction by 2% every minute until the target SpO₂ 97 – 99%.

At 85 ≤ SpO₂ ≤ 92%, the inhalation of t-He/O₂ started with 70 He and 30% O₂ at a temperature of 85 – 96 °C with a gradual increase in O₂ fraction by 2% every minute until the target SpO₂ 97 – 99%.

At SpO₂ < 85%, the inhalation of t-He/O₂ started with 65% He and 35% O₂ at the temperature of 75 – 84 °C with a gradual increase in O₂ fraction by 2% every minute. The O₂ fraction did not exceed 50%, i.e. the ratio of helium and oxygen not more than 50 : 50% while maintaining SpO₂ 97 – 99%.

The maximal allowed tidal volume (TV) was 1,000 mL. If the TV was more than 1000 ml, we interrupted the breathing cycle from the circuit of the apparatus and the patients made one or two breaths of an air mixture with FiO₂ 21%. Then, the face mask was put back on, and breathing with t-He/O₂ was continued with the same concentration of He and O₂. SpO₂ was monitored using an OxyShuttle pulse oximeter (Sensor Medics, USA). The TV was monitored with a monitor built into the Heliox-Extreme apparatus.

Statistical analysis

The statistical processing of the data was carried out using the SPSS 17.0 software package (SPSS Inc., USA). The quantitative parameters are presented as median (Me) and quartiles (lower and upper quartiles). The nonparametric

statistic methods with Mann–Whitney U-test were used to compare the variables between the groups. Friedman rank analysis of variance followed by paired comparison with the Wilcoxon test was used to assess the changes over time in each group. The differences were considered statistically significant at $p < 0.05$.

Results

No patients had any objective procedure-related side effects during the inhalation therapy with t-He/O₂. One patient refused inhalation therapy on Day 2 because he did not tolerate the fever well. From that moment on, 29 patients in Group 1 and 30 patients in Group 2 continued the therapy. None of the patients were transferred to mechanical ventilation. There were no lethal outcomes in both groups. All patients were discharged. The median hospital stay was 15 (13,35) [12,7; 34,6] days.

Changes of the PCR results over time. Group 1 showed statistically significant decrease in positive RNA tests for the SARS-CoV-2 coronavirus. According to our observations, most COVID-19 patients from Group 1 who received inhalation of t-He/O₂ had a negative PCR on Day 3 and some patients had a negative result as early as 1 day after the start of therapy. The patients in the standard therapy group has a positive test for the viral antigen from 7 days to 4 weeks from the onset of the disease, in some cases even longer (Figure 2).

Changes in the D-dimer test results over time. Group 1 showed a statistically significant decrease in the D-dimer level on Day 3 as compared to Day 7 in the Group 2. The change of D-dimer level within 10 days was significantly higher in the Group 1 (Figure 3).

Changes in the ferritin level over time. The ferritin level stayed high in both groups. The statistically significant decrease in the ferritin level was observed on Day 7 and Day 10 (Figure 4).

Changes in the CRP level over time. The standard therapy group kept a statistically significant increase in CRP on Day 3 and the statistically significant decrease on

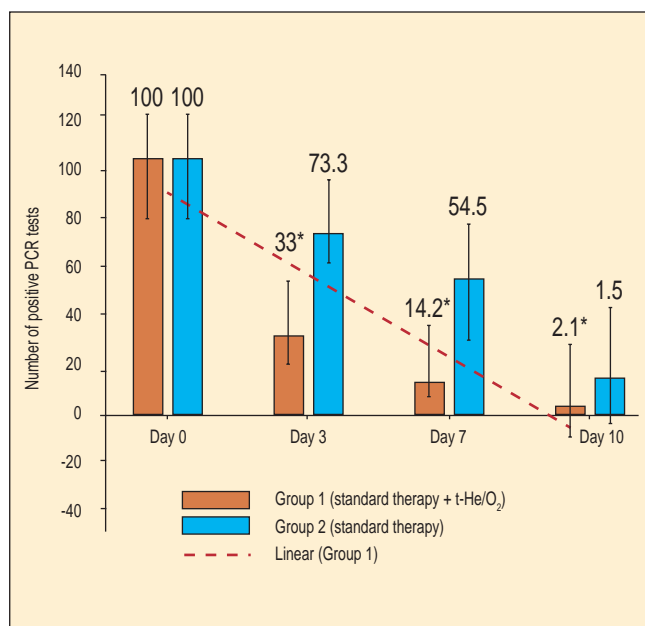


Figure 2. Number of the positive polymerase chain reaction tests in comparison groups

Note: PCR, polymerase chain reaction; t-He/O₂, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 2. Количество положительных тестов при проведении анализа методом полимеразной цепной реакции в группах сравнения
Примечание: * – $p < 0,05$.

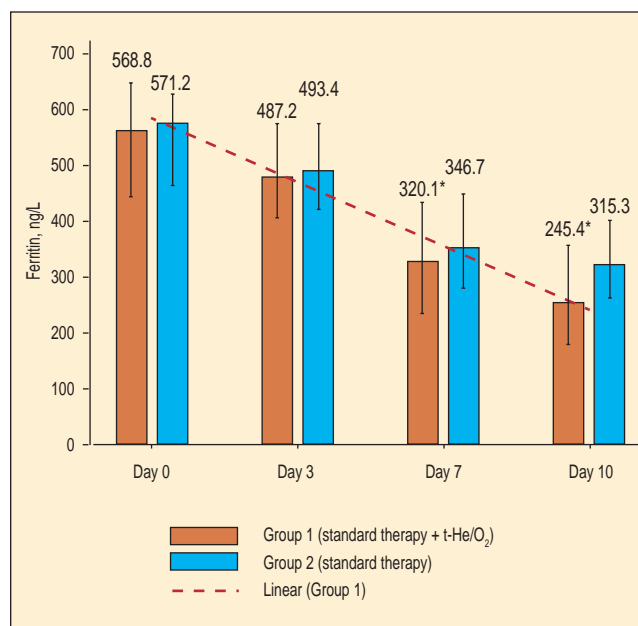


Figure 4. Dynamics of the ferritin indicator in comparison groups

Note: t-He/O₂, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 4. Динамика изменения уровня ферритина в группах сравнения
Примечание: * – $p < 0,05$.

Day 7 and Day 10. Group 1 showed a statistically insignificant increase in CRP on Day 3. The decrease in CRP level on Day 7 and Day 10 in Group 1 was statistically significant as compared to Group 2 (Figure 5).

Changes in lymphocyte levels over time. Low lymphocyte levels were reported in Groups 1 and 2 at baseline. The addition of t-He/O₂ to the complex therapy made it possible to significantly increase the level of lymphocytes

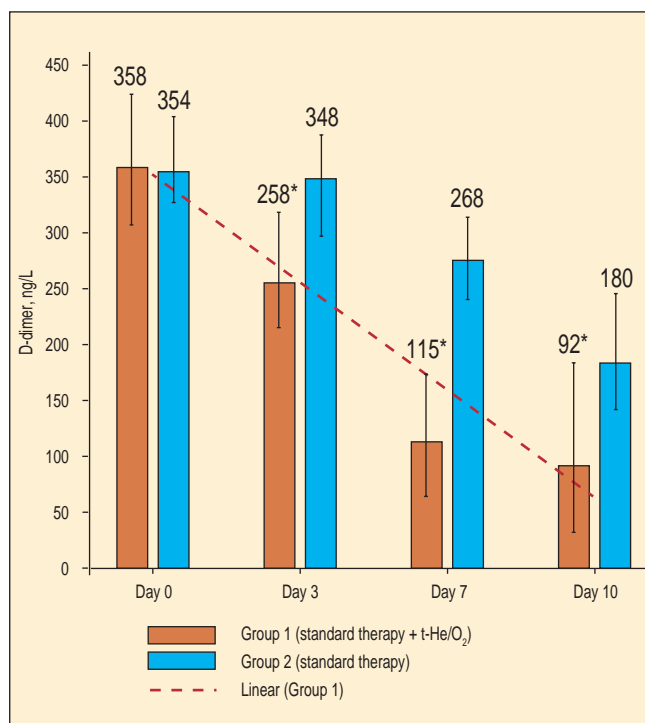


Figure 3. Dynamics of the D-dimer indicator in comparison groups

Note: t-He/O₂, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 3. Динамика изменения уровня D-димера в группах сравнения
Примечание: * – $p < 0,05$.

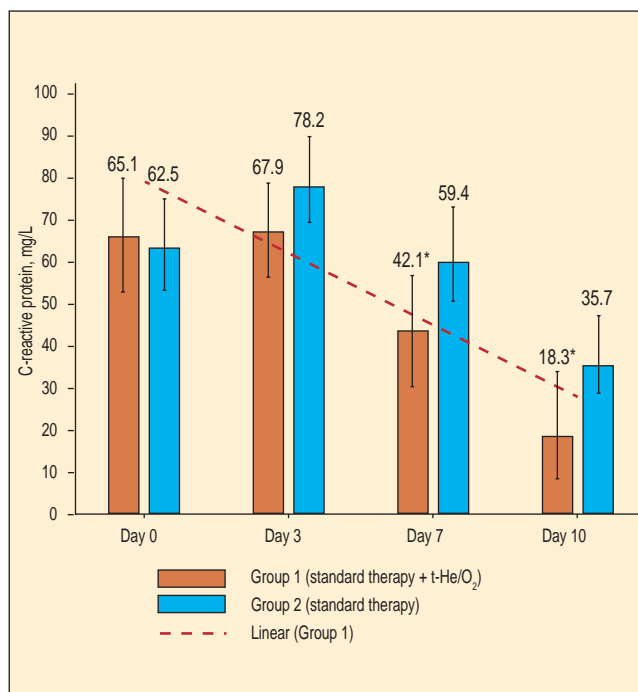


Figure 5. Dynamics of the DRR indicator in comparison groups

Note: t-He/O₂, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 5. Динамика изменения уровня С-реактивного белка у пациентов групп сравнения
Примечание: * – $p < 0,05$.

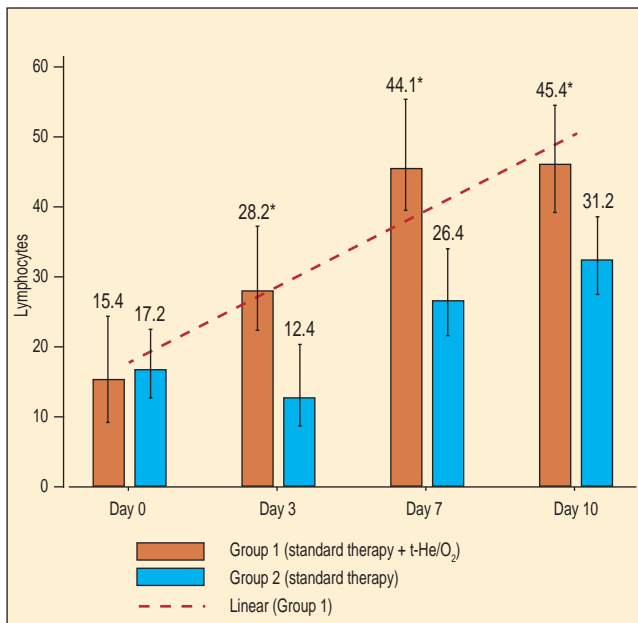


Figure 6. Dynamics of lymphocytes in the comparison groups
Note: t-He/O₂, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 6. Динамика изменения уровня лимфоцитов в группах сравнения
Примечание: * – $p < 0,05$.

in the Group 1 on Day 3 and to achieve full recovery on Day 7. Group 2 showed a statistically significant decrease in lymphocyte level on Day 3 as compared to the baseline. The lymphocyte level increased significantly on Day 3 and Day 7, but the growth was significantly lower than in Group 1 (Figure 6).

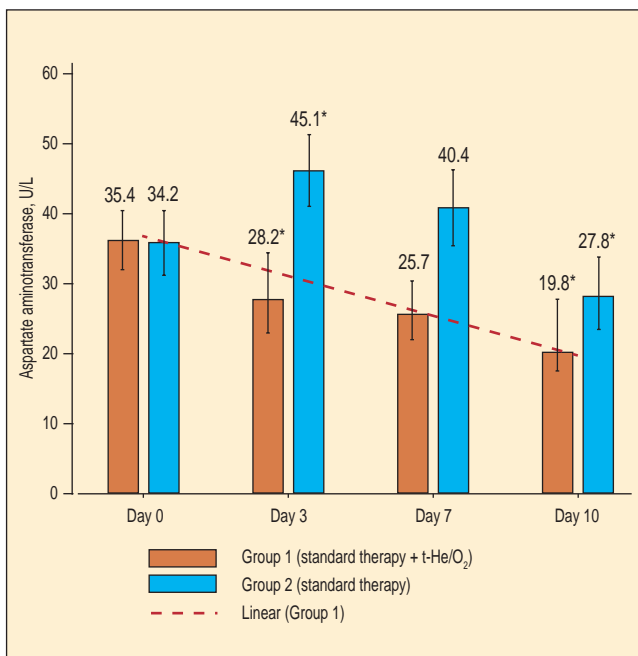


Figure 7. The dynamics of aspartateaminotransferase in the comparison groups
Note: t-He/O₂, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 7. Динамика изменения уровня аспаратаминотрансферазы в группах сравнения
Примечание: * – $p < 0,05$.

Changes in ASTs over time. High AST levels were reported in Groups 1 and 2 at baseline. Group 1 showed a statistically significant decrease in AST level on Day 3 and a continued decrease on Days 7 and 10. Group 2 showed an increase in AST on Day 3, and the difference from the baseline was statistically significant. The AST level dropped on Days 7 and 10, but a lesser extent than in Group 1 (Figure 7).

Changes in ALT levels over time. High ALT levels were reported in Groups 1 and 2 at baseline. Group 1 showed a statistically significant decrease in ALT level on Day 3 and a continued decrease on Days 7 and 10. Group 2 showed a continued growth of the ALT level on Day 3. The ALT level decreased on Day 3 and 7 but it was still significantly higher than the baseline. The ALT level decreased on Days 3 and 7 but to a lesser extent than in Group 1 (Figure 8).

Changes in IgM levels over time. The immune response was confirmed in both groups at baseline. The immune response showed a statistically significant peak on Day 7 and decreased by Day 10 in Group 1. Meanwhile, Group 2 showed the peak immune response on Day 10 (Figure 9).

Changes in IgG levels over time. Group 1 had a statistically significant increase in IgG levels on Day 3 of the t-He/O₂ therapy and a continued significant growth on Days 7 and 10. The Group 2 had a statistically insignificant increase in IgG levels on Days 3 and 7 of the standard therapy. The statistically significant increase in the IgG levels was reported on Day 10 as compared to the baseline. The increase in the IgG levels on Days 3, 7, and 10 in Group 1 was significantly higher than in Group 2 (Figure 10).

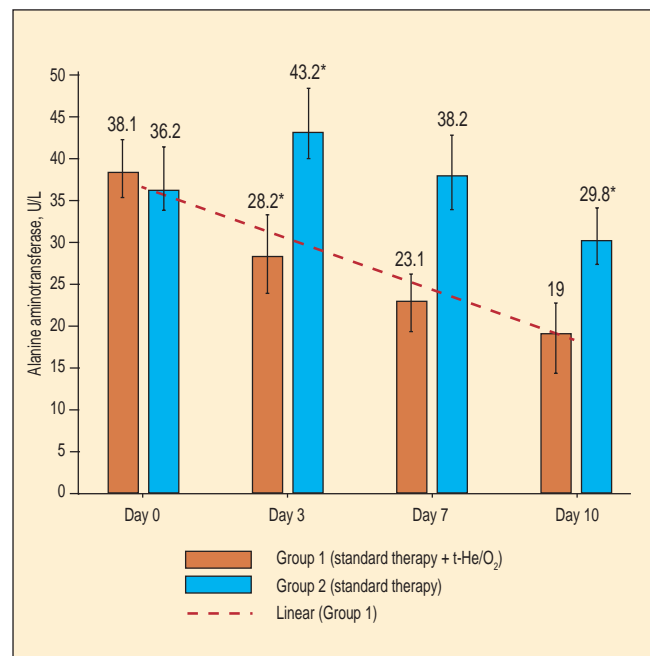


Figure 8. The dynamics of alanineaminotransferase in the comparison groups
Note: t-He/O₂, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 8. Динамика изменения уровня аланинаминотрансферазы в группах сравнения
Примечание: * – $p < 0,05$.

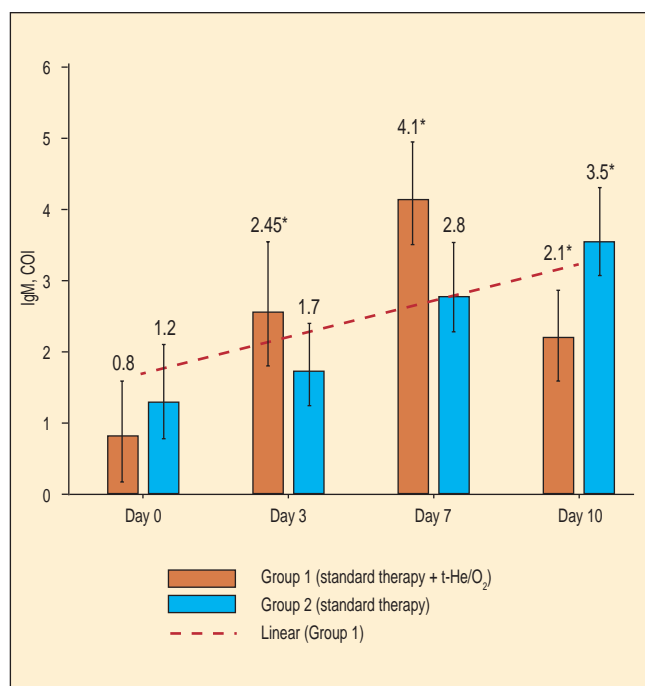


Figure 9. The dynamics of IgM in the comparison groups
Note: t-He/O₂, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 9. Динамика изменения уровня IgM в группах сравнения
Примечание: * – $p < 0,05$.

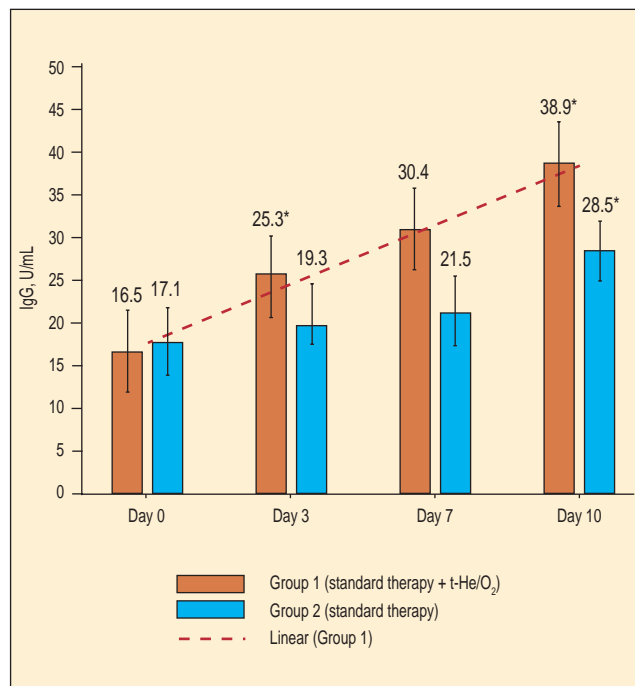


Figure 10. The dynamics of IgG in the comparison groups
Note: t-He/O₂, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 10. Динамика изменения уровня IgG в группах сравнения
Примечание: * – $p < 0,05$.

Discussion

The findings demonstrate that the full-size viral particles detected by PCR are eliminated by days 2 – 3 of t-He/O₂. The antibody production is continued, apparently, as a response to the protein products of the thermal destruction of the virus. The use of t-He/O₂ stimulates the synthesis of IgM and IgG from the first procedure. 60% of patients in Group 2 that did not receive the t-He/O₂ inhalations, had almost no IgM and IgG antibodies during the first three days. Antibody synthesis begins on the second or third day after the induction period.

The changes in the IgG and IgM levels over time clearly demonstrate that t-He/O₂ leads to activation of the immune system and stimulates production of specific antibodies in patients with the coronavirus infection.

The immune response is complex and involves various biochemical systems. In particular, CRP is considered one of the components of a complex chain of biochemical processes and one of the first respondents to bacterial and viral infections. We compared the changes in the accumulation and reduction of CRP in the course of standard treatment and treatment with t-He/O₂ inhalations. A significant difference in the response was found.

A relatively slow accumulation of CRP occurs in the typical course of the disease. In most cases, the CRP level reaches maximum on Days 2 – 4 of treatment. The CRP level decreases as the treatment is continued. In our study, inhalations with t-He/O₂ stimulate the rapid accumulation of CRP with the subsequent exponential decrease in the level of CRP.

Stimulation of the immune response with t-He/O₂ can be defined as “thermal vaccination”. Our study showed that the full-size viral particles detected by PCR are eliminated by Days 2 – 3 of t-He/O₂. Apparently, the antibody production is continued as a response to the protein products of the thermal destruction of the virus. A “classical” vaccination with a weakened or destroyed antigen takes place. The fundamental positive difference is that the process takes place in vivo with the participation of natural viral proteins, and the “thermal vaccination” can have a wide-range specificity.

The mechanism of the observed effect of stimulation of the immune response with t-He/O₂ requires further research. The kinetic model that was developed and evaluated by us² [13] explains the observed effects by an increase in the antigen concentration during thermal destruction of the virus.

Conclusion

The addition of thermal inhalation of a gas mixture of helium and oxygen (t-He/O₂) to the standard therapy of patients with the infectious disease caused by SARS-CoV-2 and with CT signs of COVID-19 pneumonia (CT1, CT2 grades) reduces the viral load by stimulating both IgG and IgM antibody production. This effect of “thermal vaccination” increases the effectiveness of treatment and reduces the markers of inflammation. We are currently studying the response of patients with the CT3 signs of pneumonia to t-He/O₂. The intermediate results demonstrate a positive effect in the critically ill patients. The results require further research and statistical analysis.

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Received: September 07, 2020

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Поступила 07.09.20

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