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HIPERBARIČNA OKSIGENACIJA KAO PRETRETMAN I TRETMAN U ISHEMIJSKO-REPERFUZIJSKOM OŠTEĆENJU

Teodora Pejović[1], Sanjin Kovačević[1], Predrag Brkić[2], Jelena Nesović Ostojić[1*]

[1] Institut za patološku fiziologiju „dr Ljubodrag Buba Mihailović“, Medicinski fakultet, Univerzitet u Beogradu, Republika Srbija
[2] Institut za medicinsku fiziologiju „Rihard Burijan“, Medicinski fakultet, Univerzitet u Beogradu, Republika Srbija

[*] Korespondencija: [*] dr Jelena Nešović Ostojić, Institut za patološku fiziologiju „dr Ljubodrag Buba Mihailović““, Medicinski fakultet, Univerzitet u Beogradu, dr Subotića 9, 11000 Beograd, Republika Srbija; e-mail: jelena.nesovic-ostojic@med.bg.ac.rs

SAŽETAK

Ishemija tkiva podrazumeva nedovoljan dotok krvi u određeno područje tela. Prekid arterijskog snabdevanja krvlju dovodi do dizbalansa između metaboličkih potreba i potražnje i razvoja hipoksije tkiva. Hipoksija tkiva indukuje brojne metaboličke promene koje rezultuju inflamacijom, povećanim stvaranjem slobodnih kiseoničnih vrsta i smrću ćelije. Ukoliko se u ishemijskom tkivu uspostavi adekvatan protok krvi doći će do povećanja ćelijskog oštećenja što se označava kao ishemijsko-reperfuzijska povreda. Ishemija i ishemijsko-reperfuzijska povreda nalaze se u osnovni brojnih oboljenja široko zastupljenih u savremenom društvu, poput infarkta miokarda, cerebralnog insulta, akutnog bubrežnog oštećenja. Za sada ne postoji način da se utiče direktno na ćelijsku hipoksiju već je kliničko lečenje hipoksičnih stanja usmereno na modulaciju globalne hipoksemije i povećanje količine kiseonika rastvorenog u krvi. Hiperbarična oksigenacija (HBO) je tretman tokom kog bolesnik udiše 100% kiseonik pod pritiskom od najmanje 1,4 atmosfere. Iako je upotreba hiperbarične terapije zabeležena još u 17.veku, danas je ovaj tretman odobren za mali broj indikacija.

Ključne reči: ishemijsko-reperfuzijsko oštećenje, hiperbarična oksigenacija, hipoksija, ishemija.

Uvod

Ishemija tkiva podrazumeva nedovoljan dotok krvi u određeno područje tela. Uzroci mogu biti anatomski - zapušenje krvnog suda embolusom, ateroskleroza i tromboza aterosklerotskog plaka, kompresija krvnog suda otokom, tumorom, torzija vaskularne peteljke ili funkcionalni - hemoragijski šok, srčana insuficijencija, vaskularni spazam (1). Prekid arterijskog snabdevanja krvlju dovodi do disbalansa između metaboličkih potreba i potražnje i razvoja hipoksije tkiva. Usled hipoksije tkiva nastaje ćelijsko oštećenje koje u zavisnosti od trajanja ishemije može biti reverzibilno ili ireverzibilno (1-2). Reverzibilnost povrede zavisi od sposobnosti mitohondrija da proizvedu ATP (3). Ponovno uspostavljanje toka krvi u ishemijskom tkivu, paradoksalno, dovodi do povećanja ćelijskog oštećenja što se označava kao ishemijsko-reperfuzijska povreda (1,2,4,5). Ishemijsko-reperfuzijska povreda povezana je sa teškim kliničkim manifestacijama poput infarkta miokarda, infarkta mozga, akutnog bubrežnog oštećenjenja, kompartment sindroma. Napretkom medicine, u svakodnevnu kliničku praksu uvedene su savremene metode revaskularizacije ishemijskih područja poput perkutane angioplastike, bajpas hirurgije, transplantacije organa, te je značajno smanjena smrtnost od ishemijskih povreda (4). Međutim, sada u prvi plan dolazi ishemijsko-reperfuzijsko oštećenje, jer za sada ne postoji tretman koji smanjuje smrt ćelija izazvanu ovom povredom (6). Kako se hipoksija nalazi u osnovi ishemijskih povreda, korišćenje kiseonika u njihovom tretmanu nameće se kao logično rešenje. Za sada ne postoji način da se utiče direktno na ćelijsku hipoksiju, već je kliničko

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HYPERBARIC OXYGENATION AS THE PRETREATMENT AND THERAPY IN ISCHEMIA-REPERFUSION INJURY

Teodora Pejovic[1], Sanjin Kovacevic[1], Predrag Brkic[2], Jelena Nesovic Ostojic[1*]

[1] Institute of Pathological Physiology "dr Ljubodrag Buba Mihailović", Faculty of Medicine, University of Belgrade, Republic of Serbia
[2] Institute of Medical physiology "Rihard Burijan", Faculty of Medicine, University of Belgrade, Republic of Serbia

[*] Correspondence: [*] dr Jelena Nesovic Ostojic, Institute of Pathological Physiology "dr Ljubodrag Buba Mihailović", Faculty of Medicine, University of Belgrade, Dr Subotica 9, 11000 Belgrade; e-mail: jelena.nesovic-ostojic@med.bg.ac.rs

SUMMARY

Tissue ischemia means insufficient blood flow to a certain area of the body. Interruption of the arterial blood supply leads to an imbalance between metabolic supply and demand and the development of tissue hypoxia. Tissue hypoxia induces metabolic changes that result in inflammation, increased production of reactive oxygen species, and cell death. If adequate blood flow is established in the ischemic tissue, there will be an increase in cellular damage, which is referred to as ischemic-reperfusion injury. Ischemia and ischemia-reperfusion injury are at the root of numerous diseases widely present in modern society, such as myocardial infarction, cerebral insult, acute kidney injury. For now, there is no way to directly affect cellular hypoxia, but the clinical treatment of hypoxic conditions is aimed at modulating global hypoxemia and increasing the amount of oxygen dissolved in the blood. Hyperbaric oxygenation (HBO) is a treatment during which the patient breathes 100% oxygen under a pressure of at least 1.4 atmospheres. Although the use of hyperbaric therapy was recorded as early as the 17th century, today this treatment is approved for a few indications.

Key words: ischemia-reperfusion injury, hyperbaric oxygenation, hipoxia, ischemia.

Introduction

Tissue ischemia is the insufficient blood flow to a certain area of the body. The causes may be anatomical – the blockage of a blood vessel by an embolus, atherosclerosis and thrombosis of atherosclerotic plaque, compression of blood vessels caused by edema, tumor, torsion of vascular pedicle or functional – hemorrhagic shock, heart insufficiency, vascular spasm (1). The interruption of arterial blood supply leads to the imbalance between metabolic supply and demand and the development of tissue hypoxia. Tissue hypoxia induces cell damage, which can be reversible or irreversible depending on the duration of ischemia (1-2). The reversibility of injury depends on the ability of mitochondria to produce ATP (3). The restoration of blood flow in the ischemic tissue paradoxically leads to an increase in cellular damage, which is characterized as ischemia-reperfusion injury (1-2,4-5). Ischemia-reperfusion injury is associated with severe clinical manifestations such as myocardial infarction, stroke, acute kidney injury, compartment syndrome. With the advances made in the field of medicine, contemporary methods of revascularization of ischemic areas have been introduced into daily clinical practice, including percutaneous angioplasty, bypass surgery, organ transplantation, and therefore, the mortality due to ischemic injury has been significantly reduced (4). However, ischemia-reperfusion injury is now brought to the forefront because so far there have been no therapies which reduce cell death caused by this injury (6). Since hypoxia is at the root of ischemic injuries, the use of oxygen for the treatment is imposed as a logical solution. For now,

lečenje hipoksičnih stanja usmereno na modulaciju globalne hipoksemije i povećanje količine kiseonika rastvorenog u krvi (8,9).

Hiperbarična oksigenacija (HBO) je tretman tokom kog bolesnik udiše 100% kiseonik pod pritiskom od najmanje 1,4 atmosfere (10). Prva dokumentovana upotreba hiperbarične terapije zabeležena je 1662. godine od strane britanskog lekara *Henshaw*-a, koji je bolesnike smeštao u kontejner sa vazduhom pod pritiskom sa idejom da se povišeni pritisak koristi u tretmanu nekih akutnih, a sniženi u tretmanu hroničnih oboljenja. Dalje tokom istorije, terapija kiseonikom pod pritiskom korišćena je u različite svrhe – lečenje dekompresijske bolesti kod ronilaca u Drugom svetskom ratu, kao supstitucija elektrokonvulzivnoj terapiji kod shizofreničara, za povećanje senzitivnosti tumorskih ćelija pre radioterapije (11). Danas, je tretman HBO odobren od strane Američke asocijacije za hranu i lekove (engl. *Food and Drug Administration, FDA*) za trinaest indikacija, a neke od njih su: nezarastajuće rane, teške opekotine, nekrotišući fasciitis, gasna gangrena, kraš povreda, dekompresioni sindrom, trovanje ugljen monoksidom, teške anemija koje se ne mogu korigovati transfuzijom (12), (tabela 1). Korišćenje HBO u terapiji drugih oboljenja još uvek je u fazi ispitivanja (13,14). Cilj ovog istraživanja je da pruži uvid u do sada poznate i pokazane efekte pretretmana i tretmana hiperbaričnom oksigenacijom tokom lečenja ishemijsko-reperfuzijskih povreda.

Metode

U ovom preglednom radu, radi što preciznijeg i sveobuhvatnijeg prikaza efekata pretretmana i tretmana hiperbarične oksigenacije na ishemijsko-reperfuzijske povrede, korišćena je literatura dobijena pretraživanjem MEDLINE baze podataka uz pomoć servisa PUBMED. Literatura objavljena na engleskom jeziku, u poslednjih 10 godina, dobijena je pretraživanjem sledećih ključnih reči: ishemijsko-reperfuzijsko oštećenje, hiperbarična oksigenacija, pretretman, neuroprotektivni efekat, akutno bubrežno oštećenje, hipoksija, ishemija.

Ishemija i ishemijsko-reperfuzijska povreda

Ishemija tkiva nalazi se u osnovi brojnih oboljenja kao što su infarkt miokarda, ishemijska kardiomiopatija, cerebralni insult, akutno bubrežno oštećenje, komparment sindrom, hronične kožne ulceracije (4,5). U ishemijskim tkivima nedovoljan dotok kiseonika dovodi do metaboličkih promena

Tabela 1. Odobrene indikacije za tretman hiperbarčnom oksigenacijom

1.	Gasna embolija
2.	Anemija (teška anemija kada se transfuzija ne može koristiti)
3.	Opekotine (teške i velike opekotine)
4.	Trovanje ugljen monoksidom
5.	Kraš povrede
6.	Dekompresivni sindrom
7.	Gasna gangrene
8.	Gubitak sluha (potpuni gubitak sluha, koji se javlja iznenada i bez poznatog uzroka)
9.	Teške infekcije kože i kostiju
10.	Radijacione povrede
11.	Kožni transplantat sa rizikom od ishemije
12.	Gubitak vida (iznenadan i bezbolan gubitak vida na jednom oku zbog blokade krvotoka)
13.	Rane (nezarastajuće rane, dijabetični čirevi stopala)

there is no way to directly affect cellular hypoxia, but the clinical treatment of hypoxic conditions is aimed at modulating global hypoxemia and increasing the amount of oxygen dissolved in the blood (8,9).

Hyperbaric oxygenation is a treatment during which a patient breathes 100% oxygen under pressure of at least 1.4 absolute atmospheres. The first reported uses of hyperbaric therapy date back to 1662, when a British doctor named Henshaw put patients into the chamber with the air under pressure. He believed that the increased air pressure was used for the treatment of acute diseases, while low pressure was used to treat chronic diseases. Further, during history hyperbaric treatment was used for different purposes – the treatment of decompression sickness in divers during the Second World War, or as an alternative for electro-convulsive therapy in schizophrenia, and in order to increase sensitivity of tumor cells before radiotherapy (11). Today, HBO treatment has been approved by Food and Drug Agency of the United States of America for thirteen indications, including the following: non-healing wounds, severe burns, necrotizing fasciitis, gas gangrene, crush injury, decompression sickness, carbon monoxide poisoning, severe anemia when blood transfusion cannot be used (Table 1) (12). The use of HBO in the treatment of other diseases is still in the research phase (13,14). The aim of this study is to give insights into the effects of HBO pre-treatment and treatment in ischemia-reperfusion injuries, which have been presented so far.

Methods

In this review article, in order to present the effects of HBO pre-treatment and therapy on ischemia-reperfusion injuries in a precise and comprehensive way, we used literature that was obtained through a search of MEDLINE database with the help of PUBMED service. The literature has been published in the English language in the last ten years and it was obtained through a search of the following words: ischemia-reperfusion injury, hyperbaric oxygenation, preconditioning, neuroprotection, acute kidney injury.

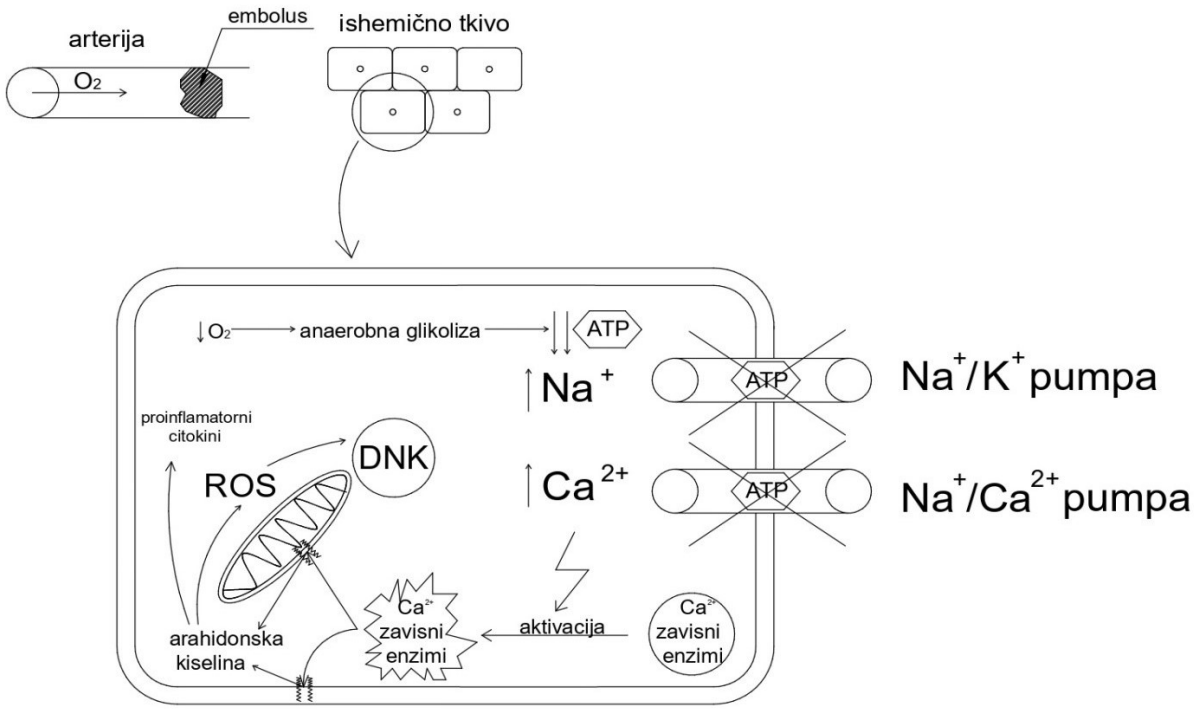
Ischemia and ischemia-reperfusion injury

Tissue ischemia is at the root of many diseases such as myocardial infarction, ischemic cardiomyopathy, cerebral insult, acute kidney injury, compartment syndrome, chronic skin ulcerations (4,5). In the ischemic tissues, the

Tabela 1. Approved indications for hyperbaric oxygenation therapy

1.	Air and gas bubbles in blood vessels
2.	Anemia (severe anemia whem blood transfusion cannot be used)
3.	Burns (severe and large burns treated at a specialized burn center)
4.	Carbon monoxide poisoning
5.	Crush injury
6.	Decompression sickness (diving risk)
7.	Gas gangrene
8.	Hearing loss (complete hearing loss that occurs suddenly and without any known cause)
9.	Infection of the skin and bone (severe)
10.	Radiation injury
11.	Skin graft flap at risk of tissue death
12.	Vision loss (when sudden and painless in one eye due to blockage of blood flow)
13.	Wounds (non-healing, diabetic foot ulcers)

– postepeno se smanjuje oksidativni metabolizam, a energija se dobija anaerobnom razgradnjom glukoze (2,5). Anaerobnim metabolizmom, proizvodi se manja količina energije, remeti se rad jonskih pumpi (natrijum-kalijumove, natrijum-kalcijumove, natrijum-vodonične) pa se u ćeliji nakupljaju kalcijum (Ca^{2+}), natrijum (Na^{+}) i vodonik (H^{+}), smanjuje se unutarćelijska pH, povećava se njena osmolarnost i ćelija bubri. Smanjenju unutarćelijske pH doprinosi i povećanje koncentracije NADH koji indukuje prelazak piruvata u laktat. Povećanje koncentracije Ca^{2+} aktivira Ca^{2+} zavisne ATP-aze, fosfolipaze koje oštećuju ćelijsku i mitohondrijsku membranu. Iz membrana se oslobađa arahidonska kiselina od koje nastaju proinflamatorni citokini i slobodne kiseonične vrste (engl. *Reactive oxygen species, ROS*) (2,5,15) (slika1). Pored povećanog stvaranja ROS-a, dodatan problem je smanjenje aktivnosti antioksidativnih enzima – superoksid dizmutaze, katalaze, glutation peroksidaze. Ovaj disbalans vodi ćeliju u smrt (15). Poseban vid ćelijske povrede predstavlja postishemijsko oštećenje. Naime, iako je tokom ishemije neophodna brza reperfuzija tkiva, paradoksalno, ponovno uspostavljanje krvotoka u tkivu u kom već postoji ćelijska povreda dovodi do povećanog stvaranja ROS-a posredstvom tri glavna sistema - sistema ksantin oksidaze, sistema NADPH oksidaze i sistema sintaze azot monoksida (engl. *Nitric oxide synthases, NOS*) (16). Ksantin oksidaza i ksantin dehidrogenaza su enzimi koji učestvuju u metabolizmu purina. Ksantin dehidrogenaza koristi NAD^{+} kao krajnji primalac elektrona, dok ksantin oksidaza koristi O_2 kao primalac elektrona. U ishemijskom tkivu, zbog smanjene količine ATP-a dolazi do pretvaranja ksantin dehidrogenaze u ksantin oksidazu. Tokom reperfuzije tkiva, novonastala ksantin oksidaza vrši pretvaranje hipoksantina u ksantin koristeći kiseonik kao krajnji primalac elektrona pri čemu nastaju superoksidni anjon i vodonik peroksid (17). U stanju hipoksije dolazi do pojačane aktivnosti hipoksijom indukovanog faktora 1 alfa (engl. *Hypoxia-inducible factor-1-alpha, HIF-1α*) koji aktivira enzime iz porodice NADPH oksidaza. Ovi enzimi kao krajnji primalac elektrona koriste kiseonik pri čemu nastaju superoksidni anjon i vodonik peroksid koji izazivaju oksidativni stres (18,19). Pozitivnom povratnom spregom, oksidativni stres dalje dovodi do povećane aktivnosti HIF- 1α. Ponovnim uspostavljanjem krvotoka u ishemijskom tkivu dolazi do oslobađanja brojnih hemijskih medijatora kao što su fosfolipaza A2, interferon γ, interleukin 1 β koji povećavaju aktivaciju NADPH oksidaza i dalje promovišu nastanak



Slika 1. Shematski prikaz ćelijskih promena u ishemijskom tkivu

insufficient oxygen flow leads to metabolic changes – oxidative metabolism is gradually reduced, while energy is obtained by anaerobic dissolution of glucose (2,5). Anaerobic metabolism produces the smaller amount of energy, disturbs the work of ion pumps (sodium-potassium, sodium-calcium, sodium-hydrogen), and therefore, calcium (Ca^{2+}), sodium (Na^{+}), and hydrogen (H^{+}) are accumulated in the cell, decreases cellular pH, thus causing its hyperosmolarity and cell swelling. The increase in the concentration of NADH, which induces the conversion of pyruvate to lactate, contributes to the decrease of cellular pH. The increase in Ca^{2+} concentration activates Ca^{2+} dependant ATP-ase, phospholipase that damage cell and mitochondrial membrane. Arachidonic acid is released from membranes, thus producing the proinflammatory cytokines and reactive oxygen species (ROS) (2,5,15) (Figure 1). In addition to the increased production of ROS, the decrease of antioxidative enzymes activities is also problematic – superoxide dismutase, catalase, glutathione peroxidase. This imbalance leads to cell death (15). A specific type of cell injury is post-ischemic injury. Namely, although fast tissue reperfusion is needed during ischemia, paradoxically, the restoration of blood flow in the already ischemic tissue leads to the increased production of ROS through three main systems – the xanthine oxidase system, the NADPH oxidase system, nitric oxide synthases system (NOS) (16). Xanthine oxidase and xanthine dehydrogenase are enzymes that take part in purine metabolism. Xanthine dehydrogenase uses NAD+ as the final electron acceptor, while xanthine oxidase uses O_2 as the electron acceptor. In the ischemic tissue, due to the reduced amount of ATP, xanthine dehydrogenase is shifted to xanthine oxidase. During the tissue reperfusion, the newly created xanthine oxidase induces hypoxanthine to form xanthine, using oxygen as the final electron acceptor, during which superoxide anion and hydrogen peroxide are released (17). In the hypoxic state, the activity of hypoxia-inducible factor-1-alpha (HIF-1α) increases and it activates enzymes from the family NADPH oxidase. These enzymes use oxygen as the final electron receptor, while superoxide anion and hydrogen peroxide, which cause oxidative stress, are released (18,19). Due to the positive feedback loop, oxidative stress further leads to the increased activity of HIF-1α. The restoration of blood flow in the ischemic tissue causes the release of numerous chemical mediators such as phospholipase A2, interferon γ, interleukin 1ß which increase the activation

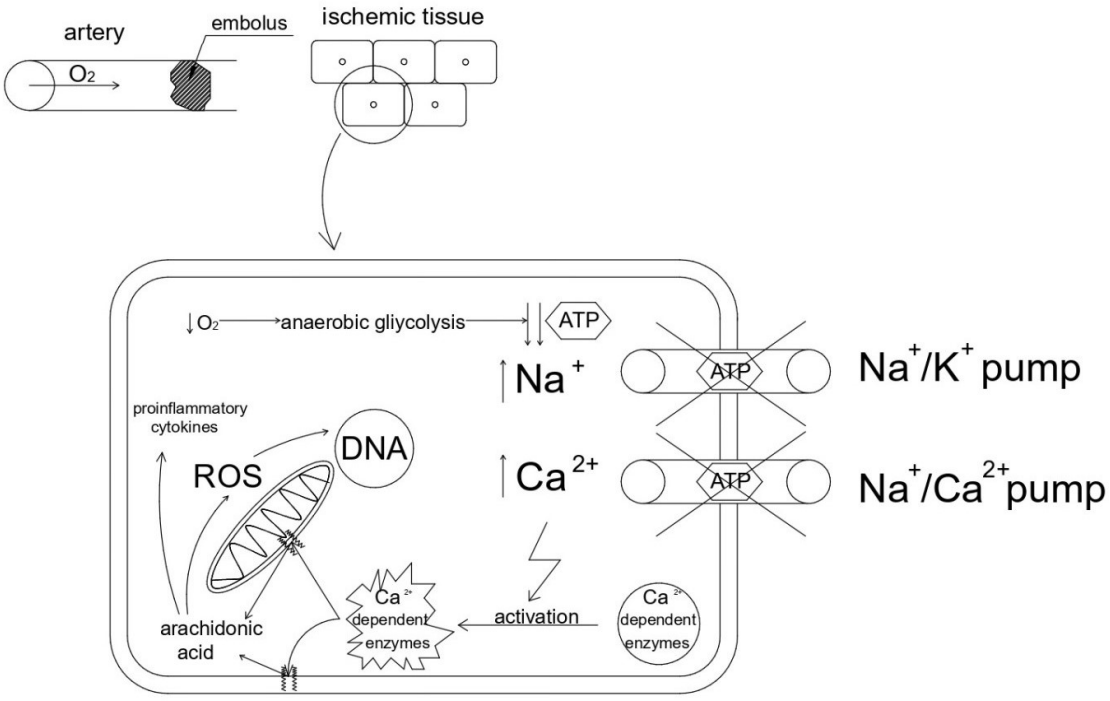


Figure 1. Tissue ischemia

slobodnih kiseoničnih radikala (20,21). Tri poznata tipa sintaze NOS – endotelni, neuronski i inducibilni vrše konverziju L-arginina u L-citrulin pri čemu se oslobađa azot monoksid (NO) koji ima antiinflamatornu ulogu. U stanju hipoksije, aktivnošću ovih enzima dolazi do stvaranja superoksidnog anjona koji promoviše oksidativni stres (22). Reaktivne kiseonične vrste oštećuju DNK, dovode do endotelne disfunkcije i pokretanja inflamacije. Inflamatorna kaskada i oksidativni stres dalje oštećuju ćelijske strukture što dovodi do smrti ćelije (15).

Hiperbarična oksigenacija

Hiperbarična oksigenacija (HBO) je tretman koji podrazumeva udisanje čistog, 100%-og kiseonika pod pritiskom od najmanje 1,4 atmosfere (ATM) (10). Ipak, za odobrene indikacije uglavnom se koriste pritisci veći od 2 ATM. Zbog toksičnosti koju izlaganje kiseoniku pod pritiskom ispoljava, gornja granica pritiska koja se u kliničkoj praksi primenjuje je 3 ATM. Trajanje tretmana je obično između 60 i 90 minuta. Povišen pritisak u komori je važan jer prema Henrijevom zakonu, povećanje pritiska gasa u vazduhu povećava njegovu rastvorljivost u tečnostima. Shodno ovom principu fizike, udisanjem kiseonika pod pritiskom povećava se njegova količina u krvi. Danas su u upotrebi komore dizajnirane da prime jednog bolesnika, kao i one koje istovremeno mogu primiti veći broj bolesnika (10,23,24).

Pretretman i tretman hiperbaričnom oksigenacijom

Tretman HBO može biti koristan u terapiji mnogih bolesti u čijoj osnovi se nalazi hipoksija. Pretretman i terapija HBO su pokazali posebno dobre efekte kod ishemijsko-reperfuzijskih povreda mozga i srca, a pozitivni efekti ostvareni su i u tretmanu ishemijsko-reperfuzijskog oštećenja bubrega. Kao što je napred pomenuto, udisanje kiseonika pod pritiskom povećava njegovu rastvorljivost u krvi (24). Ovo stanje hiperoksigenacije ima određene blagotvorne efekte – povećava se količina kiseonika koja se doprema do ishemijskog područja što je bitno za obnavljanje oksidativnog metabolizma, takođe povećanje količine kiseonika u krvi dovodi do vazokonstrikcije koja je važna, jer se smanjuje edem tkiva i poboljšava mikrocirkulacija (13,14,25-27). Na eksperimentalnim animalnim modelima, pokazano je da pretretman i tretman HBO ima blagotvorno dejstvo na očuvanje strukture i funkcije ćelija u različitim ishemijskim tkivima, a takođe se ostvaruje protektivni efekat od štetnih dejstava postishemijske reperfuzije (10,25-27). Studije pokazuju da pretretman i tretman HBO dovodi do hiperoksigenacije tkiva i stvaranja kiseoničnih „rezervoara“ koji ćeliju štite u stanjima iznenadne hipoksije, stimuliše proizvodnju antioksidanasa, obnavlja aerobni metabolizam čime se povećava proizvodnja ATP-a, smanjuje disfunkcija mitohondrija, te štiti ćelija od smrti (10,25-27). Nedavno objavljena eksperimentalna studija sprovedena na pacovima Wistar soja kojima je indukovano ishemijsko akutno bubrežno oštećenje, pokazala je da pretretman HBO dovodi do smanjenja lipidne peroksidacije u plazmi (28). Takođe, pretretman HBO, smanjuje nivoe uree i kreatinina i značajno poboljšava procenjenu brzinu glomerulske filtracije (engl. *estimated Glomerular filtration rate, eGFR*) kod jedinki kojima je indukovano akutno bubrežno oštećenje. U skladu sa ovim rezultatima je i statistički značajno smanjenje nivoa markera oštećenja bubrega 1 (engl. K*idney injury molecule-1, KIM-1*) u plazmi jedinki izlaganih ovom pretretmanu (28). Pretretman HBO doprinosi zaštiti od ishemijsko-reperfuzijskog oštećenja stimulacijom ekspresije hem oksigenaze 1, enzima koji igra važnu ulogu u regulaciji ćelijske proliferacije, diferencijacije, apoptoze, te štiti bubreg u akutnom bubrežnom oštećenju (29). Eksperimentalno ispitivanje izvedeno na pacovima kojima je indukovano ishemijsko-reperfuziono oštećenje jetre pokazalo je da se markeri oštećenja jetre smanjeno oslobađaju kod grupe jedinki koje su prethodno podvrgnute pretretmanu HBO. Takođe, u ovoj grupi primećeno je i poboljšanje mitohondrijskog disanja (30,31). Smanjenjem oštećenja mitohondrija smanjuje se i oslobađnje citohroma c i inhibira nastanak apoptoze (31). Pretretman HBO režnjeva kože pacova kojima je izazvana ishemijsko-reperfuziona povreda dovodi do smanjene ekspresije proapoptotskog proteina Bax, povećane ekspresije antiapoptotskog proteina Bcl-2 te se poboljšava preživljavanje ćelija u ishemijskom tkivu, a takođe dolazi i do poboljšanja mikrocirkulacije (32). Povećana ekspresija antiapoptotskog Bcl-2 proteina pokazana je i kod spontano hipertenzivnih i normotenzivnih pacova kojima je indukovano akutno bubrezno oštećenje (29).

Jedan od vodećih uzroka smrt u svetu je moždani udar, a čak 80% od svih cerebralnih in-

of NADPH oxidase and further promote the creation of reactive oxygen species (20,21). Three known types of NOS synthases – endothelial, neuronal and inducible convert L-arginine into L-citrulline, when nitric monoxide, which has an anti-inflammatory role, is released. In the hypoxic state, the activities of these enzymes induce the creation of superoxide anion which promotes oxidative stress (22). Reactive oxygen species damage DNA, lead to the endothelial dysfunction and instigate inflammation. The inflammatory cascade and oxidative stress further damage cell structures, thus leading to cell death (15).

Hyperbaric oxygenation

Hyperbaric oxygenation (HBO) is a treatment which includes breathing pure, 100% oxygen under pressure of at least 1.4 atmospheres (ATM). However, pressures higher than 2 ATM are used for approved indications. Due to the fact that exposure to oxygen under pressure may be toxic, the pressure applied in the clinical practice does not exceed 3 ATM. The duration of session is usually between 60 and 90 minutes. The increased pressure in the chamber is important because, according to Henry's law, the increase in pressure in the air causes higher dissolubility in fluids. In accordance with this principle of physics, inhaling oxygen under pressure increases its amount in the blood. Chambers, which are designed to accommodate one patient, are used today, as well as chambers that may accommodate multiple patients at the same time (10,23,24).

Hyperbaric oxygen pretreatment and therapy

The hyperbaric oxygen therapy may be useful in the treatment of many diseases with underlying hypoxia. The pretreatment and therapy using HBO have shown particularly good effects on ischemic-reperfusion injuries of heart and brain, while positive effects have been achieved in the treatment of ischemic-reperfusion injury of kidneys. As it has already been mentioned, inhaling oxygen under pressure increases its dissolubility in the blood (24). This state of hyperoxygenation has certain beneficial effects – the amount of oxygen that is brought to ischemic area increases, which is important for the restoration of oxidative metabolism. Also, the increase in the amount of blood leads to vasoconstriction which is important because tissue edema is reduced and microcirculation improves (13,14,25-27). It has been shown on experimental animal models that the HBO pretreatment and therapy have a beneficial effect on the maintenance of structure and function of cells in different ischemic tissues, while also a protective effect is achieved regarding the harmful effects of post-ischemic reperfusion (10,25-27). Studies have shown that HBO pretreatment and therapy lead to hyperoxygenation of tissues and creation of oxygen "reservoirs" that protect cells in case of sudden hypoxia, stimulate the production of antioxidants, restore the aerobic metabolism, thus increasing the production of ATP, reducing the mitochondrial dysfunction and protecting cells from cell death (10,25-27). A recently published experimental study, which was conducted on Wistar rats with induced ischemic acute kidney injury, has shown that HBO preconditioning leads to the reduction of lipid peroxidation in plasma (28). Also, HBO preconditioning reduces the levels of urea and creatinine and significantly improves the estimated glomerular filtration rate in induced acute kidney injury in rats. In accordance with these results is the statistically significant reduction of kidney injury marker (kidney injury molecule-1, KIM-1) in the plasma of rats exposed to this pretreatment (28). HBO pretreatment contributes to the protection from ischemic-reperfusion injury by stimulating the expression of hem oxygenase 1, the enzyme which has a significant role in the regulation of cell proliferation, differentiation, apoptosis, and therefore, protects the kidney in acute kidney injury (29). Experimental research of induced ischemic-reperfusion liver injury in rats has shown that markers of liver damage are released less in the group of rats that were previously exposed to HBO preconditioning. Also, the improvement of mitochondrial respiration was noticed in this group (30,31). The reduction of mitochondrial damage causes the decrease in cytochrome c release and inhibits apoptosis (31). HBO preconditioning of skin flaps in rats with induced ischemia-reperfusion injury leads to the reduced expression of pro-apoptotic protein Bax, increased expression of anti-apoptotic Bcl-2 and therefore the survival of cells improves in the ischemic tissue, as well as microcirculation (32). The increased expression of anti-apoptotic

sulta su ishemijskog tipa. Lečenje ovog entiteta je dosta ograničeno. Pokazalo se da HBO tretman pomaže u lečenju jer smanjuje cerebralni edem koji nastaje nakon infarkta mozga, poboljšava cerebralnu cirkulaciju i snabdevanje ishemijskog područja kiseonikom te ograničava gubitak periinfarktnog tkiva. Ovim tretmanom smanjuje se nivo proinflamatornih citokina, indukuje angiogeneza i regrutovanje progenitorskih ćelija u oštećene regione (33). Interesantno je da HBO tretman 7 dana nakon ishemijskog moždanog udara doprinosi boljem neurološkom oporavku (34).

U kliničkoj praksi, tretman HBO je značajan u terapiji dijabetesnog stopala jer utiče na mnoge komponente zapaljenja i regeneracije tkiva. Pojedine studije ukazuju da tretman HBO indukuje povećanje markera angiogeneze poput epidermalnog faktora raste (engl. *Epidermal growth factor, EGF*). Ovaj tretman takođe smanjuje incidencije anaerobnih infekcija i amputacije stopala (35).

Zaključak

Eksperimentalno je pokazano da pretretman i tretman HBO u velikoj meri koriste u lečenju ishemijsko-reperfuzijskih povreda. Stvaranje kiseoničnih „rezervoara“ u ishemijskom tkivu, obnavljanje oksidativnog metabolizma, poboljšanje mikrocirkulacije, stimulacija sinteze antioksidanasa, poboljšanje bubrežne funkcije, neuroprotektivni efekat, indukcija angiogeneze samo su neki od dobrobitnih efekata koje ova terapija pruža. Međutim, za sada ne postoji dovoljan broj kliničkih ispitivanja kojima bi se potvrdili blagotvorni efekti i ispitali rizici izlaganja kiseoniku pod pritiskom u humanoj populaciji. Iako postoji veliki broj oboljenja u čijoj osnovi se nalazi hipoksija i gde bi potencijalno mogla da se primeni terapija HBO, za sada postoji samo mali broj odobrenih indikacija za njeno korišćenje. Kako je potencijal ove terapije nedovoljno iskorišćen, u budućnosti nam je potreban veći broj studija i kliničkih ispitivanja za razvoj adekvatnih HBO protokola.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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Bcl-2 protein has been shown in spontaneously hypertensive and normotensive rats with induced acute kidney injury (29).

Stroke is one of the leading causes of death globally, and even 80% of all cerebral insults are ischemic-related. The treatment of this entity is very limited. It has been shown that HBO therapy helps in the treatment because it reduces cerebral edema, which develops during cerebral insult, it improves cerebral circulation and oxygen supply to the ischemic region, and therefore limits the loss of peri-infarct tissue. This treatment reduces the level of pro-inflammatory cytokines, induces angiogenesis and recruitment of progenitor cells into damaged regions (33). It is interesting that HBO treatment 7 days after ischemic cerebral insult contributes to a better neurological recovery (34).

In clinical practice, HBO therapy is important in the treatment of diabetes foot because it affects various components of inflammation and tissue regeneration. Some studies have shown that HBO therapy induces the increase in angiogenesis markers such as epidermal growth factor (EGF). This therapy also reduces the incidence of anaerobic infections and foot amputations (35).

Conclusion

Experiments have shown that HBO pre-treatment and therapy are used to a large extent in the treatment of ischemia-reperfusion injury. The creation of oxygen “reservoirs” in ischemic tissue, restoration of oxidative metabolism, improvement of microcirculation, stimulation of synthesis of antioxidants, improvement of renal function, neuroprotective effect, induction of angiogenesis are some of beneficial effects provided by this therapy. However, the number of clinical trials is not sufficient to prove the beneficial effects and investigate risks of exposure to oxygen under pressure in human population. Although there is a great number of diseases with underlying hypoxia, in which HBO therapy could potentially be used, few indications have been approved so far for its use. As the potential of this therapy has not been sufficiently used, more studies and clinical trials will be necessary in the future for the development of adequate HBO protocols.

Competing interests

Authors declare no competing interests.

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