



Research Article

On the possibility of using hyperbaric oxygenation in the treatment of sars-cov-2 infected patients

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Received: 08 October, 2020

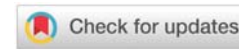
Accepted: 18 November, 2020

Published: 19 November, 2020

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Keywords: Hyperoxia; COVID-infection; Treatment; Mechanisms

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Abstract

The article substantiates the feasibility of including Hyperbaric Oxygenation (HBO) in the treatment of patients infected with SARS-CoV-2. Possible mechanisms of therapeutic influence of hyperbaric oxygen on the course of the pathological process in the body of patients infected with SARS-CoV-2 are considered. The role of urea as a non-specific antioxidant adaptogen in the mechanisms of the therapeutic effect of HBO is considered. The important role of assessing the patient's condition at the time of oxygenation for the correct choice of modes and the number of HBO sessions is shown. It is concluded that it is appropriate to include in the therapy of SARS-CoV-2 infected patients with "soft" HBO regimens (1.3-2.0 ATA, isopression time 45-90 min), regardless of the degree and duration of hypoxemia.

Against the background of the pandemic of a new coronavirus infection caused by SARS-CoV-2, which has engulfed our planet, the lack of an effective etiotropic method of treatment for this pathology has predetermined a high mortality rate among those infected. One of the leading causes in the pathogenesis of this infectious disease is the development of hypoxia in the patient's body. The formation of this pathological process in an organism infected with SARS-CoV-2 follows several mechanisms. First, as a result of the development of an inflammatory process in the lung tissue, leading to a violation of the diffusion of oxygen through the alveolocapillary membrane. Secondly, due to a violation of the oxygen transport function of hemoglobin, caused by exposure to viral proteins. Thirdly, it is a violation of microcirculation due to the formation of microthrombi in the capillaries. The combination of these factors explains the low effectiveness of normobaric oxygen therapy, including invasive lung's ventilation, used for hypoxemia caused by COVID-associated pneumonia.

Meanwhile, in the world of medical science, there has long been a method for effective treatment of severe hypoxic conditions, including those caused by pulmonary pathology. This is hyperbaric oxygenation (HBO), i.e. treatment with oxygen under high pressure. Why has there not been a proper place in the treatment of SARS-CoV-2 coronavirus infection?

This is due to the fact that most doctors have an idea about the toxicity of high concentrations of oxygen to the cell [1,2], which is reflected in the latest European Handbook to hyperbaric medicine [3]. This does not take into account the fact that in many studies, the ability of hyperbaric oxygen to activate free radical processes and lipid peroxidation, Deplete the body's antioxidant system, was found in HBO modes not used in the clinic [4,5]. This concerns the inadequacy of the time chosen by researchers to safely find the body in hyperoxia, which negatively affects the antioxidant system of the lungs [6].

Experiments have shown that the use of HBO in a therapeutic mode (2 hours, 50 minutes), daily for 18 days does not cause depletion of the enzyme and metabolic links of the antioxidant system in the lungs of rats [7]. Similar data were obtained in the study of phylogenetically dissimilar structures of the rat brain after the course use of HBO in a similar mode [8]. It was found that a single application of HBO in a therapeutic mode (1.5 ATA, 60 min) significantly increases the stability of the pulmonary alveoli, regardless of the age of the animal [10]. However, the research of P. I. Koshelev, et al. [9], which studied the influence of various modes of HBO course application on the structural organization of lung tissue in rabbits with experimental abscess, is of particular interest. The animals received a course of 8-13 sessions of HBO in the mode 2 ATA, 45 min. The difference was only in the number



of daily sessions: in the first group—once a day, in the second group 2 times a day, in the third group—3 times a day. All the animals underwent HBO sessions satisfactorily. However, morphological research has established, that the optimal mode that does not lead to destructive changes in the healthy part of the lung against the background of a pronounced therapeutic effect of HBO in the affected area of the lung is a course of 8 sessions of HBO in the mode of 2 hours, 30–45 minutes, 1 session per day. In other cases, HBO had a destructive effect on the lung tissue, the degree of which was directly dependent on the number of HBO sessions [9]. Experimental studies served as the basis for the successful use of HBO by Soviet doctors in patients with suppurative lung pathology [11–13]. Later it was shown that the addition of HBO (2.5). 90 min, twice a day, the average number of HBO sessions was (23 ± 11) to treat 13 patients with anaerobic pleuropulmonary infection revealed *"an impressive clinical effect of HBO» (D.Mathieu): 12 patients survived, one patient died of disseminated candidiasis three weeks after the end of the course of HBO, but her lung abscess resolved [3].*

The inclusion of HBO (1,3–1,6 ATA, 30 min) in the complex treatment of patients with pulmonary tuberculosis found that *"despite the fact that a number of laboratory parameters after HBO returns to their original values, a new condition occurs in the body after oxygenation, which is characterized by an improvement in overall health, normalization of sleep, and the disappearance of shortness of breath» [14].* This is an example of a hyperoxic condition state of organism, which is one of the biological effects of hyperoxia [15], it is based on the formation of new functional systems that increase the sanogenesis potential of the sick body in conditions of super-saturation of the body with oxygen [16]. The inclusion of the course (9 ± 1.3 session) LPG (1,3 ATA) in complex treatment of patients with chronic obstructive pulmonary disease revealed the ability of hyperbaric oxygen to reduce the severity of respiratory failure, increase exercise capacity, improve the quality of life and social adaptation of this category of patients [17].

The above data show that HBO 1,3–2,5 ATA does not have a negative effect on the antioxidant system of a healthy lung and a diseased lung, does not cause destructive changes in the lung tissue with the correct choice of HBO regimens and the number of sessions during its course use. This leads to the conclusion that it is possible to include HBO in the treatment of patients with COVID-19-associated pneumonia. However, it is necessary to determine the indications for its use of HBO in patients with COVID-19, as well as in the modes of oxygenobarotherapy.

We should immediately note that the inclusion of HBO in the therapy of SARS-CoV-2 infected patients solely as a means of eliminating hypoxemia initially narrows our understanding of the possibilities of hyperbaric oxygen in this pathology. The fact is that hyperbaric oxygen, used for therapeutic purposes in conditions of pathology, acts not so much as an antihypoxic factor, but as an adaptogenic regulator of metabolic processes occurring in the patient's body [18]. At the same time, the mechanisms of adaptation to hyperoxia, fixed in the process of evolution, are triggered, which is manifested by an increase

in the sanogenic potential of the sick organism, leading to its recovery [18]. Due to this, the therapeutic effect of HBO is preserved in the post-hyperoxic period even in the conditions of " reversion " of hypoxia [19–21].

According to Leonov's doctrine of hyperoxic sanogenesis [22], oxygen, appearing millions of years ago in the atmosphere, acted as a pathogen for anaerobic life forms that existed at that time, giving them one choice: to adapt to new conditions or die. As a result the creation of new oxygen dependent forms of life began through the adaptive and hereditary variability of previous biological formations. At the same time, they gradually acquired the reactive ability to respond in aerobic conditions to any external and internal stimulus with standard adaptive acts; stereotypical metabolic, functional and structural changes. Atmospheric oxygen has become an active participant in the process of natural selection genetic programs of adaptation of eukaryotic cells with the maximum probability of survival of the organism [22]. As a result, in the course of evolution, which took place during the gradual saturation of the Earth's atmosphere with oxygen, stereotypical reactions of their cells and functional – metabolic systems to super-saturation with oxygen were formed and fixed in the "genetic memory" of organisms which ensure not only its safe presence in a hyperoxic environment, but also increase its resistance to pathogenic factors [22,23].

One of these reactions is hyperoxic dilation of the pulmonary vessels, which formed and became fixed in mammals in the course of evolution [24]. At the same time oxygen free radicals play an important role in dilatation of pulmonary vessels (Figure 1). here is every reason to say that hyperoxic dilation of the pulmonary vessels, as a universal reaction of the body's adaptation to hyperoxia, can serve as one of the arguments in favor of including HBO in the treatment of COVID-associated pneumonia, which, as is known, can be accompanied by the development of pulmonary hypertension.

AOS – antioxidant system, AT II – angiotensin II, OR – Oxygen radicals, Pg – простгландины, vdPg – vasodilating prostoglandins vcPg – vasoconstrictor prostoglandins. Bold arrow – mechanism of formation polyperoxides dilatation of pulmonary arterioles [24].

Meanwhile, hyperbaric oxygen still has properties that allow us to recommend its use in SARS-CoV-2-infected patients. First, it is the ability of HBO to regulate the formation of pro-inflammatory cytokines IL-1, TNF- α and IL-6 [24], which are endogenous pyrogens and cause tissue destruction. This allows us to expect in oxygenated patients infected with SARS-CoV-2, both an abortive course of fever and a decrease in destructive processes, primarily in the tissues that are targets of the coronavirus.

Secondly, the ability of HBO to stimulate the formation and retention of a natural endogenous adaptogen-urea antioxidant in the patient's body against the background of stimulation of diuresis [25,26]. As a result, the content of urea in the lung tissue, as well as in the blood, increases with HBO [7,25] By stabilizing the lysosome membrane under hyperoxia, urea

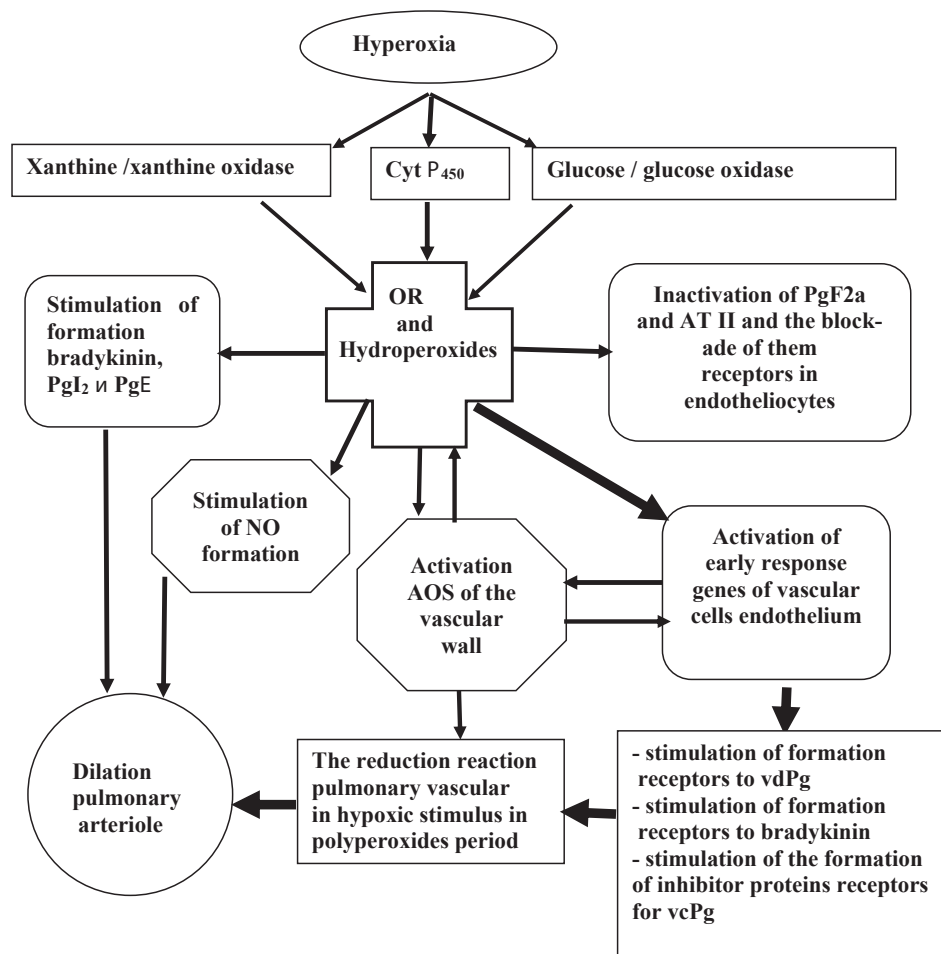


Figure 1: Mechanism of participation of reactive oxygen species (ROS) and hydroperox-ides in hyperoxic dilatation of pulmonary vessels in a healthy adult body

reduces their permeability to lysosomal enzymes [28], thereby preventing cell autolysis. This is especially important in the post-hyperoxic period, when there may be a "reversion" of hypoxia. By inhibiting radical formation on iron-containing blood proteins, urea simultaneously increases its antioxidant potential [29]. Forming a complex compound with heparin, urea prolongs the physiological action of the latter [30]. If we add to this the ability of HBO to disaggregate platelets in experimental DIC-syndrom [31], there is every reason to expect a similar effect of HBO when it is included in the therapy of SARS-CoV-2 - infected patients, given the high risk of developing thrombotic complications in them. In mammals, urea is easily converted from a free state to a protein- and lipoprotein-bound state [27], which is activated in hyperoxia [28]. Therefore, it cannot be excluded that activation of this process by hyperbaric oxygen in epithelial cells, including pneumocytes, which are targets of SARS-CoV-2, will lead to certain changes in the physical and chemical properties of their membranes. This will manifest itself as an inhibition of exocytosis of the virus inside the cell, and a change in the conformation of the receptors located on its surface, which will lead to a decrease in their affinity for the S1 SARS-CoV-2 spike protein. At the same time the possibility of urea at elevated concentrations in the medium to enter into reversible binding with the angiotensin converting enzyme 2 (ACE 2) receptor is

not excluded. The possibility of such reversible binding of urea has been demonstrated in other proteins and enzymes [28,32]. The proposed mechanisms of the sanogenic effect of urea in HBO therapy of SARS-CoV-2 infected patients are shown in Figure 2.

Third, we should not discount the ability of hyperbaric oxygen to stimulate the T-cell link of the immune system, both by directly affecting the functional activity of lymphocytes [33] and by stimulating their formation [34]. The latter is important in the conditions of lymphopenia that develops with COVID infection. The experiment demonstrated the ability of HBO to increase the survival rate of mice with experimental tick-borne encephalitis [35].

The ability of HBO to change the pharmacodynamics and pharmacokinetics of drugs [36] does not exclude a reduction in the background of HBO therapy of side effects of antiviral drugs used in the treatment of COVID-19, as well as an increase in their antiviral action. It cannot be excluded that conformational changes in the hemoglobin molecule observed in HBO [22] will interfere with the effect of viral proteins on it, and adaptive morphogenetic changes occurring in the erythrocyte membrane in HBO [22] will determine the decrease in its permeability to the virus. The ability of HBO to increase

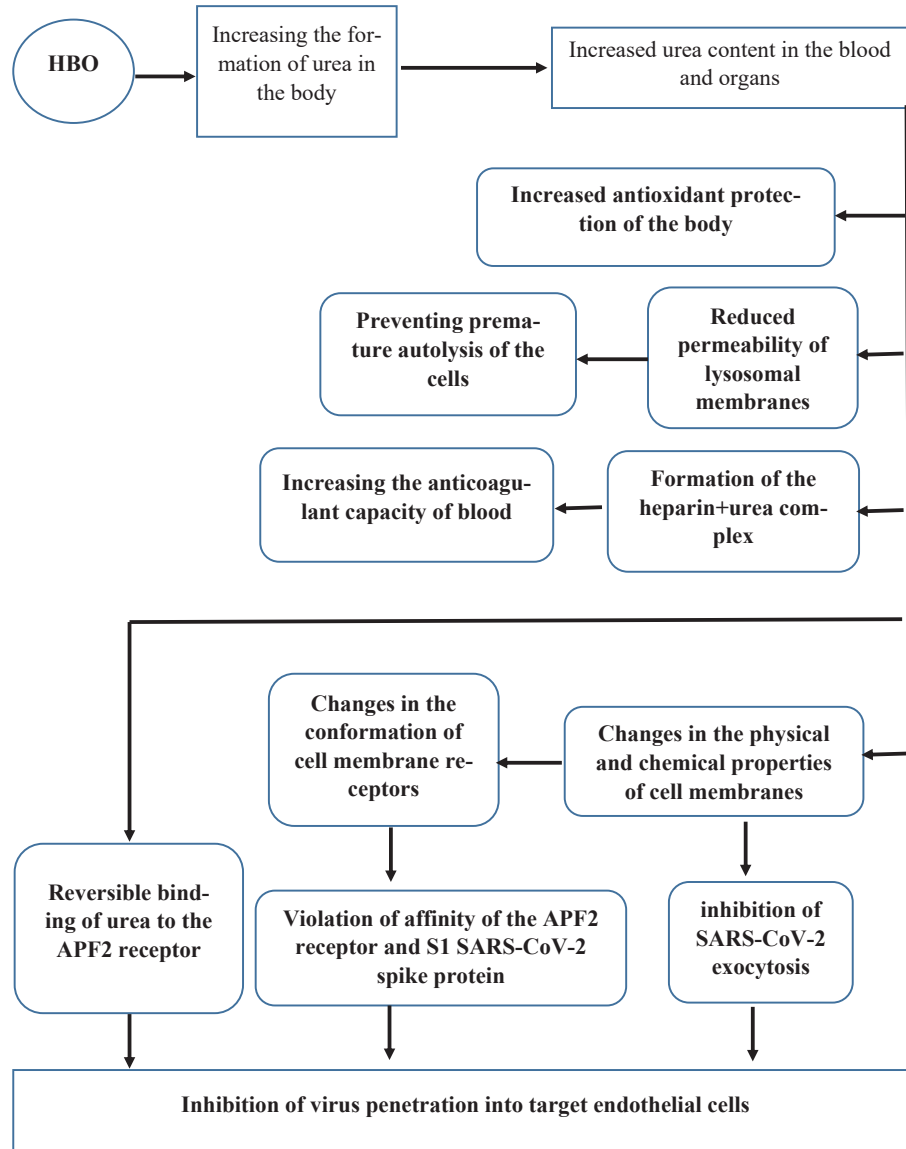


Figure 2: Suggested mechanisms of implementation of some therapeutic effects of hyper-baric oxygen in SARS-CoV-2-infected patients with urea.

the breadth of therapeutic action of antibiotics [37], have a bacteriostatic effect on *Staphylococcus aureus*, *Proteus* [38], increase the sensitivity of microbes to antibiotics and reduce the seeding of pathogenic microflora from the blood [39] this makes it possible to use HBO in the case of bacterial infection in patients with COVID-associated pneumonia.

Based on the above, we can conclude that it is appropriate to include in SARS-CoV-2 therapy infected patients in "soft" HBO regimens (in 1.6–2.0 ATA, isopression time 45–90 min), infection regardless of the degree and duration of hypoxemia. The latter should be taken into account only when choosing the atmospheric pressure of the pressure chamber and the time of isopression. The fact is that hyperoxia (as well as hypoxia) stimulates free radical processes in the body, which activate all three links of antioxidant protection, formed and fixed in the process of evolutionary transformation of the atmosphere from an oxygen-free to an oxygen environment [22]. Therefore, the more severe hypoxemia, and therefore tissue hypoxia, at the

time of oxygenation, the more likely the risk of depletion of one or all of the links of this system. This is especially important for patients with comorbidities (diabetes, heart failure), who already have "problems" with the body's antioxidant system. Therefore, the use in these conditions, automatic in "hard" mode or "soft", but a long time isopress (90 min), as well as unjustified increase in the number of HBO sessions creates the risk of negative effects of hyperoxia on the patient's body. In the end, this will lead to discrediting HBO as one of the components of COVID-associated pneumonia therapy. To avoid this, the use of HBO should occur only when the patient's body is "ready to perceive hyperbaric oxygen as a therapeutic factor" [16]. This implies an important role period before the beginning of HBO as in the assessment of the patient's condition at the moment of oxygenation in order to select modes HBO, as well as the decision on the use of oxygenated patients with prescribed medications and (or) medical procedures before or after hyperoxic exposure.



Hyperbaric oxygenation is not a panacea! However, in the capable hands of a doctor, as many years of experience shows, it is the "saving straw" that pulls the seemingly hopeless patient out of the strong embrace of death.

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Citation: Savilov P (2020) On the possibility of using hyperbaric oxygenation in the treatment of sars-cov-2 infected patients. J Surg Surgical Res 6(2): 160-165.
DOI: <https://dx.doi.org/10.17352/2455-2968.000122>