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Hyperbaric oxygenation for resuscitation and therapy of elderly patients with cerebral and cardio-respiratory dysfunction

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1. ABSTRACT

Hyperbaric oxygenation therapy (HBOT) has been gaining an increasing recognition as a versatile therapeutic approach. This article reviews the application of hyperbaric oxygenation as a method for resuscitation and therapy of elderly patients with cerebral and cardio-respiratory dysfunction, in acute as compared to chronic impairments. The vital role of proper dosage of HBO therapy to ensure both the efficacy and safety of the treatment is emphasized. We argue that in the acute stages of brain and cardiorespiratory impairment, the adequate hyperbaric oxygen dose is the most important condition for obtaining maximum therapeutic effect, due to the powerful anti-hypoxic capabilities of this method. In contrast, during the chronic course of such impairments, there is an increased importance of safe dosing for the prevention of oxygen intoxication. Further dosage adjustments need to be made for the elderly as compared to younger patients, while examining and taking into consideration long term therapy effects. Some potential geroprotective mechanisms of HBO therapy are considered, that may be analogous to other geroprotective medications.

2. INTRODUCTION: HYPERBARIC OXYGENATION AS A PRIORITY RESUSCITATION MEASURE

Hyperbaric oxygenation therapy (HBOT) has been gaining an increasing recognition as a versatile therapeutic approach. Starting from the 1960s, the list of indications for HBOT has been expanding. As of 2016, according to the Undersea and Hyperbaric Medicine Society (UHMS), there are now 14 different diseases and syndromes indicated for HBOT, with various etiology and pathogenesis, from carbon monoxide poisoning through severe anemia to crush injury, compartment syndrome and other acute traumatic ischemias (1). During all those years, extensive laboratory studies and clinical observations have endeavored to further expand this list of indications to include the use of HBOT against diseases and impairments of vital organs, in particular in elderly subjects. Some of the most promising studies have involved the use of hyperbaric oxygen against acute ischemic, hemorrhagic and traumatic brain injury. As early as the 1960s and 1970s, there were published the first results of clinical observations of HBO therapy in patients suffering from acute cerebral ischemia (ACI) (2-5). The evaluation of the effects of hyperbaric oxygen therapy in all these works was based on neurological and electroencephalographic (EEG) surveillance. Despite the wide variety of manifestations and severity of the ischemic stroke, the authors noted the general positive influence of HBO therapy on this condition. However, it was observed that the speed and completeness of recovery from stroke were different in different patients.

A considerable contribution to this study was made in the 1970s through early 1980s in the N.V.Sklifosovsky Research Institute of Emergency Medicine in Moscow. At that time, they gathered the largest number of observations (124 stroke patients who underwent HBO therapy), which confirmed the positive results of earlier studies (6). In addition, researchers of that institute reached a number of other important conclusions regarding the influence of HBO on the progression of acute stroke. In particular, they found that patients who suffered acute

cerebral ischemia and underwent HBO therapy, had a dramatically reduced incidence of typical complications, such as secondary stroke, pneumonia, lung edema, de-compensation of cardiac function. As a result of these positive therapeutic effects, the lethality rate among patients who had received HBO therapy was reduced 2.4. times as compared to the control group (6).

Further important development in hyperbaric oxygen therapy against stroke was the introduction in the early 1990s of new technologies to monitor blood flow and metabolism in the brain. The clinic of Dr. Neubauer was the first to show the existence of the ischemic brain penumbra and reperfusion after hyperbaric oxygen therapy, using sequential single photon emission computerized tomography (SPECT) scans (7,8). The use of this technology provided real objective basis to evaluate the restoration of the blood flow and metabolism in ischemic brain foci, as achieved during the actual course of hyperbaric oxygenation. That clinic treated over 350 patients (aged 3 to 93 years), with severe brain impairments as a result of ischemic, thrombolytic and hemorrhagic stroke, traumatic brain injury and anoxic encephalopathy (9). Despite the established "hopeless prognosis," late HBO treatment, that started 6 months up to 14 years after the stroke event, demonstrated its capacity as a safe and efficient therapy.

Thus, by the end of the 1990s, the experience of the clinical centers that had used HBOT for many years, proved the potential effectiveness of this therapy against the above conditions. However, despite the HBO therapy's clear capacity to restore brain perfusion and metabolism, there was also a noted variability in the speed of recovery of the monitored parameters in different patients. Without entering into details that can affect the curability of various impairments (such as the volume of the brain impairment loci, the patient's age, physical status etc.) we should note that one of the main "logistic" reasons for this variability is the large variability in the time intervals separating the time of injury from the time of HBO therapy (6,9).

Another major reason for the uncertainty and variability of therapeutic results is the scarcity of patient-specific dosage assessments. Notably, until the early 2000s, no data could be found in the specialist literature about the correct calculation of HBOT doses and units in patients with acute ischemic stroke (AIS). Accordingly, there were no data about the dependence of the results of the stroke treatment on the doses of hyperbaric oxygen applied (the dose response). Our group (Rogatsky *et al.*, 2003)(10) retrospectively analyzed the published data on clinical studies, performed in different hyperbaric therapy centers (a total of 265 patients). The dose of HBOT (Dhbot) was calculated as the product of intra-barochamber pO2 (ATA), the duration of a single HBOT exposure (hours), and the number of HBOT treatments. The efficacy of HBOT (Efhbot) was established according to the number of patients who showed a significant clinical improvement in their neurological state in the course of HBOT (the percent of the total number of patients). The level of HBOT efficacy in each study was compared with a corresponding value of HBOT dose. A comparison of the data demonstrated a marked tendency for higher efficacy with increasing the average total HBOT dose. The coefficients of correlation between these parameters were quite high ($r = 0.9.2$). The maximum possible value of HBOT efficacy is 100%, which corresponds to the average HBOT dose values of no less than 30 units (ATA*h*N). These data suggest that using optimal total HBO doses may provide a maximum possible therapeutic effect when treating patients against acute ischemic stroke.

Since the publication of that work, over 10 years ago, its content has drawn considerable attention of experts in different countries, including leading specialists in the US and Europe (11-14). However, to the best of our knowledge, the discussion and practical utilization of our idea about the use and optimization of HBOT dosage in treating acute ischemic stroke, took place only in China (15) and Taiwan (16). This is understandable, considering the fact that the practical use of HBOT against acute stroke is officially recommended by national medical associations of China, Taiwan as well as Russia (in contrast to the list of indications of the US-incorporated Undersea and Hyperbaric Medical Society). As a result, presently, in the former countries, hundreds of patients have received timely and highly effective HBO therapy against acute ischemic stroke. As shown by an analysis of special literature published in those countries, in the last decade, the best results of HBO efficacy (ranging between 80-96%) were obtained precisely under those conditions (as were first determined in our work in 2003) which employed the optimal highest total HBOT doses of no less that 30-60 agreed units (see the data in (15)). To the best of our knowledge, during this decade, there were no works published in the "Western" literature that would experimentally either confirm or reject the idea of the dependence of HBO therapy efficacy in acute ischemic stroke on HBOT dosage.

It may be seen that, in the US and EU, the once successfully initiated clinical studies of HBO therapy against acute ischemic stroke, have become virtually halted. The reason for this abandonment may have to do with the uncertainty and variability of therapeutic results, under the highly precarious acute and often critical clinical states, at the absence of clear-cut dosage regimentation. This may have contributed to the stronger involvement of the pioneers and enthusiasts of HBO therapy with using it against chronic, rather than acute, brain impairments, including late and severe outcomes of ischemic, hemorrhagic and traumatic brain impairments in patients who did not

receive timely and adequate HBO therapy in the earlier stages of the disease (9,17-19).

In contrast, in Russia, during this period and up to date, there have been actively researched the possibilities of wider and more intensive application of HBOT against acute diseases and impairments of the brain (20-22). These works summarized the use of HBOT in patients with acute cerebral pathology during neuro-resuscitation. Analysis of the results in 750 patients after early surgical treatment of intracranial aneurism, intracranial hemorrhage, traumatic brain injury, as well as brain tumors, demonstrated the feasibility, safety and efficacy of the use of HBOT in such patient categories. The works showed principally new approaches to the use of hyperbaric oxygen under these conditions. Thus they indicated the efficacy of HBOT application for the most severe patients, requiring respiratory support. There was developed the methodology for using HBOT under artificial pulmonary ventilation. It was reported that earlier inclusion of HBO therapy in the combined treatment of such patients facilitated a more rapid recovery of vital functions, prevented complications of the resuscitation period, and accelerated regression of neurological symptoms. A principally important component of this therapeutic strategy is the monitoring of the gas composition of arterial blood, the speed of the brain blood flow, and intracranial pressure (20-22).

The efficacy of HBO therapy against acute brain impairments has been also indicated by its application against traumatic brain injury (TBI). The research of HBO therapy against traumatic brain injury has been led for many years by G.L. Rockswold's group (23-26). This group now apparently has the greatest experience in using HBOT in the early period of severe traumatic brain injury. They have reached the conclusion that hyperbaric oxygen therapy in combination with normobaric oxygen therapy substantially improved oxidative metabolism in relatively uninjured brain and in pericontusional tissue, diminished intracranial hypertension and improved biomarkers of cerebral oxygen toxicity. There was shown a significant reduction in mortality and improved favorable outcome as measured by Glasgow Outcome Scale (26). Other researchers reached similar conclusions about the positive influence of HBOT on the acute period of severe traumatic brain injury (27,28). The experience of these groups shows that, with precise and competent application, utilizing modern equipment, HBO therapy can produce highly effective results in patients with the most severe acute brain diseases and impairments.

Nonetheless, as indicated above, there are still considerable shortcomings in the development of scientific strategy for HBOT application against acute injuries and diseases of the brain, especially for the elderly. The question of therapeutic dosing of HBOT is undoubtedly a strategic one, same as the dosing of any other medicines or therapeutic interventions. We believe, in many cases, by reducing the oxygen "burden", while successfully accomplishing the task of minimizing oxygen toxicity risk, the therapists nonetheless may "underachieve" in the task of combating hypoxia and its consequences. Also, not in all the cases oxygen and CO_2 levels in arterial blood (PaO_2 and $PaCO_2$) are monitored, which is necessary in order to control and maintain adequate levels of pulmonary gas exchange, with regulated parameters of ventilation and controlled oxygen concentration. These shortcomings, especially the deficit of optimal dose evaluation, with lack of differentiation for particular conditions or age groups, may negatively affect the results of treatment of the most severe patients, especially the elderly. We believe that in such cases, scientifically grounded and individually regulated therapeutic dosing of HBOT could further improve the prognosis not only for the survival of the severe patients, but also reduce the risk and level of disability in this wide patient cohort.

3. THE USE OF HBOT IN TREATING AGING-RELATED DISEASES

The question of dosing HBO therapy is critical also for the treatment of patients with chronic forms of brain impairment (18). However, in the acute stages of brain impairment, the adequate hyperbaric oxygen dose is the most important condition for obtaining maximum therapeutic effect, due to the powerful anti-hypoxic capabilities of this method. In contrast, during the chronic course of cerebral impairment, there has been a traditional strong emphasis on careful dosing for the prevention of oxygen intoxication (due to the need for repeated long-term application). At the same time, the range of oxygen doses can vary extremely widely (18). Yet recently a greater attention has been drawn also to differential therapeutic effects of particular dosages under chronic conditions, though the great complexity and uncertainty of dose-effects in relation to particular conditions and molecular mechanisms of action has been noted (19).

Surprisingly, in the recently published work from the Sagol Center of Hyperbaric Medicine and Research (Israel), there is a special note that the incidence of severe oxygen toxicity under HBOT in patients with chronic forms of brain injury is very rare. According to their data, it is 1:62,614 (29). Moreover, when analyzing the results of their studies in recent years (with 2,324 patients), the authors emphasize that "strict operational protocols, including pre-HBOT evaluations and in-chambers monitoring, are essential and improve patient safety." When these are applied, according to the authors, hyperbaric oxygen therapy can be seen as one of the safest medical treatments currently available. In a very

short study period of 2010–2014, that group showed not only the effectiveness of HBO therapy in the late stages of ischemic and traumatic brain impairment, but also provided patho-physiological evidence for the anatomic, functional and metabolic recovery or "rejuvenation" of the brain by HBOT (30-32). However, in our opinion, the results that are being obtained by the group not only do not diminish, but rather emphasize the need for enhancing HBOT research also for the acute stages of brain impairment. We believe that the still high levels of disability, morbidity and mortality, in particular due to acute ischemic stroke, justify such an urgent need.

Based on many years of experience using hyperbaric oxygenation against acute and chronic diseases and injuries of the brain with various etiology, R.A. Neubauer and P.G. Harch proposed using HBOT to produce aging-ameliorating or "anti-aging" (geroprotective) effects (33,34). The optimal regimens and dosages of oxygen are a necessary condition for the success of such application. The putative anti-aging properties of hyperbaric oxygen may be seen as an outcome of its general protective effect on the organism, improving its energy metabolism. Such protective effect of HBOT under different stress conditions was described by F. Imperatore's group in animal models (35-37). The authors presented evidence for the protective and preventive effects of HBOT in a rat model of circulatory shock, caused by zymosan injection. With HBO treatment, survival improved and peritoneal inflammation decreased. HBOT (at 2 ATA) also prevented multiple-organ failure, including damage of the lungs, liver and small intestine, after intraperitoneal zymosan application. These results, in fact, confirm our earlier data concerning the marked protective effects of HBO against the development of acute respiratory dysfunction in rats as a result of intrapulmonary injection of oleic acid. In the experimental group, the performance of only one session of HBOT significantly diminished the intensity of spreading arterial hypoxemia and the mortality rate as compared to the control group (38).

Yet, the mechanisms of potential general protective and/or geroprotective effects of HBOT, if such are indeed present, are yet to be elucidated. The question of dosages may be also crucial for determining the mechanisms of HBO therapeutic or geroprotective effects. High dosages of hyperbaric oxygen should intuitively induce oxidative stress, with high reactive oxygen species (ROS) production, which has been considered one of the main sources of molecular damage in aging for over half a century (39). Indeed, oxidative damage has been observed under HBOT, among other effects potentially contributing to cataract development (40). Yet, it is also appreciated that at certain levels ROS may stimulate tissue regeneration (41). And yet at certain dosages, hyperbaric oxygen may produce stimulatory "hormetic" effects, which may in fact increase anti-oxidant protection, via stimulation of anti-oxidant defense systems (42). The protective effects of HBOT by stimulating heat shock protein expression (43) and stem cell mobilization (44) have also been suggested. In a related way, chronic systemic inflammation has been long implicated as a major source of age-related damage (45). Furthermore, excessive neuro-inflammation has been a sustained therapeutic target (46). HBOT has been commonly reported to produce an anti-inflammatory effect, which has been implicated as one of its major therapeutic mechanisms, for both age-related chronic and acute conditions (like AIS) (47). Yet, there is also a growing realization that pro-inflammatory effects may be essential for tissue regeneration, including neuro-regeneration (48).

Generally, the role of HBOT for regeneration, in particular angiogenesis, via stimulation of various tissue growth factors, has been uncertain. Some studies associate the therapeutic effects of HBOT with hormetic stimulation of angiogenesis, as indicated in microvascular endothelial cell line (42). Yet, others posit definite anti-angiogenesis effects, e.g. via inhibiting hypoxia inducible factor (HIF-1) and vascular endothelial growth factor (VEGF), neutrophil infiltration, and matrix metalloproteinases MMP-2 and MMP-9, that promote angiogenesis which is assumed to be involved in the wrinkling of the skin and suppressed by HBOT (49). Tissue specific effects and energy requirements may be strongly involved, hence the therapeutic effects of HBOT may be complicated not just by the uncertainty of the general dosages for particular conditions and individuals, but also by the uncertainties of dosages for particular tissues.

Closely related to hormesis, HBOT may exert protective anti-ischemic effects through ischemic preconditioning, that is applying a certain sub-threshold dosage of HBOT that would induce a transient, sublethal ischemia that would confer tolerance to subsequent, more severe ischemia (47). This mechanism opens the possibility for using HBOT as a preventive therapy for the elderly. Some of the mechanisms of preconditioning were associated with enhanced expression of protective enzymes, such as Sirtuins (50), enhanced MAPK and autophagy (51) and inhibiting the mTOR pathway (52). Thus, the mechanisms of preconditioning by HBOT may have similarity with the application of other geroprotective medicines (e.g. Sirtuin-stimulating or mTOR inhibiting drugs (53,54)), producing a general improvement of energy metabolism, yet potentially with fewer pharmacogenic side effects. Yet, this possibility will yet require extensive investigation, necessitating a very careful consideration of the dosages.

Another complicating factor for a potential geroprotective HBO therapy mechanism may be related to its long-term vs. short term effects. In any

hypothetical "anti-aging effects," there may be a danger of transient short term benefits being followed by long term deleterious effects (55). An obvious way to rule out such harmful effects may be by long term observations. Yet, there is a general scarcity of long-term observations for almost any application of HBO therapy. Thus a series of Cochrane systematic reviews on HBOT application against acute coronary syndrome (56), chronic wounds (57), and as an adjunctive therapy against traumatic brain injury (58) have come to an almost uniform conclusion that there is considerable evidence for short term benefits, while the long term effects are more uncertain. The suggestion for improvement, in these reviews, is also quite uniform, emphasizing the need for more precise quantification, personalization and long terms assessment of the treatments: "an appropriately powered trial of high methodological rigour is justified to define those patients (if any) who can be expected to derive most benefit from HBOT" (56). The present review concurs with this suggestion.

The short vs. long term effects may be related to the HBOT mechanisms of action. Thus a study in leukocytes from divers exposed to intense oxidative stress by HBO found an initial telomere elongation (that could be interpreted as increasing cell regenerative potential), which however was followed by telomere length reduction (a potential sign of accelerated aging). The authors generalize this phenomenon for tissue and organismal aging and "highlight the importance of longitudinal follow-up of individuals exposed to excessive hyperbaric oxidative stress" (59). Indeed there may be a need for a systemic, long term evaluation of oxygen therapy effects, as a part of a whole-organism whole-life-course model of energy resources expenditures. Such models are currently only nascent (60). Still, those complexities do not call for a reducing of HBO research, but rather for its intensification, in view of the clear benefits for a considerable number of patients under certain conditions. Studies need to intensify to better define such conditions, in particular the dosages, "not because they are easy, but because they are hard."

4. HBOT EFFECTS ON THE CARDIORESPIRATORY SYSTEM IN THE AGED

Considering the question of using HBO therapy for aging-amelioration or general health improvement for the elderly, it may be presumed that one of the main problems for HBOT use for such purposes can be the danger of toxic effects of excessive oxygen on the brain and lungs (61). Another, no less important (perhaps even more important) problem for such cases is the general reduction of adaptive capabilities exacerbating with age. This reduction of adaptive capacity is accompanied by increasing risk of cardio-respiratory and malignant diseases with aging (62). Due to these and other potential diseases and injuries of aging (infections, traumas, etc), the necessary aggressive diagnostic and therapeutic measures (including surgical interventions, chemotherapy and radiotherapy) can become additional stress factors for the elderly patients. In some of such cases, such stress burden can lead to severe complications in the cardio-respiratory system (pneumonia, lung edema, acute respiratory distress syndrome, etc.). It is known, for example, that the mortality rate from acute respiratory distress syndrome (ARDS) in the US is quite high – about 3-5 per 100,000 persons (63). Moreover, the risk of this complication with lethal outcome in elderly patients is much higher (64-66). Insofar as the main purpose of the present review is to survey the possibilities of using HBO therapy to alleviate critical states in the elderly, caused by severe diseases and impairment of the brain and cardio-respiratory system, it is important to consider the morphological-functional characteristics of the cardio-respiratory system of the elderly under non-critical and critical conditions.

Several cardio-respiratory parameters may serve as good markers of aging. Arguably, such markers may be clinically valuable and conveniently interpretable for a practicing physician, alongside the many "biomarkers of aging" based on predominantly molecular-biological, e.g. genetic, epigenetic and other "omic" age-related alterations that are currently investigated (67,68). A case can also be made that cardio-respiratory parameters routinely employed in emergency and intensive care medicine may be good candidates for biomarkers of aging as they have proved their utility as real-time indicators of the organism's vitality and energy. Often, in general frailty assessments, energy levels in the elderly are evaluated simply by asking the question "Do you feel full of energy?" (69) Yet, there may be more objective measures of the aging organism's energy level, by such means as spirometry, oximetry, hemodynamic, electrochemical and spectroscopic energy metabolite measurements (70), as well as other structural and functional parameters of the cardiorespiratory system, that can provide improved indication for therapy.

Thus, aging is characterized by a number of alterations in the right ventricle and pulmonary vascular system (71). Pulmonary artery pressure and vascular resistance rise with aging, mostly because of the increasing arterial stiffness of the pulmonary vasculature (72,73). Ultrasound imaging showed a reduction of the early right and left ventricular diastolic filling and myocardial velocities (74). Aging is also characterized by reduced contractility and relaxation of the left ventricle and diminishment of systolic and diastolic function of the right ventricle (75). Another marker of aging is the reduction of the velocity of myocardial contraction and early diastolic filling rate in the left ventricle (76). The anatomical and physiological

effects of aging on the lungs are similar to the effects of mild chronic obstructive pulmonary disease (COPD). Aging leads to a progressive impairment of lung function, involving a reduction of vital capacity and an increase of residual volume. The airways generally tend to collapse during expiration. All the components of the respiratory dead space are enlarged. The inspired gas is badly mixed. Ventilation is insufficiently matched with perfusion. There is a decline of pulmonary diffusion capacity and enhanced breathing work (77). The integration and development of various functional impairments of the cardio-respiratory system with aging, lead to the progressive impairments of the diastolic and systolic functions of the myocardium. This is accompanied by the gradual decline of gas exchange capacity of the lungs, and in the most severe cases results in gradual decline of oxygen concentration in the arterial blood, which can in turn exacerbate the myocardium dysfunction (78). All the deteriorative changes in the cardio-respiratory system generally manifest in the reduction of maximal oxygen uptake (VO_2max) which has been considered one of the most informative parameters for biological age evaluation (79-81). This type of "physiomic" parameters of aging (81), focusing on energy metabolism measurements, may supplement various other "omic" markers of aging.

These characteristics are especially important when considering the possibility of using HBOT for elderly rehabilitation (33,34). In particular, the limitation of maximum oxygen uptake may have direct implications for HBO therapy efficacy in the elderly. There is an evident need, with high potential utility, to know the consequences of the hyperbaric oxygen therapy on the structure and function of the cardio-respiratory system of the elderly patients. Unfortunately, this question has not yet been adequately addressed. So far, chronological or physiological age has scarcely been considered as a distinct and discriminative factor. The data available in the literature for common "age-related" conditions are not consistent and often even contradictory. Thus, it was demonstrated that the use of HBOT in 52 chronic ischemic heart disease patients, after 12-15 sessions, significantly reduced and even stopped the occurrence of angina pectoris, significantly alleviated the symptoms of cardiac insufficiency, improved the contractility of the myocardium (82). HBOT was also used in 31 patients suffering from paroxysmal tachyarrhythmias in ischemic heart disease. As the authors reported, thanks to ongoing HBO therapy, the frequency and duration of the paroxysms was decreased, followed by long-term remission (83). HBO treatment was also reported to decrease the number of extrasystoles. It was additionally shown that HBOT improved myocardial contractility in patients with chronic ischemic heart disease (84).

At the same time, the literature includes indications for potential adverse effects, such as lung edema when using HBOT against chronic ischemic heart disease. Thus, there were reports about 3 cases of lung edema connected with HBOT. All the three patients were of advanced age (one 50+ and two 75+), and had a non-healing wound of the foot (in 2 patients) and of the chest (in one patient) after chest radiotherapy for breast carcinoma (85). All the 3 patients had heart disease and reduced left ventricular (LV) ejection fraction (EF). The authors recommended caution when using HBOT in heart failure patients with reduced cardiac ejection fraction. There was also a reported case of acute lung edema in an 80 year old patient with ischemic cardiomyopathy (ejection fraction 25%), noninsulin-dependent diabetes mellitus and peripheral vascular disease – which was the indication for HBO therapy. The patient had no clear signs of heart failure prior to HBOT (86). However, his overall hypoxic predisposition, according to the authors, might have been a risk factor for the emergence of acute lung edema during HBOT. In another intriguing report, contrary to the formerly described cases of HBOT-induced pulmonary edema, the authors described the development of HBOT-induced lung edema in a patient with moderate diastolic dysfunction with normal ejection fraction. According to the authors, in this case, a possible mechanism of HBOT-induced lung edema may involve increasing LV afterload, rising LV filling pressure, increasing oxidative myocardial stress, increasing pulmonary capillary permeability, or inducing pulmonary oxygen toxicity. The authors recommend caution when HBO treating patients with low cardiac EF or diastolic dysfunction (87).

We believe that one of the main factors for reducing the risk of emergence and development of pulmonary edema, under HBO conditions, should be the optimization of the regimen and dosage of the hyperbaric oxygen used in each particular case. Analysis of the literature and our experience led us to hypothesize that under acute and severe hypoxia, occurring in patients with severe diseases and injuries of the brain and cardio-respiratory system, the tolerance to hyperbaric oxygen is apparently much higher than for patients with impairments in the same organs, but in a chronic "stable" stage of these diseases. This hypothesis, obviously, needs to be tested. However, in our observations of daily sessions (with a course of up to 2 weeks) of HBO therapy for intensive care of 8 thoracic trauma patients, we have never encountered a single case of emergence and development of oxygen toxicity or acute pulmonary edema, induced by HBO. Moreover, the application of HBOT prevented the development of Acute Respiratory Distress Syndrome (ARDS) in the most severe patients with thoracic injury (88) (see below for details).

Similarly, there was no oxygen toxicity noted during the reduction of pulmonary complications and lethality thanks to the use of HBOT against acute stroke in the large scope study (124 patients) by Lebedev's

group (6). In the recent years, additional promising results were published regarding the use of HBO therapy for patients with severe brain injuries, where the therapeutic effects were the more pronounced the more severe was the patient's state (21). In contrast, as mentioned above, in the observations of Neubauer's and Harch's groups, the use of hyperbaric oxygen and even air, months and years after the onset of the trauma or disease, required a very careful dosing with a tendency to reduce the oxygen concentration in every particular treatment (9,18). We believe that increasing attention to the state of the cardio-respiratory function of the patients, especially the elderly, under HBOT, and increasing research in this area, will not only decrease the incidence and risk of oxygen intoxication, but can also open new possibilities for improving the efficacy of HBOT for both prevention and elimination of severe vital organ impairments.

5. ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Considering the diagnosis and improvement of the cardio-respiratory function, of special interest is the use of HBOT to prevent acute cardio-respiratory impairments that lead to the highest mortality in the elderly (64-66). The improvements of cardio-respiratory function in blast trauma can be seen as a paradigmatic show case (89,90). Notably, the US CDC contemporary instructions for "mass trauma preparedness" recommend the use of HBOT for "some cases of blast lung injury" (91). As an illustration, we can present our results using HBOT to treat patients with severe closed chest trauma (88). Such traumas are one of the main "suppliers" of ARDS (92,93) due to the emergence of lung contusion at the time of severe mechanical chest injury (94-96). Following the trauma, the basic parameters of cardiorespiratory function were monitored, such as PaO_2 mmHg – arterial partial pressure of oxygen; PaO_2/FiO_2 – the ratio of the partial pressure of oxygen to the fraction of inspired oxygen; SVI ml/m^2 – stroke volume index; CI L/min/m^2 – cardiac index. As shown by the retrospective analysis of the monitoring data, severe chest trauma is first accompanied by a steady decrease of all these parameters, which is a characteristic patho-physiological sign for such local traumas. Later on, despite using the entire appropriate array of intensive therapy, these parameters' dynamics became irreversible for the group of patients with lethal outcome. At the same time, in the re-convalescing group, the conducted array of intensive therapy was accompanied by stopping the negative parameters dynamics, followed by their gradual normalization. Analysis of the clinical and laboratory data showed that the main component of the severe pathological state in these patients was the deep depression of the cardiorespiratory function due to ARDS. This was shown, among other indications, by the arterial blood gas parameters. Thus, the level of PaO_2/FiO_2 in the most severe patients was below 200-250, which is an accepted criterion for ARDS, regardless of its initial causes (97,98). The lethality level in the group of patients with severe blunt chest trauma accompanied by ARDS, who had received conventional therapy, was 77%. This high lethality corresponded to the lethality levels common for the most severe forms of ARDS, according to the literature of the 1980s-1990s, and even up to date (99,100).

In contrast, in the group of patients with the same severe form of chest trauma who, in addition to the conventional therapy, also received a concomitant course of HBO therapy, despite the initial typical decline of the basic parameters of the cardiorespiratory function, nonetheless there was observed the rapid deceleration of the negative parameters dynamics with their subsequent active recovery up to the normal levels (including the most informative diagnostic parameter for such cases - PaO_2/FiO_2). As a result of using this therapeutic strategy, this group of patients had quite a favorable course of the early post-traumatic process, as well as showed a complete lack of lethality. Thus, it was shown that the trauma-related depression of the basic parameters of cardiorespiratory function and ARDS development were effectively stopped and alleviated only under HBO therapy performed in parallel with conventional intensive therapy. In our observations, this therapeutic strategy ensured normalization of the corresponding parameters of gas exchange and pumping function of the heart, thus preventing lethality in the patients (88). In fact, the obtained results confirmed the earlier laboratory studies on experimental models of severe and critical conditions that demonstrated the preventive and protective properties of HBO therapy (35-38).

The dynamics of two additional gas parameters that are commonly monitored in the arterial blood – namely pH and $PaCO_2$ – in our observations were not characteristic or statistically significant, except for the tendency toward metabolic acidosis in the first stage of the process in patients with a comparatively more severe blood loss, which however was restored already in the first hours after admission to the hospital. Nonetheless the consideration of pH and CO_2 changes may be advisable, as they may shed light on the possible mechanisms of the therapy, with reference to normal balanced O_2/CO_2 levels in the blood and favorable electric charge conditions for protein homeostasis, that may have special significance for the aging process (101).

6. CONCLUSION

The data from special literature on hyperbaric medicine, including our results, recommend hyperbaric oxygenation as a promising therapeutic method specifically for emergency and intensive care medicine. In particular, hyperbaric oxygenation can play a very important

potential role for the intensive care of elderly patients, i.e. the patients with reduced adaptive capabilities, highly vulnerable to sudden and intensive stress factors of the external and internal environment. However, the applying in the elderly patients of the intensive, patho-physiologically justified medical technologies, including HBOT, necessitates the more active and comprehensive study of their cardio-respiratory function. As shown earlier (10,88), the monitoring of the gas composition of the arterial blood is a necessary condition to perform effective HBO therapy against life-threatening conditions in patients with rapidly developing cardiorespiratory dysfunction, regardless of its causes – especially for the elderly patients.

We believe that the above data from the literature, including our results, testify that by now there is a sufficient positive experience of HBOT application against acute critical conditions, caused by severe diseases and traumas of the brain. This experience opens the possibility for more effective therapy of elderly patients. At the very least, this experience may be sufficient to recommend more research for an active and competent expansion of HBO therapy as an effective means of protection and rescue for this patients category. The presented material about the clinical use of HBOT as an effective means to prevent and eliminate acute respiratory distress syndrome is very important, considering the extent of this phenomenon, its multiple etiologies, and the still high level of lethality, especially among the elderly patients.

Considering the research expansion for the therapeutic capabilities of high oxygen concentrations in elderly patients, it appears very important to use it as a means of rehabilitation to prevent adverse outcomes, such as stroke, thrombosis, infarction, etc. characteristic for the aging subjects. In the final analysis, these adverse effects result from a lack of oxygen supply to the vital tissues for which HBOT can provide an efficient and timely solution. In the future, the problems of oxygen delivery to the vital tissues may be tackled from additional angles, such as oxygenated microparticles (102) or pharmacological means (53,54). Still, hyperbaric oxygenation remains one of the most effective clinical means of oxygen delivery to deep vital tissues, hence promising for the treatment of severe consequences of the aging process. Such an application is still in the initial stages of development. Yet, in case of successful development, it can produce demographically meaningful results, improving the healthspan of the rapidly growing aging population through adequate rehabilitative oxygen therapy.

It should be reemphasized here that the question about the efficacy of using HBOT against acute severe impairments of the brain and vital thoracic organs (such as acute ischemic stroke, ARDS and others) is still debated. Apparently, a necessary condition to resolve this dispute and achieve effective therapy should be proper HBO dosing, which necessitates acquiring data on dose effects in each pathological state. Without such data, definitive conclusions regarding the indication or counter-indication for HBOT may not be justified. Furthermore, more research needs to be done on the age-specific responses in the elderly as compared to the younger patients, whose therapeutic regimens and benefits may be different. This distinction has been scarcely addressed in the literature. Long term vs. short term effects also need to be more carefully examined in a holistic “life-course” evaluation approach. Another distinction that needs to be kept in mind is between the application of HBOT under acute conditions (emergency HBOT) as opposed to the chronic course of the same condition (maintenance HBOT) as in turn opposed to preclinical development of the condition (preventive HBOT). The regimens, dosages, toxicities and risk factors under such conditions may be different, which will require further investigation. Specifically, while HBO therapy may be a priority resuscitation measure for people under acute conditions, with urgent oxygen requirements, in cases of chronic and preventive treatments a greater care may be needed to avoid the possibility of oxygen toxicity or disruption of an established metabolic balance by HBOT. In the future, it will be necessary to fine-tune the dosages and regimens of HBO treatments according to the particular applications. A necessary condition for such research will be the use of advanced precision technologies, enabling the monitoring of anatomical and functional changes of impaired vital organs and blood gas exchange balance in real time. It is hoped that such personalization and precision of HBO therapy will be achieved in the future.

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