

Advanced Intermittent Hypobaric/Hyperbaric Method Enhanced and Cured Type 2 Insulin-Independent Diabetes Mellitus Patients: A Clinical Trial

Sahar Ahmed Abdalbary¹Ph.D; Alaa Balbaa²Ph.D; Khaled A. Zed³ Ph.D.,
¹Ph.D., Orthopaedic Physical Therapy, Faculty of Physical Therapy, Cairo University, Egypt.

²Professor of Orthopaedic Physical Therapy and Former Dean of Physical Therapy Faculty, Cairo University, Egypt.

³Professor Doctor, former executive director of the Japanese Ministry of State for Science and Technology Policy, and former R&D director of the Advance Institute of Science and Technology, Japan, Biomedical Department.

Corresponding Authors

Sahar Ahmed Abdalbary Street 107, Maadi, Cairo, Egypt 11431

Tel no.: +20-100-5047018 - +81-90-1817-0369 Fax no.: +20-225264342

Email: saharabdalbary@gmail.com & drzed@jcom.zaq.ne.jp;

veritasjapan@jcom.zaq.ne.jp

Abstract

Background:

Advanced intermittent hypoxia-normoxia KZ-001 (manufactured in Japan under the Japanese Wellness Science and Technology) is a combination of a fine-tuned hypobaric (hypoxia) and hyperbaric (hyperoxia) chamber. It is a new Japanese method that uses both aerospace and high-terrestrial altitude research or training to stimulate the effects of high altitude on the human body, especially hypoxia and hyperoxia.

Objectives:

This study aimed to test two hypotheses in response to advanced intermittent hypoxia-normoxia KZ-001 stratification based on its mechanism of action and to answer the following clinical question: Do patients' glycated hemoglobin (HbA1c) levels decrease when undergoing advanced intermittent hypoxia-normoxia KZ-001 treatment?

Material and methods:

This was an observational clinical trial approved by, from January 2019 to August 2020.

Outpatients from the endocrine and internal medicine clinics of who met the following criteria were included in the study: clinical diagnosis of type 2 diabetes mellitus (type2DM), ages ≥ 30 and ≤ 60 years, currently treated with one or two classes of oral glucose-lowering therapy (given either as separate or combined medications), diabetes duration ≥ 12 months, no change in diabetes treatment (new treatments or dose change)

within the past 3 months, HbA1c level >58 mmol/mol (>7.5%) and ≤110 mmol/mol (≤12.2%), and able and willing to provide informed consent. A total of 100 patients (40 women and 60 men) were recruited.

Period of treatment depends on given cases started from 48 to 480 hours seasons. Each treatment session lasted for 50 min thrice with 10-min breaks in between, making sure to drink water during sessions. These were repeated for 12 sessions that lasted for 4 weeks, taking 48 h for three sessions per week.

The patients' HbA1c levels were measured after completing the sessions for 2 days and after one year.

Results:

The initial HbA1c level (mean ± SD) was 8.30 ± 0.75 and at randomization was 6.27 ± 0.68 using the paired t-test. Significant differences were observed between patients before and after treatment (p = 0.001). The patients were followed up one year after treatment completion through random HbA1c testing (mean ± SD = 6.77 ± 0.8; p = 0.336, with no significant difference), without any change in their treatment regimen or even their lifestyle.

Conclusions: Hypobaric/hyperbaric chamber treatment is an adjuvant to the standard therapy in insulin-independent T2DM patients, without replacing and/or delaying medical treatment, with favorable results. Provided that this therapeutic tool is available, it can contribute to decreased amputation rates and reduce the cost of standard treatment, hospitalization, drugs, and use of operating theaters.

Keywords: Hypobaric/hyperbaric chamber, Type 2 diabetes mellitus, Clinical trial

Introduction

Conventional hyperbaric oxygen therapy (HBOT) is a well-known process in which a patient inhales 100% oxygen with a pressure >1 ATA, while a hypobaric therapy is the reduction of oxygen when exposed to a higher altitude¹.

From a historical perspective, the first hyperbaric chamber was designed in Russia in 1662; later, it was built by the British clergyman, Nathaniel Henshaw. It used compressed air, as oxygen was not identified and not yet discovered. In 1775, Joseph Priestly discovered oxygen, but he called it dephlogisticated air. The French chemist Antoine Lavoisier, who lived after Priestly, later named it oxygen. In 1928, the Steel Ball Hospital (hyperbaric hotel) was invented in Germany. It was a six-floor hospital with 72 luxurious rooms. It was eventually closed down because of the lack of evidence supporting the use of hypobaric treatment in some medical conditions such as cancer and diabetes. In 1937, the first medical application of hypobaric treatment was achieved and was used for the treatment of decompression sickness², which can be explained through Boyle's law.

A few cardiac surgeries in the 1950s were performed in an operating room that was designed as a large multiplace chamber, which are no longer in use due to their high costs and the invention of recent ventilators that deliver enough oxygen during surgery³.

Advanced intermittent hypoxia-normoxia KZ-001 (manufactured in Japan under the Japanese Wellness Science and Technology) is a combination of a fine-tuned hypobaric (hypoxia) and hyperbaric (hyperoxia) chamber. It is a new Japanese method that uses both aviation and high-altitude aerospace research or training to reproduce the effects of high altitude on the human body, especially decreased oxygen and hyperoxia.

Real-life oxygen concentrations provide a clear index of tissue metabolic levels in different physiological or pathological cases.

Epigenetic influences on Brain function varies in different environment milieu; metabolic activity and oxygen increases as in the bold haemoglobin needed to manage the brain multiple task.

The oxygen demands must be precisely controlled in the brain in relation to the local demand caused by metabolic activity. Using different oxygen probes, the actual oxygen content has been reported to range from 1% to 5% and even lower in some areas of the brain. Therefore, we used an optical fiber luminescent oxygen sensor (MICROX TX3, fiber-optic oxygen meter) to directly measure the oxygen content in the entire cerebral area as well as real-time temporal changes in PO₂ in various cerebral regions, particularly in the SVZ and DG, where neurogenesis occurs in relation to reduced external oxygen content⁴.

Hyperbaric oxygen treatment is defined as breathing pure oxygen in a pressurized environment and is a well-known therapy for decompression sickness, likely caused due to scuba diving. Conditions treated with HBOT include major infections, air or gas embolism, and wounds that could not be alleviated due to diabetes or radiation injury.

In a HBOT chamber, the air pressure is increased two to three times higher than the normal air pressure. Under these conditions, the lungs can carry more oxygen than would be possible during inspiration of pure oxygen at normal air pressure.

When the blood gathers this extra oxygen throughout the body, it helps kill bacteria and promotes the release of substances called growth factors and stem cells, which enhance healing⁵.

HBOT is a therapy that comprises the administration of 100% oxygen at a high environmental pressure, causing a direct increase in tissue oxygenation⁶. It also mobilizes stem cells that enhance vasculogenesis⁷.

Hypoxia induces several activities from the individual level to the regulation and function of the cell nucleus. Prolonged exposure to low oxygen tension is the main cause of most disease states. New approaches in the study of molecular biology have begun to address the gap between cellular responses to hypoxia and physiology. Hyperbaric oxygen treatment is a therapy for hypoxic- and inflammatory-driven states. This study explains

hypoxia, the physiological changes associated with hypoxia, the effects that occur in cells during hypoxic states, and the effect of hyperbaric oxygen treatment in patients suffering from diseases with underlying hypoxia⁸.

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia and is classified into two main types: type 1 DM (T1DM) and type 2 DM (T2DM). T1DM is an autoimmune disease that results in a permanent deficiency of insulin secretion, whereas T2DM is characterized primarily by a decrease in insulin secretion, typically accompanied by insulin resistance (IR). T2DM has become one of the most serious health challenges of the twenty-first century, with considerable societal implications worldwide. Since the 1980s, the prevalence of T2DM globally has rapidly increased. Although T2DM has been traditionally recognized as a disease of the middle-aged and elderly, since the 2000s, the greatest relative increase in T2DM incidence and prevalence has been observed in younger adults (i.e., individuals aged)⁹.

For example, well-characterized macrovascular and microvascular complications include cardiovascular disease (CVD), retinopathy, neuropathy, and chronic kidney disease. However, more diverse and nonvascular diabetes complications are becoming common, including nonalcoholic fatty liver disease, psychiatric disease (e.g., depression), cancer, cognitive impairment, infections, and disability¹⁰.

The main target of this study was to test two hypotheses of the advanced intermittent hypoxia-normoxia KZ-001 stratification based on its mechanism of action and to answer the following clinical question: Do patients' glycated hemoglobin (HbA1c) level decrease when undergoing to advanced intermittent hypoxia-normoxia KZ-001 treatment?

Material and Methods

Study design

This was an observational clinical trial approved by Japan and South Africa Private clinics, from January 2019 to August 2020.

Participants

A total of 100 patients (40 women and 60 men) were recruited from outpatient endocrine and internal medicine clinics at Japan and South Africa private Centers

A. Inclusion criteria

Patients were screened using the following criteria: a clinical diagnosis of T2DM, age ≥ 30 and ≤ 60 years old, currently treated with one or two classes of oral glucose-lowering therapy (given either as separate or combined medications), diabetes duration ≥ 12 months, no change in diabetes treatment (new treatments or

dose change) within the previous 3 months, HbA1c level >58 mmol/mol ($>7.5\%$) and ≤ 110 mmol/mol ($\leq 12.2\%$), and able and willing to provide informed consent.

B. Exclusion criteria

The exclusion criteria were as follows: changes in glucose-lowering therapy or dose within the last 3 months; ALT level >2.5 times the upper limit of the assay normal range or known liver disease, specifically bilirubin level >30 $\mu\text{mol/L}$, which is associated with other evidence of liver failure; under insulin treatment within the last 12 months; pregnant women, breastfeeding women, or those planning a pregnancy during the study period; already participated in another clinical trial investigating a medical product; unable or unwilling to provide informed consent. Women of childbearing potential must be willing to use an effective method of contraception from the time consent is signed until treatment discontinuation. A negative pregnancy test is required within 7 days prior to treatment initiation and will be required for continuation at each study visit.

Outcome measures

In line with the World Health Organization guidelines, response to therapy was assessed by measuring the HbA1c level¹¹. The primary outcome was a decrease in HbA1c value a 4-week treatment period. If a participant is unable to complete a full 4-week treatment period, HbA1c level will be measured again and included in the main analysis. After one year, participants achieved the desired HbA1c values.

Preparation of patients for treatment

Patients were approved for hospitalization after a medical doctor checks their vital signs such blood pressure and heart rate, ECG findings, and HbA1c levels, while wearing comfortable clothes during the procedure.

For patient safety, items such as lighters or battery-powered devices that produce heat are not allowed in the chamber. In addition, it may be necessary to remove petroleum-based hair and skin care products, as they are potential fire hazards. Patients were instructed by the healthcare team on how to prepare for the therapy and during the therapy.

Figure 1: The KZ-001 Advanced chamber of hypobaric /hyperbaric

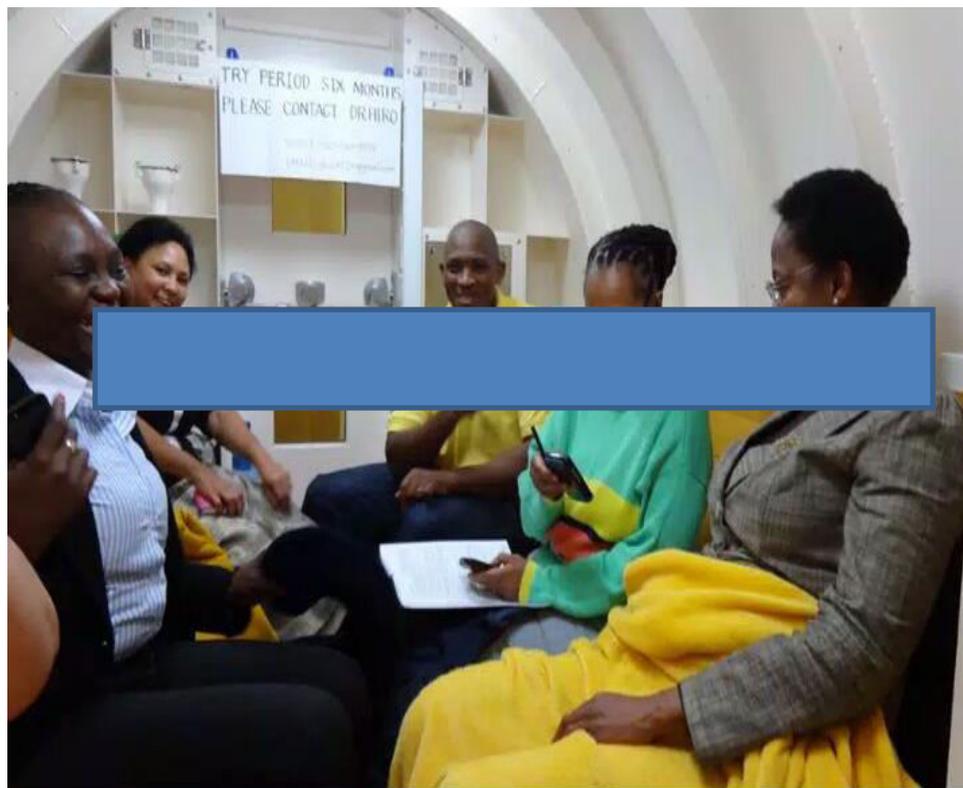


Figure 2. Inside the advanced KZ001 Chamber

Each treatment session lasted for 3 h. Patients stepped into the device for 50 min thrice with 10-min breaks in between, making sure to drink water during this period. These were repeated for 12 sessions that lasted for 4 weeks, taking 48 h for three sessions per week. The chamber can accommodate up to six patients.

The patients' HbA1c levels were measured after completing the sessions for 2 days and after one year.

Statistical analysis

The datasets were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21 software. The alpha level was set to 0.05.

Descriptive statistics including the number of patients, number of males and females, and age using the mean and standard deviation is shown in **Table 1**.

Table 1. Demographic data

Character	Number
Total	100
Female	40
Male	60
Age	43 ± 13.2

Results

This study included 100 patients with T2DM (40 women and 60 men with a mean age of 43 ± 13.2 years).

The initial HbA1c level (mean ± SD) was 8.30 ± 0.75 and at randomization was 6.27 ± 0.68 using the paired t-test. Significant differences were observed between patients before and after treatment (p = 0.001; **Table 2**).

The patients were followed up one year after treatment completion through random HbA1c testing (mean ± SD = 6.77 ± 0.8, p = 0.336, with no significant differences), without any change in their treatment regimen or even their lifestyle (**Table 3**).

Table 2. Comparison of patients' HbA1c levels before and after treatment

	Before treatment	After treatment	P value
HbA1c level	8.30 ± 0.75	6.27 ± 0.68	0.001

Table 3. Comparison of patients' HbA1c levels after treatment and one year after treatment

	After treatment	One year after treatment	P value
HbA1c level	6.27 ± 0.68	6.77 ± 0.8	0.336

Discussion

This study investigated the effect of advanced intermittent hypoxia-normoxia KZ-001 treatment on HbA1c levels.

T2DM is a complex metabolic and endocrine disorder due to the interaction of genetic and environmental factors, altering insulin functionality in peripheral tissues, as well as in pancreatic β -cells. Underlying pathologies such as increased body weight and obesity are the main causes of T2DM development. In conclusion, insulinemia in diabetic patients may be the same as that of euglycemic individuals but are proportionally insufficient in the hyperglycemic states. Delayed insulin action, for determined levels of the hormone, is defined as IR. When β -cells undergo IR, insulin hypersecretion occurs, which compensates for the lack of hormonal action. Hyperglycemia manifests only when there is a relative insulin hyposecretion to glucose stimulus¹².

In conclusion, half of patients with diabetes are unaware of their disease and are thus more susceptible to developing diabetic complications. However, the charges of dealing with diabetes can be unaffordable in terms of money spent and lives lost. In 2015, approximately 5.0 million people died due to diabetes, although in the same year, more than 12% of the global health costs were spent for the disease and its complications. Diabetes complications are common among patients with T1DM or T2DM but, at the same time, are responsible for their high morbidity and mortality. The chronic complications of diabetes can either be microvascular or macrovascular, with the former having a much higher prevalence. Microvascular complications include neuropathy, nephropathy, and retinopathy, while macrovascular complications include CVD, stroke, and peripheral artery disease (PAD). Diabetic foot syndrome has been defined as the presence of foot ulcers associated with neuropathy, PAD, and infection and is the major cause of lower limb amputation¹³.

The most recently developed group of hypoglycemic drugs (2013) is an SGLT2 inhibitor that partially blocks renal glucose reabsorption, which is increased in T2DM patients.

They reduce glycemia through glucosuria, independent of insulin. Many of these drugs are readily available, and other benefits have been explained for them, lowering the risk of CVD as the most important. Because of the main pathogenic alterations in T2DM, the corresponding hypoglycemic drugs were employed in the usual clinical practice¹⁴.

Different treatment approaches, such as HBOT, are newly available to prevent, treat, and reduce the complications of this disease. Clinical studies explain that the mechanism of action of HBOT contributes to their improvement, reversing the hypoxemic state in tissues, sometimes reaching up to 300–400 mmHg¹⁵. HBOT also modulates mitochondrial oxidative stress in the signaling pathway of endothelial growth factors and¹⁶ increases the vascular-tissue concentration differential. In addition, HBOT has been reported to increase the expression of growth factors and their receptors, which are essential for the development of angiogenesis¹⁷. This supports our results when the blood glucose level decreased, and our patients did not complain, which continued for one year.

Hypoxia is an imbalance of oxygen in the organs, tissues, and cells, causing oxygen deficiency or an excessive need for oxygen. Basically, this study states that normal body or cellular functions such as a heart muscle beating or a neuron firing an action potential can also be explained as homeostasis. Hypoxia can be transient, acute, or chronic. Individual tissues have different oxygen tensions and oxygen needs; on average, tissues during rest utilize 5–6 mL of O₂ per deciliter of blood delivered. Hypoxia is better known as a component of the pathology of many disease states, such as ischemia¹⁵.

When a patient's body is subjected to intermittent oxygenation, HbA1c levels significantly improve (p = 0.001).

Ischemia decreases the blood flow to tissues obstructing the delivery of oxygen, glucose, and nutrients while retaining waste products such as carbon dioxide. In this case, ischemia is a subtype of hypoxia in which extra insults prevent baseline function. Both oxygen and glucose are very important for aerobic metabolism; however, hypoxia decreases the energy cell cycle by inducing an oxygen imbalance, preventing cells from functioning normally. If oxygen delivery is insufficient, anaerobic metabolism occurs. Anaerobic metabolism can only deliver a small amount of energy to cells. Glucose breaks down into pyruvate, resulting in cell energy production. Pyruvate is then converted into lactic acid. If hypoxia cannot be converted and aerobic metabolism is restored, cell death and tissue scarring occur, immediately leading to organ dysfunction and death. Other causes of hypoxia include carbon monoxide (CO) poisoning, asphyxiation, sleep apnea, severe anemia, high-altitude sickness, and ventilation-perfusion mismatch. Oxygen delivery is impaired in all these states, similar to ischemia, but different mechanisms¹⁶.

The use of hyperbaric drugs in the case of CO poisoning produces adverse results. Utilizing 100% oxygen at a pressure of 2.5 atm, the half-life of carboxyhemoglobin can be decreased to 20 min. The higher partial pressure of oxygen contained in HBOT

permits oxygen to more rapidly titrate the CO from the hemoglobin, thus decreasing the oxygen and energy deficits in the body. A faster opposite agent for CO poisoning is correlated with less sequelae¹⁸.

Oxygen enters in the bloodstream from ambient air during breathing. Air passes through the trachea and then into the respiratory areas of the lungs and proceeds to the bronchioles and alveoli. However, the pulmonary capillaries exchange enough oxygen in the blood, either attached to hemoglobin or dissolved in the plasma, while excreting CO₂. The oxygenated blood is then pumped by the heart into the left atrium and then the left ventricle, where it is released into the systemic circulation. Oxygenated blood is available for delivery into cells once it reaches the corresponding capillary bed¹⁹, thereby improving the blood glucose levels.

The limitations of our study were the number of samples, prolonged session durations, and the decreased number of available references in this subject since the combination of hypobaric and hyperbaric treatment is still new.

Conclusions

The hypobaric/hyperbaric chamber treatment is an adjuvant to the standard therapy in insulin-dependent T2DM patients, without changing and/or delaying medical therapy, with promising results. Provided that this therapeutic tool is available, it can contribute to decreased amputation rates and reduce the cost of standard treatment, hospitalization, medications, and use of operating rooms. The results obtained in this study prove that this treatment had a favorable and permanent effect in patients, identifying a difference between the improvement obtained at the end of the treatment and one year after. This enhances the availability of new studies that will precisely determine other treatment modalities that could be used as an effective adjuvant therapy, focusing on parameters such as the number of sessions in lesser time and at a basic metabolic rate.

This study will allow adapting HBOT, with a high level of degree of specification, to the clinical requirements of the population treated at this hospital, thus tailoring screening parameters to induce successful patient eligibility in using this type of treatment, leading to early improvement in patients who can return to their daily activities at the earliest possible time.

Acknowledgment

The corresponding author would like to acknowledge Mr. AbdallahaSelim for his support in the production of this article.

Funding statement

The KZ-001 concept and financial support of this work had been obtained by Khaled A. Zed (Computational Neuroscience PhD; drzed@jcom.zaq.ne.jp), former executive director to the Japanese Ministry of State for Science and Technology Policy and former R&D director of the Advance Institute of Science and Technology, Japan, Biomedical Dept.

Authors Contributions:

. **A B:** Analysis, Review & Editing, interpretation supervision.

. **SA:** Analysis, Review & Editing, interpretation supervision.

KZ: Data Collection Conceptualization, designing, Acquisition, analysis, review, and editing, interpretation supervision.

References

- 1-Hampson NB. Hyperbaric oxygen: a plea for uniform nomenclature [Letter]. Undersea Hyperb Med 1999 Winter;26:267.
- 2-Hills BA. A role for oxygen-induced osmosis in hyperbaric oxygen therapy. Med Hypo 1999;52:259–263.
- 3- Tibbles PM, Edelsberg JS. Hyperbaric-Oxygen Therapy. N Engl J Med 1996 Jun 20;334:1642–1648.
- 4- Erecińska M, Silver IA. Tissue oxygen tension and brain sensitivity to hypoxia. RespirPhysiol2001;128:263–276.
- 5- Zupet P, Princi T, Finderle Z. Effect of hypobaric hypoxia on heart rate variability during exercise: a pilot field study. Eur J ApplPhysiol2009;107:345–350.
- 6- Milovanova TN, Bhopale VM, Sorokina EM, Moore JS, Hunt TK, Hauer-Jensen M, et al. Hyperbaric oxygen stimulates vasculogenic stem cell growth and differentiation in vivo. J ApplPhysiol2009;106:711–728.
- 7- Thom SR, Bhopale VM, Velazquez OC, Goldstein LJ, Thom LH, Buerk DG. Stem cell mobilization by hyperbaric oxygen. Am J Physiol—Hear CircPhysiol 2006;290:H1378–H1386.
- 8- Semenza GL. Oxygensensing, homeostasis, and disease. N Engl J Med 2011;365:537–547.
- 9- Dean H, Moffatt ME. Prevalence of diabetes mellitus among Indian children in Manitoba. Arct Med Res 1988;47 (Suppl. 1):532–534.
- 10- Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: a review of current evidence. Diabetologia2019;62:3–16.
- 11- WHO. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus, 2011. Available: www.who.int/diabetes/publications/report-hba1c_2011.pdf.

- 12- Taylor R. Type 2 diabetes: etiology and reversibility. *Diabetes Care* 2013;36:1047–1055.
- 13-International Diabetes Federation, *IDF Diabetes Atlas*, International Diabetes Federation, Brussels, Belgium, 7th ed., 2015.
- 14- Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019;393:31–39.
- 15- Jain KK, Baydin SA *Textbook of Hyperbaric Medicine*, 5th ed. Cambridge MA: Hogrefe, Publishers Huber, editors, 2009.
- 16- Lambertsen CJ, Dough RH, Cooper DY, Emmel GL, Loeschcke HH, Schmidt CF. Oxygen toxicity: effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. *J ApplPhysiol*1953;5:471–486.
- 17-Skeik N, Porten BR, Isaacson E, et al.Hyperbaric oxygen treatment outcome for different indications from a single center. *Ann VascSurg*2015;29:206–214.
- 18- Rose JJ, Wang L, Xu Q, et al. Carbon monoxide poisoning: pathogenesis, management, and future directions of therapy. *Am J RespirCrit Care Med* 2017;195:596–606.
- 19- Francis A, Baynosa R. Ischaemia–reperfusion injury and hyperbaric oxygen pathways: a review of cellular mechanisms. *Diving Hyperb Med* 2017;47:110–117.