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Hyperbaric oxygenation in transplantology

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The ability to eliminate any form of oxygen debt by transporting oxygen to organs and tissues, by dissolving it in body fluids, brings hyperbaric oxygenation to a new level of application in transplantology. The review discusses the pathophysiological aspects of hyperbaric oxygenation during ischemia and reinfusion, especially when used in transplantology, and also investigations on the use of hyperbaric oxygenation in model experiments and in clinical practice. Analysis of the efficacy of hyperbaric oxygenation therapy at various stages of the transplantation process (preconditioning, donation, organ storage, in the early and late

post-transplant periods) allows us to conclude that this method should be more widely involved in transplantation practice.

Keywords*:* hyperbaric oxygenation, transplantology, ischemic reperfusion injury

AO, antioxidants

ATA, Absolute Atmosphere

ATP, adenosine triphosphate

CD45+, cluster of differentiation, leukocyte differentiation antigen

cyt *C*, cytochrome *C*

HBO, Hyperbaric oxygenation therapy

HIF-1α, Hypoxia-induced factor 1-alpha

HIF-2α, Hypoxia-induced factor 2-Alpha

IL-1β, Interleukin-1β

IL-6, Interleukin-6

IRP, ischemia-reperfusion injury

LPO, Lipid Peroxidation

MHC, the major histocompatibility complex

mPTP, mitochondrial permeability transition pore

mtDNA, mitochondrial DNA

NADPH oxidase, nicotinamide adenine dinucleotide phosphate, reduced form

NO, Nitric oxide

NOS, NO-synthase, nitric oxide synthase

NOX, NAD(P)H oxidase

O_2, oxygen

PBMC, peripheral blood mononuclear cells

PO_2, partial pressure of oxygen

ROS, reactive oxygen species

SOD, superoxide dismutase

TNF-α, tumor necrosis factor-alpha

VEGF, vascular endothelial growth factor

Introduction

One of the urgent problems in transplantology remains the ischemia-reperfusion injury (IRI) of the graft, leading to the development of complications in the early postoperative period [1]. Hyperbaric oxygenation (HBO) is recognized as a method capable of eliminating any form of oxygen debt, and providing the oxygen delivery to organs and tissues by oxygen dissolution in body fluids [2, 3]. Since the 1960s HBO has gained an increasing recognition as a universal therapeutic method. The list of indications for HBO is constantly expanding, and the Society of Underwater and Hyperbaric Medicine (UHMS) has indicated HBO as a treatment method for 14 diseases and syndromes with various etiologies and pathogenesis: carbon monoxide poisoning, severe anemia, crash syndrome, compartment syndrome, and other acute ischemia types of traumatic origin [4, 5].

Throughout these years, numerous laboratory studies and clinical observations have been trying to expand the list of indications that should include the use of HBO to combat diseases and disorders of vital organs. The use of hyperbaric oxygen against the acute ischemia, hemorrhagic and traumatic brain injuries was noted in most promising studies. So, in the early 1960s and 1970s, the first results of the clinical HBO therapy observations in patients with acute cerebral ischemia were published [6, 7]. In those studies, the assessment of the HBO impact was based on neurological and electroencephalographic data. Despite the diversity of the course and severity of ischemic stroke, the authors note a general positive effect of HBO on the condition of those patients. However, the

speed and degree of recovery in different patients who had a stroke varied.

In the 1990s, one of the significant events in strengthening the position of HBO was the introduction of new technologies for monitoring the blood flow and brain metabolism in stroke. The clinic of Dr. Neubauer for the first time showed the presence of a penumbra and reperfusion zone for cerebral ischemia, and also demonstrated the effectiveness of HBO therapy for this pathology using single-photon emission computed tomography [8, 9]. The use of this technology created a real objective basis for assessing the restoration of blood flow and metabolism in the presence of ischemic lesions in the brain, directly during the course of HBO [10-12].

Basic operating principles

The therapeutic effect of HBO is based on breathing with pure oxygen under high pressure, which allows increasing the partial oxygen tension in tissues suffering from hypoxia, enhancing the degree of oxidative phosphorylation and stimulating the mechanisms of energy production, providing not only a substitutional, but also metabolic effect. It is difficult to find a method that most effectively affects all organs and systems with a minimum of contraindications and side effects [13-15]. When 100% oxygen is inhaled under a pressure above atmospheric during a session, the oxygen dissolved in plasma is delivered, which ensures an increase in the oxygen capacity of body fluids that in this case become effective carriers of oxygen to cells. With increasing the pressure in the pressure chamber during the HBO session, the content of plasma oxygen increases by 2.3 vol. for each excess atmosphere, the content of plasma oxygen increases by 2.3 vol.%. So, at a pressure in the pressure chamber equal to 1.5–2 ATA, the oxygen content in the plasma is 4.34

vol.%, and the partial pressure of oxygen increases to 1000–1400 mm Hg due to the oxygen dissolved in the plasma.

A significant increase in the oxygen tension in the blood plasma accelerates its diffusion into the intercellular fluid and lymph, providing the replacement effect of hyperbaric oxygen. So, with an excess pressure of 3 ATA, the increased oxygen capacity of the plasma can satisfy the body's need for oxygen without the participation of hemoglobin. The positive effects of hyperbaria are the result of eliminating not only hypoxia itself, but also largely occur due to the effect of hyperbaric $_{O2}$ on the neurohumoral regulation of organs and systems of the body.

The oxygen capacity of body fluids during HBO increases mainly due to the dissolution of oxygen in them. The ability of HBO to increase the oxygen capacity of the blood served as the basis for using this method in conditions where hemoglobin is completely or partially excluded from the breathing process, i.e. with anemic and toxic forms of hemic hypoxia.

Even with a relatively low capillary blood flow velocity, high arterial PO_2 provides a more intense diffusion of gas into the tissue. However, an increase in $_{O2}$ tension in the arterial end of the capillary does not lead to a similar (strictly linear) rise of PO_2 in tissues and cells. The degree of its growth in various organs depends on their vascularization, local blood flow conditions, as well as on the oxygen capacity of tissues and the intensity of metabolism. By increasing the oxygen capacity of body fluids, HBO creates certain opportunities for the deposition of a certain amount of $_{O2}$ in tissues. The life span of a person depends on the size of this oxygen reserve when the blood circulation is completely off, as well as the life span of the tissues does in case of its regional violation.

Compared with conventional oxygen therapy, HBO has the following advantages:

- compensates for virtually any form of oxygen deficiency and, above all, the hypoxia due to the loss or inactivation of a significant part of the circulating hemoglobin;

- lengthens the extent of effective diffusion in tissues;

- provides the metabolic needs of tissues while reducing the volumetric blood flow velocity;

- creates a certain reserve of oxygen in the body.

The direct effect of hyperbaric oxygen can be divided into compression, antihypoxic and hyperoxic ones.

The replacement (antihypoxic) effect of HBO is well studied and is the pathophysiological basis for the use of HBO, mainly in hypoxic situations (in case of poisoning, acute circulatory failure, shock conditions, etc.). The replacement effect of HBO, which is important in eliminating hypoxia and its consequences, is limited by the exposure time to HBO and quickly disappears after the end of the session; the final effect, which persists for a long time, is determined by the hyperoxic effect of hyperbaric oxygen. It is known that HBO can lead to both positive (therapeutic effect) and negative (toxic effect) consequences. It is not always easy to draw a clear line between these effects, since the metabolic changes associated with the realization of a higher oxidative potential occur long before the clinical manifestation of its toxic effect. In vivo oxygenation of the body, histotoxic hyperoxia is most common. Despite the fact that with a combination of various causative factors of hyperoxia (for example, an increase in the volume of tissue blood flow while reducing oxygen consumption), the cellular PO_2 can significantly increase, not a single one of the endogenous forms of hyperoxia leads to the development of oxygen poisoning. This is the prerogative of exogenous hyperoxia only, in which there is an abrupt increase in arterial and tissue PO_2.

Hyperoxia is associated with metabolic activity, and, first of all, with intracellular consumption of oxygen. Under conditions of hyperoxia, the oxygen diffusion into a cell is facilitated, the oxidative phosphorylation is activated with an increase in synthesizing macroergs, the microsomal oxidation is stimulated, the utilization of toxic products is increased, the glucose oxidation is accelerated, and lactose levels are reduced, which indicates the activation of the Krebs cycle. The basis for the therapeutic use of hyperbaria is a change in the parameters of the body's oxygen regime and the resulting clinical and physiological effects:

- Bioenergetic (the normalization of the energy balance of a cell);
- Detoxification (the prevention of the formation of toxic metabolites and the activation of their destruction);
- Regulation of metabolic activity;
- Biosynthetic (the acceleration of protein synthesis);
- Morphoreparative (the activation of repair processes);
- Immunocorrection (the stimulation or, depending on the $_{O2}$ dose, the suppression of the immune system);
- Antibacterial (the suppression of the vital activity of microorganisms);
- Pharmacological (strengthening or weakening of the effect of drugs);
- Release (release of inactivated hemoglobin and cytochrome cydase);
- Radio modifying (an increased radiosensitivity of malignant tumors);
- Vasopressor (an increased spasm of arterioles, decreased intracranial pressure, a decongestant effect);

- compression (the reduction in the volume of intestinal gases, free gas bubbles in the blood vessels in a decompensation disease, pulmonary barotrauma and post-traumatic embolism);

- economizing (reducing the functioning level of organs and systems of the body);

- Microcirculatory (an increase in the number of functioning vessels thanks to lymphatic capillaries) [15].

Thus, hyperbaric $_{O2}$ can be considered, first, as a specific factor that provides the functions of oxygen-dependent redox systems, and second, as a non-specific factor that mobilizes physiological and metabolic adaptation reactions in different pathological processes of hypoxic and nonhypoxic origin.

In addition to its antihypoxic (replacement) effect, HBO also has a nonspecific (metabolic) effect, which affects the pathogenesis and sanogenesis of a wide range of diseases.

Pathophysiological aspects of hyperbaric oxygenation

One of the main problems in organ transplantation is ischemic-reperfusion injury of the graft, which can cause complications in the post-transplant period, including the acute rejection [1].

In the stage of ischemia, when the blood flow to tissues discontinues and oxygen is lacking, the metabolic pathway switches from mitochondrial oxidative phosphorylation (Fig. 1A), in which 36 adenosine triphosphate (ATP) molecules are formed per one glucose molecule, into a less energy-efficient anaerobic glycolysis (Fig. 1B), proceeding in the cytosol with the formation of only 2 ATP molecules. Additionally, metabolic products, including lactate, accumulate in the cell, which leads to a decrease in intracellular pH and to acidosis [16]. Under conditions of ATP deficiency, the enzyme dysfunction, a decrease

in the transmembrane potential and efficiency of mitochondrial and cell membrane pumps are observed; in addition, a low pH is an inducer of mitochondrial pore (mPTP) closure , which generally leads to an increase in the concentration of Na^+ and Ca^{2+} in mitochondria [17, 18]. Disorders of the membrane transport also lead to a deficiency of antioxidant defense components [19], which causes the accumulation of reactive oxygen species (ROS) generated in mitochondria [20]. An increase in the Ca^{2+} concentration in mitochondria also plays a significant role in enhancing the production of ROS through the factor induced by 1-alpha hypoxia (HIF-1α-induced activation of NOX (NADPH oxidase)) [16]. Under conditions of the excess ROS and activation of their generation processes, the intensification of lipid peroxidation (LPO) is observed, which causes damage to lipids, the oxidation chain proteins, and cell membranes in mitochondria [16].

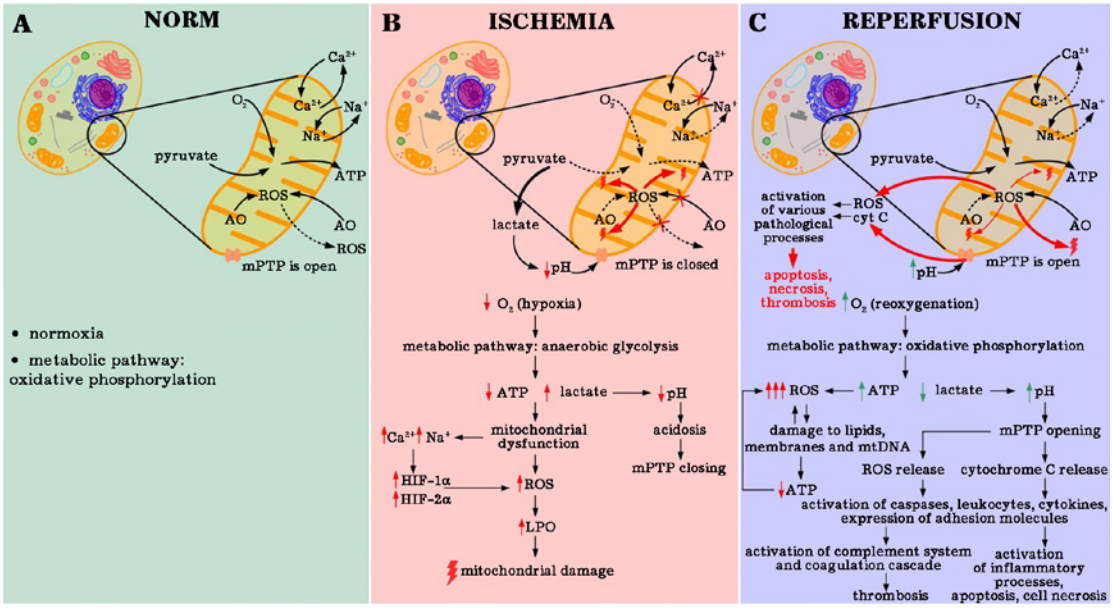

Fig. 1. The scheme of pathophysiological processes in the norm (A), in ischemia (B), and in reperfusion (C) (author's illustration)

However, the most significant effects occur during reperfusion (Fig. 1B), since a cascade of metabolic, molecular, cellular, and other

reactions is triggered [16]. Reoxygenation leads to a reverse transition from the anaerobic glycolysis activated during ischemia to the oxidative phosphorylation, which allows mitochondria to synthesize ATP again. However, due to the damage inflicted by ROS to the mitochondrial structures, an even greater formation of active radicals occurs [21], which causes irreversible damage, involving mitochondrial DNA (mtDNA) [22], and the inhibition of ATP synthesis [18, 23]. Normalization of intracellular pH during reinfusion, as well as an increase in ROS, activates the opening of the mitochondrial pore [16, 18], which, on the one hand, leads to a supersaturation of mitochondria with Ca^{2+} and to a subsequent activation of calpain [17], and, on the other hand, promotes the release of active radicals and several other compounds, including cytochrome *C* (cyt *C*), which cause the activation of caspases [16]. Further, a decrease in the level of nitric oxide [16], the activation of leukocytes [24], neutrophils [16], the expression of cytokines [17] and adhesion molecules [17, 24] are observed. The combination of processes is the reason for the activation of cascades of cell death reactions due to apoptosis and necrosis. In addition, the complement system and the coagulation cascade are activated, which ultimately can lead to thrombosis in the microvasculature of the graft [16, 24].

Understanding the processes occurring during ischemia and reperfusion, allows us to identify a significant number of target points for the application of HBO therapy in order to minimize the degree of IRI at an early stage.

Thus, the effectiveness of HBO was shown both at the stage of ischemia (Fig. 2A) and reperfusion (Fig. 2B), which is characterized by a decrease in mitochondrial damage [25], a restoration of the activity of oxidative enzymes [26], an increase in the activity of nitric oxide synthase (NOS) and an increase in the synthesis of nitric oxide (NO) [27],

the activation and proliferation of peripheral blood mononuclear cells (PBMC) [28], the decreased lipid peroxidation [29–31], leukocyte adhesion to endothelial cells [32], neutrophil sequestration [33], cytokine levels (TNF-α, IL-1β, IL-6) [34, 35], expression HIF-1α [36, 37], the affinity of the molecules of the major histocompatibility complex (MHC) class I [35], inhibiting the leukocyte differentiation antigen SD45+ [28], the inhibition of apoptosis [35, 36, 38].

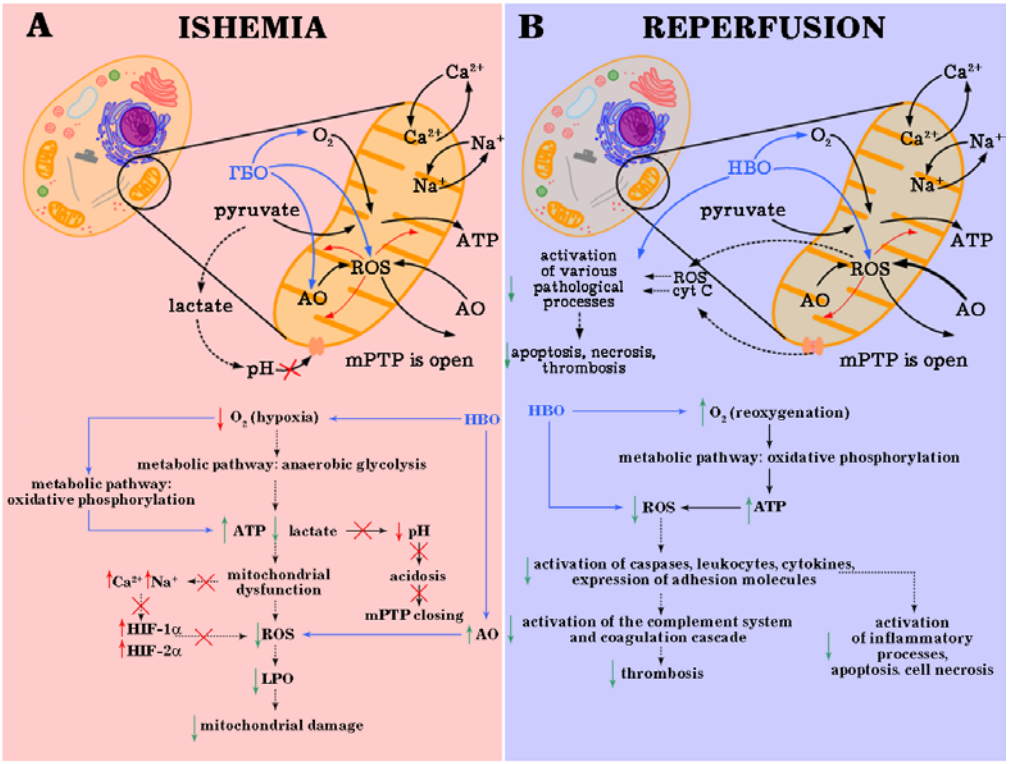

Fig. 2. The scheme of pathophysiological processes in ischemia (B) and reperfusion (C) under HBO conditions (author's illustration)

Additionally, at this stage, the effect of IRP can be reduced due to pharmacological regulation, for example, it is known that cyclosporine is an inhibitor of mitochondrial pores [39]. Thus, the use of additional inhibitory processes occurring during ischemia and reperfusion in combination with HBO can lead to a decrease in the IRI severity.

Hyperbaric oxygenation is an organ protective tool

The first studies on the use of HBO in the field of transplantation were conducted in the 60s of the last century [40] and aimed at studying the effect of HBO on the safety of organs during their storage. So, in model experiments on the example of the transplant kidney [41, 42], liver [43–45], it was shown that storing the organ under hyperbaric conditions could significantly increase the viability of the transplanted organ. Despite the declining interest in this topic associated with the emergence of new preservative solutions in the 80s, and the complexity of HBO equipment, but thanks to the recently emerged new knowledge about the cellular and molecular mechanisms of HBO, and the commercially available small and light hyperbaric pressure chambers, the studies of the effect of HBO on transplanted organs during their storage again begin to attract attention [46, 47]. For example, the development of new perfusion devices using HBO technology can increase the safety of the ultrastructure of hepatocytes and glycogen [48].

In addition, a pre-treatment under HBO conditions showed a positive effect on the survival rate of organ and tissue grafts when used in wound reconstructive surgery [34, 49, 50].

One of the noteworthy studies was the description of 2 clinical cases of HBO therapy use in donors with brain death before organ harvesting and transplantation, which showed that organs stored in this way *in vivo* may have less cellular damage due to ischemia, reperfusion, and absence of reflux phenomena [51].

Hyperbaric oxygenation in the post-transplant period

The studies on the impact of HBO therapy in the post-transplant period, which, in our opinion, deserve special attention, are mainly represented by animal model experiments. For example, a positive effect

was shown for transplantation of bone fragments in rabbits [52], transplantation of pancreas islet cells in mice [36, 53], ischemic reperfusion injury to the kidney in rats [29, 54–56], and ischemic reperfusion injury to the liver in rats [57], and liver regeneration in rats after resection [58, 59]. In addition, HBO causes an increase in the synthesis of vascular endothelial growth factor (VEGF) [36, 60], induces tolerance [28], and increases transplant survival [33, 61].

And only a small number of studies have been devoted to the study of the HBO therapy effect in the post-transplant period in humans. Most of them are the studies of patients with impaired liver function [62–69].

As in the model experiments described above, a favorable effect of HBO therapy after hepatectomy was found in liver cancer patients, which manifested itself in a decreased risk of developing hyperbilirubinemia or liver failure [63], a decreased level of bilirubin, aspartate aminotransferase, bile acids, and an increased hepatocyte proliferation after liver resection in living donors [64], lowering the risk of developing liver necrosis [65]. The HBO therapy was shown to speed up the inclusion of collateral blood flow during hepatic artery thrombosis (31 days in the control group versus 14 days in the group of HBO-treated patients), which can reduce the risk of early graft dysfunction and the need for retransplantation, and also increases the length of the period to liver transplantation (12.7 days in the control group and 157 in the study group) [66]. A number of studies [67, 68] present similar data reflecting the effect of HBO therapy on the recanalization of the hepatic artery in its thrombosis and restoration of liver function to normal or close to normal condition. In addition, there is evidence of the HBO effect on the reduction of graft edema [67]. An important study is the one reflecting an improvement in the condition of patients in a waiting list before liver transplantation [69]. So, there was a decrease in the number and intensity

of episodes of encephalopathy, the absence of signs of spontaneous bacterial peritonitis, gastrointestinal bleeding and a decrease in the degree of ascites; a general improvement in the state of recipients was observed within a few weeks after a series of HBO sessions.

As for the transplantation of other organs (kidney, heart, lungs), only a few studies have been found, however, showing very encouraging results of the HBO therapy use in transplantation practice. For example, it was shown that in the early post-transplantation period after a kidney transplant, the recipients treated with HBO sessions showed an accelerated recovery of diuresis, normalization of the level of urea compared with the control group of patients [70]. The patients after heart transplantation who received the HBO therapy showed a stimulated formation of collagen matrix [71]. There is a positive effect of HBO therapy in patients after lung transplantation, in particular, in those with infectious complications, when other methods were ineffective or unsuitable [72, 73].

Conclusion

Although the mechanisms of hyperbaric oxygenation action are not yet fully understood and some aspects of physiological processes under conditions of hyperoxia remain unclear, the efficacy of this therapy at various stages of the transplantation process (preconditioning, organ donation, organ storage, in the early and late post-transplant periods) allows us to conclude that this method should be more widely involved transplantation practice.

References

1. Xiao B, Xia W, Zhang J, Liu B, Guo S. Prolonged cold ischemic time results in increased acute rejection in a rat allotransplantation model.

J Surg Res. 2010;164(2):e299–e304. PMID: 20934711 https://doi.org/10.1016/j.jss.2010.08.012

2. Efuni SN. *Rukovodstvo po giperbaricheskoy oksigenatsii (teoriya i praktika klinicheskogo primeneniya).* Moscow: Meditsina Publ.; 1986. (In Russ.).

3. Whelan HT, Kindwall E. *Hyperbaric Medicine Practice.* 4th ed. North Palm Beach: Best Publishing Company; 2017.

4. Weaver LK. (ed.) *Undersea and hyperbaric medical society. Hyperbaric oxygen therapy indications.* 13th ed. North Palm Beach: Best Publishing Company; 2014.

5. Rogatsky GG, Stambler I. Hyperbaric oxygenation for resuscitation and therapy of elderly patients with cerebral and cardio-respiratory dysfunction. *Front Biosci (Schol Ed).* 2017;9:230–243. PMID: 28410116 https://doi.org/10.2741/s484

6. Neubauer RA, End E. Hyperbaric oxygenation as an adjunct therapy in strokes due to thrombosis. A review of 122 patients. *Stroke.* 1980;11(3):297–300. PMID: 7394869 https://doi.org/10.1161/01.str.11.3.297

7. Lebedev VV, Isakov YuV, Pravdenkova SV. Vliyaniye giperbaricheskoy oksigenatsii na klinicheskoye techeniye i oslozhneniya v ostrom periode ishemicheskikh insul'tov. *Burdenko's Journal of Neurosurgery.* 1983;3:37–42. (In Russ.).

8. Neubauer RA, Gottlieb SF, Kagan RL. Enhancing "idling" neurons. *Lancet.* 1990;335(8688):542. PMID: 1968553 https://doi.org/10.1016/0140-6736(90)90777-3

9. Neubauer RA, Gottlieb SF, Miale A Jr. Identification of hypometabolic areas in the brain using brain imaging and hyperbaric oxygen. *Clinical nuclear medicine.* 1992;17(6):477–481. PMID: 1617842 https://doi.org/10.1097/00003072-199206000-00010

10. Neubauer RA, Neubauer V, Gerstenbrand F. Late treatment of severe brain injury with hyperbaric oxygenation. *J Am Physic Surg.* 2005;10(2):58-59.

11. Rogatsky GG, Shifrin EG, Mayevsky A. Optimal dosing as a necessary condition for the efficacy of hyperbaric oxygen therapy in acute ischemic stroke: a critical review. *Neurol Res.* 2003;25(1):95–98. PMID: 12564134 https://doi.org/10.1179/016164103101201003

12. Levina OA, Romasenko MV, Krylov VV, Petrikov SS, Goldin MM, Evseev AK. Hyperbaric oxygenation therapy at acute cerebral diseases and brain damages. The new opportunities and new solutions. *Russian journal of neurosurgery.* 2014;(4):9–15. (In Russ.). https://doi.org/10.17650/1683-3295-2014-0-4-9-15

13. Mathieu D. (ed.) *Handbook on hyperbaric medicine.* Berlin: Springer; 2006.

14. Jain KK. *Textbook of hyperbaric medicine.* Göttingen: Hogrefe& Huber Publishers; 2009.

15. Teplov VM, Razumnyy NV, Povzun AS, Batotsyrenov BV, Logunov KV, Rusakevich KI, et al. *Vozmozhnosti primeneniya giperbaricheskoy oksigenatsii v neotlozhnoy meditsine i reanimatsii.* Uchebno-metodicheskoye posobiye. St. Petersburg; 2017. (In Russ.).

16. Krezdorn N, Tasigiorgos S, Wo L, Turk M, Lopdrup R, Kiwanuka H, et al. Tissue conservation for transplantation. *Innov Surg Scie.* 2017;2(4):171–187. PMID: 31579751 https://doi.org/10.1515/iss-2017-0010

17. Kosieradzki M, Rowiński W. Ische-mia/reperfusion injury in kidney transplantation: mechanisms and prevention. *Transplant Proc.* 2008;40(10):3279–3288. PMID: 19100373 https://doi.org/10.1016/j.transproceed.2008.10.004

18. Walters AW, Porter GA Jr, Brookes PS. Mitochondria as a drug target in ischemic heart disease and cardiomyopathy. *Circ Res.* 2012;111(9):1222–1236. PMID: 23065345 https://doi.org/10.1161/CIRCRESAHA.112.265660

19. Ahmed E, Donovan T, Yujiao L, Zhang Q. Mitochondrial targeted antioxidant in cerebral ischemia. *J Neurol Neurosci.* 2015;6(2):pii:17. PMID: 26937332 https://doi.org/10.21767/2171-6625.100017

20. Kezic A, Spasojevic I, Lezaic V, Bajcetic M. Mitochondria-targeted antioxidants: future perspectives in kidney ischemia reperfusion injury. *Oxid Med Cell Longev.* 2016;2016:2950503. PMID: 27313826 https://doi.org/10.1155/2016/2950503

21. Murphy MP. How mitochondria produce reactive oxygen species. *Biochem J.* 2009;417(1):1–13. PMID: 19061483 https://doi.org/10.1042/BJ20081386

22. Jassem W, Fuggle SV, Rela M, Koo DD, Heaton ND. The role of mitochondria in ischemia/reperfusion injury. *Transplantation.* 2002;73(4):493–499. PMID: 11889418 https://doi.org/10.1097/00007890-200202270-00001

23. Jassem W, Heaton ND. The role of mitochondria in ischemia/reperfusion injury in organ transplantation. *Kidney Int.* 2004;66(2):514–517. PMID: 15253700 https://doi.org/10.1111/j.1523-1755.2004.761_9.x

24. Collard CD, Gelman S. Pathophysiology, clinical manifestations, and prevention of ischemia–reperfusion injury. *Anesthesiology.* 2001;94(6):1133–1138. PMID: 11465607 https://doi.org/10.1097/00000542-200106000-00030

25. Sgarbi G, Giannone F, Casalena GA, Baracca A, Baldassare M, Longobardi P, et al. Hyperoxia fully protects mitochondria of explanted

livers. *J Bioenerg and Biomembr*. 2011;43(6):673–682. PMID: 22015484 https://doi.org/10.1007/s10863-011-9390-3

26. Thomas MP, Brown LA, Sponseller DR, Williamson SE, Diaz JA, Guyton DP. Myocardial infarct size reduction by the synergistic effect of hyperbaric oxygen and recombinant tissue plasminogen activator. *Am Heart J.* 1990;120(4):791–800. PMID: 212101010 https://doi.org/1016/0002-8703(90)90194-3

27. Baynosa RC, Naig AL, Murphy PS, Fang XH, Stephenson LL, Khiabani KT, et al. The effect of hyperbaric oxygen on nitric oxide synthase activity and expression in ischemia-reperfusion injury. *J Surg Res.* 2013;183(1):355–361. PMID: 23485074 https://doi.org/10.1016/j.jss.2013.01.004

28. MacKenzie DA, Sollinger HW, Hullet DA. Decreased immunogenicity of human fetal pancreas allografts following hyperbaric oxygen culture. *Transplant Proc.* 2003;35(4):1499–1502. PMID: 12826204 https://doi.org/10.1016/s0041-1345(03)00362-2

29. Gurer A, Ozdogan M, Gomceli I, Demirag A, Gulbahar O, Arikok T, et al. Hyperbaric oxygenation attenuates renal ischemia-reperfusion injury in rats. *Transplant Proc.* 2006;38(10):3337–3340 PMID: 17175266 https://doi.org/10.1016/j.transproceed.2006.10.184

30. Godman CA, Joshi R, Giardina C, Perdrizet G, Hightower LE. Hyperbaric oxygen treatment induces antioxidant gene expression. *Ann NY Acad Sci.* 2010;1197:178–183. PMID: 20536847 https://doi.org/10.1111/j.1749-6632.2009.05393.x

31. Chen MF, Chen HM, Ueng SW, Shyr MH. Hyperbaric oxygen pretreatment attenuates hepatic reperfusion injury. *Liver*. 1998;18(2):110–116. PMID: 9588769 https://doi.org/10.1111/j.1600-0676.1998.tb00135.x

32. Zamboni WA, Roth AC, Russell RC, Graham B, Suchy H, Kucan JO. Morphologic analysis of the microcirculation during reperfusion of ischemic skeletal muscle and the effect of hyperbaric oxygen. *Plast Reconst Surg.* 1993;91(6):1110–1123. PMID: 8479978 https://doi.org/10.1097/00006534-199305000-00022

33. Kihara K, Ueno S, Sakoda M, Aikou T. Effects of hyperbaric oxygen exposure on experimental hepatic ischemia reperfusion injury: relationship between its timin-g and neutrophil sequestration. *Liver Transpl.* 2005;11(12):1574–1580. PMID: 16315298 https://doi.org/10.1002/lt.20533

34. Qi Z, Gao CJ, Wang YB, Ma XM, Zhao L, Liu FJ, et al. Effects of hyperbaric oxygen preconditioning on ischemia-reperfusion inflammation and skin flap survival. *Chin Med J (Engl).* 2013;126(20):3904-3909. PMID: 24157154

35. Muralidharan V, Christophi C. Hyperbaric oxygen therapy and liver transplantation. *HPB (Oxford).* 2007;9(3):174–182. PMID: 18333218 https://doi.org/10.1080/13651820601175926

36. Sakata N, Chan NK, Ostrowski RP, Chrisler J, Hayes P, Kim S, et al. Hyperbaric oxygen therapy improves early posttransplant is let function. *Pediatr Diabetes.* 2010;11(7):471–478. PMID: 20144181 https://doi.org/10.1111/j.1399-5448.2009.00629.x

37. Choudhury R. Hypoxia and hyperbaric oxygen therapy: a review. *Int J Gen Med.* 2018;11:431–442. PMID: 30538529 https://doi.org/10.2147/IJGM.S172460

38. Chaves JC, Fagundes DJ, Simões M de J, Bertoletto PR, Oshima CT, Taha MO, et al. Hyperbaric oxygen therapy protects the liver from apoptosis caused by ischemia-reperfusion injury in rats. *Microsurgery.* 2009:29(7):578–583. PMID: 19399878 https://doi.org/10.1002/micr.20664

39. Pozhilova EV, Levchenkova OS, Novikov VE. The regulatory role of mitochondrial pora and the possibility of its pharmacological modulation. *Reviews on clinical pharmacology and drug therapy*. 2014;12(3):13–19. (In Russ.). https://doi.org/10.17816/RCF12313-19

40. Malazai AJ, Worku DG, McGee J, vanMeter K, Slakey DP. The history of hyperbaric oxygen therapy and kidney transplant surgery. *Undersea and Hyperbaric Medicine*. 2011;38(4):247–255. PMID: 21877553

41. Lillehei RC, Manax WG, Bloch JH, Eyal Z, Hidalgo F, Longerbeam JK. In vitro preservation of whole organs by hypothermia and hyperbaric oxygenation. *Cryobiology*. 1964;1(2):181–193. PMID: 5333442 https://doi.org/10.1016/0011-2240(64)90010-0

42. Ladaga LG, Nabseth DC, Besznyak I, Hendry WF, McLeod G, Deterling RA. Preservation of canine kidneys by hypothermia and hyperbaric oxygen: Long term survival of autografts following 24-hour storage. *Annals of surgery*. 1966;163(4):553–558. PMID: 5327272 https://doi.org/10.1097/00000658-196604000-00007

43. Slapak M, Wigmore RA, MacLean LD. Twenty-four hour liver preservation by the use of continuous pulsatile perfusion and hyperbaric oxygen. *Transplantation*. 1967;5(4):1154–1158. PMID: 4860607 https://doi.org/10.1097/00007890-196707001-00052

44. Uchida H, Ruiz JO, Alho AV, Schult-z LS, Loken MK, Lillehei RC. In vitro and in vivo assessment of the preserved liver under hypothermia and hyperbaria without perfusion. *Trans Am Soc Artif Intern Organs*. 1970;16:300–306. PMID: 4916736

45. Spilg H, Uys CJ, Hickman R, Saunders SJ, Terblanche J. Twelve-hour liver preservation in the pig using hypothermia and hyperbaric oxygen. Br J Surg. 1972;59(4):273–276. PMID: 4553587

46. Yu SY, Chiu JH, Yang SD, Yu HY, Hsieh CC, Chen PJ, et al. Preconditioned hyperbaric oxygenation protects the liver against ischemia-reperfusion injury in rats. *J Surg Res.* 2005;128(1):28–36. PMID:15964020https://doi.org/10.1016/j.jss.2005.04.025

47. Tran NQ, Malcontenti-Wilson C, Hammoud S, Millar I, Christophi C, Muralidharan V. Hyperbaric oxygen therapy reduces the severity of ischaemia, preservation and reperfusion injury in a rat model of liver transplantation. *HPB (Oxford).* 2012;14(2):103–114. PMID: 22221571 https://doi.org/10.1111/j.1477-2574.2011.00410.x

48. Giannone FA, Treré D, Domenicali M, Grattagliano I, Baracca A, Sgarbi G, et al. An innovative hyperbaric hypothermic machine perfusion protects the liver from experimental preservation injury. *Scientific World Journal.* 2012;2012:573410. PMID: 22593698 https://doi.org/10.1100/2012/573410

49. Svehlik J Jr, Zábavniková M, Guzanin S, Svehliková G, Svehlik J Sr. Hyperbaric oxygenotherapy as a possible means of preventing ischemic changes in skin grafts used for soft tissue defect closure. *Acta Chir Plast.* 2007;49(2):31–35. PMID: 17684838

50. Francis A, Baynosa RC. Hyperbaric oxygen therapy for the compromised graft or flap. *Adv Wound Care (New Rochelle).* 2017;6(1):23–32. PMID: 28116225 https://doi.org/10.1089/wound.2016.0707

51. Bayrakci B. Preservation of organs from brain dead donors with hyperbaric oxygen. *Pediatr Transplantat.* 2008;12(5):506–509. PMID: 18672481 https://doi.org/10.1111/j.1399-3046.2007.00858.x

52. Sawai T, Niimi A, Takahashi H, Ueda M. Histologic study of the effect of hyperbaric oxygen therapy on autoge-nous free bone grafts. *J Oral Maxillofac Surg.* 1996;54(8):975–981. PMID: 8765387 https://doi.org/10.1016/s0278-2391(96)90396-1

53. Juang JH, Hsu BR, Kuo CH, Uengt SW. Beneficial effects of hyperbaric oxygen therapy on islet transplantation. *Cell Transplant.* 2002;11(2):95–101. PMID: 28853948 https://doi.org/10.3727/096020198389825

54. Solmazgul E, Uzun G, Cermik H, Atasoyu EM, Aydinoz S, Yildiz S. Hyperbaric oxygen therapy attenuates renal ische-mia/reperfusion injury in rats. *Urol Int.* 2007;78(1):82–85. PMID: 17192739 https://doi.org/10.1159/000096941

55. Rubinstein I, Abassi Z, Milman F, Ovcharenko E, Coleman R, Winaver J, et al. Hyperbaric oxygen treatment improves GFR in rats with ischaemia/reperfusion renal injury: a possible role for the antioxidant/oxidant balance in the ischaemic kidney. *Nephrol Dial Transplant.* 2009;24(2):428–436. PMID: 18799609 https://doi.org/10.1093/ndt/gfn511

56. Ramalho RJ, de Oliveira PS, Cavaglieri RC, Silva C, Medeiros PR, Filho DM, et al. Hyperbaric oxygen therapy induces kidney protection in an ischemia/reperfusion model in rats. *Transplant Proc.* 2012;44(8):2333–2336. PMID: 23026586 https://doi.org/10.1016/j.transproceed.2012.07.020

57. Silveira MR, Margarido MR, Vanni JC, Nejo JR, Castro-E-Silva O. Effects of hyperbaric oxygen the-rapy on the liver after injury caused by the hepatic ischemia-reperfusion process. *Acta Cir Bras.* 2014;29(Suppl 1):29–33. PMID: 25185053 https://doi.org/10.1590/s0102-86502014001300006

58. Özden TA, Uzun H, Bohloli M, Toklu AS, Paksoy M, Simsek G, et al. The Effects of hyperbaric oxygen treatment on oxidant and antioxidants levels during liver regeneration in rats. *Tohoku J Exp Med.* 2004;203(4):253–265. PMID: 15297730 https://doi.org/10.1620/tjem.203.253

59. Tolentino EC, Castro e Silva O, Zucoloto S, Souza ME, Gomes MC, Sankarankutty AK, et al. Effect of hyperbaric oxygen on liver regeneration in a rat model. *Transplant Proc.* 2006;38(6):1947–1952. PMID: 16908331 https://doi.org/10.1016/j.transproceed.2006.06.066

60. Sheikh AY, Gibson JJ, Rollins MD, Hopf HW, Hussain Z, Hunt TK. Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. *Arch Surg.* 2000;135(11):1293–1297. PMID: 11074883 https://doi.org/10.1001/archsurg.135.11.1293

61. Kaelin CM, Im MJ, Myers RA, Manson PH, Hoopes JE. The effects of hyperbaric oxygen on free flaps in rat. *Arch Surg.* 1990;125(5):607–609. PMID: 2331219 https://doi.org/10.1001/archsurg.1990.01410170053011

62. Lv H, Han CH, Sun XJ, Liu WW. Application of hyperbaric oxygen in liver transplantation. *Med Gas Res.* 2016.6(4):212–218. PMID: 28217293https://doi.org/10.4103/2045-9912.196903

63. Ueno S, Tanabe G, Kihara K, Aoki D, Arikawa K, Dogomori H, et al. Early post-operative hyperbaric oxygen therapy modifies neutrophile activation. *Hepatogastroenterology.* 1999;46(27):1798–1799. PMID: 10430348

64. Suehiro T, Shimura T, Okamura K, Okada T, Okada K, Hashimoto S, et al. The effect of hyperbaric oxygen treatment on postoperative morbidity of left lobe donor in living donor adult liver transplantation. *Hepatogastroenterology.* 2008;55(84):1014–1119. PMID: 18705320

65. Castro-e-Silva O, Sankarankutty AK, Martinelli AL, Souza FF, Teixeira AC, Feres O, et al. Therapeutic effect of hyperbaric oxygen in hepatic artery thrombosis and functional cholestasis after orthotopic liver transplantation. *Transplantat Proc.* 2006;38(6):1913–1917. PMID: 16908321 https://doi.org/10.1016/j.transproceed.2006.06.062

66. Mazariegos GV, O'Toole K, Mieles LA, Dvorchik I, Meza M, Briassoulis G, et al. Hyperbaric oxygen therapy for hepatic artery thrombosis after liver transplantation in children. *Liver Transpl Surg.* 1999;5(5):429–436. PMID: 10477845 https://doi.org/10.1002/lt.500050518

67. Grover I, Conley L, Alzate G, Lavine J, Van Hoesen K, Khanna A. Hyperbaric oxygen therapy for hepatic artery thrombosis following liver transplantation: Current concepts. *Pediatr Transplantat.* 2006;10(2):234–239. PMID: 16573613 https://doi.org/10.1111/j.1399-3046.2005.00415.x

68. Franchello A, Ricchiuti A, Maffi L, Romagnoli R, Salizzoni M. Hyperbaric oxygen therapy in liver transplantation; is its uselimited to the management of hepatic artery thrombosis? *Transpl Int.* 2010;23(9):e49–e50. PMID: 19807898 https://doi.org/10.1111/j.1432-2277.2009.00979.x

69. Kreimer F, de Araújo-Jr GC, Campos JM, Euclides DMF, D'Albuquerque LAC, Ferraz ÁAB. Preliminary results of hyperbaric oxygen therapy on patients on the waiting list for liver transplantation. *ABCD (São Paulo).* 2011;24(1):48-51. http://dx.doi.org/10.1590/S0102-67202011000100010

70. Romasenko MV, Levina OA, Pinchuk AV, Storozhev RV, Rzhevskaya ON. Use of hyperbaric oxygenation in the combination therapy of posttransplant kidney patients in the early postoperative period. *Transplantologiya.The Russian Journal of Transplantation.* 2011;(2–3):75–79. (In Russ.). https://doi.org/10.23873/2074-0506-2011-0-2-3-75-79

71. Petzold T, Feindt PR, Carl UM, Gams E. Hyperbaric oxygen therapy in deep sternal wound infection after heart transplantation. *Chest.* 1999;115(5):1455–1458. PMID: 10334171 https://doi.org/10.1378/chest.115.5.1455

72. Higuchi T, Oto T, Millar IL, Levvey BJ, Williams TJ, Snell GI. Preliminary report of the safety and efficacy of hyperbaric oxygen therapy for specific complications of lung transplantation. *J Heart Lung Transplant.* 2006;25(11):1302–1309. PMID: 17097493 https://doi.org/10.1016/j.healun.2006.08.006

73. Shabunin AV, Mitrokhin AA, Vodneva MM, Gautier SV, Poptsov VN, Golovinskiy SV, et al. Giperbaricheskaya oksigenatsiya pri transplantatsii organov (klinicheskiy opyt na primere transplantatsii legkikh). *Russian Journal of Transplantology and Artificial Organs.* 2016;18(S):71. (In Russ.).

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