Hyperbaric oxygen therapy, intermittent breathing of 100% oxygen at a pressure upper than sea level, has been shown to be some of the neuroprotective effects and used therapeutically in a wide range of neurological disorders. This review summarizes current knowledge about the neuroprotective effects of hyperbaric oxygen therapy with their molecular mechanisms in different models of neurological disorders.

**Key words:** apoptosis; clinical trial; hyperbaric oxygen; inflammation; *in vitro*; *in vivo*; neuroprotection; oxidative stress

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**INTRODUCTION**

Nervous system diseases are one of the leading causes of death and disability worldwide due to the limitation of effective treatment strategies. Although some promising strategies have been reported in the animal models of nerves system disorders, they often fail to work in clinical practice. Therefore, new treatment strategies need to be developed and exploited. Within the previous decades, various pharmaceutical compounds as well as various therapeutic methods with neuroprotective effects have been described, including high pressure oxygen therapy as a nondrug and noninvasive therapy. Hyperbaric oxygen (HBO) therapy (HBOT) is defined as the intermittent breathing of pure oxygen inside a hyperbaric chamber at a pressure above sea level. During HBOT, the amount of dissolved oxygen in the plasma as well as saturated hemoglobin with oxygen increases, leading to greater oxygen availability to the organs. It is well documented that HBOT has neuroprotective effects against experimental spinal cord injury (SCI), brain injury, neurodegenerative disease, peripheral nerve injury, and neurotoxicity models of rodents. On the other hand, clinical evidence to support the neuroprotective properties of HBOT is limited. In regard to the neuroprotective effects of HBOT, accumulating evidence indicates an association between the beneficial effects to a variety of biological properties mainly anti-oxidative, anti-inflammatory, and anti-apoptotic properties, in addition to improvement of oxygen supply and neural metabolism. This paper presents an up-to-date review of the neuroprotective effects of HBOT with its molecular mechanisms in different models of neurological disorders in three parts.

**In Vivo Studies**

A lot of *in vivo* experimental studies have been conducted on the HBOT neuroprotection and its underlying molecular mechanisms, summarized in Additional Tables 1–5.
through downregulation of matrix metalloproteinase (MMP)-2, IL-6, and MMP-9 and upregulation of VEGF.\textsuperscript{30} Another study documented that HBOT through inducible NOS (iNOS) mRNA-iNOS-nitric oxide signaling pathway can promote the neuroprotection following SCI.\textsuperscript{13} The inflammatory process is one of the major causes of secondary SCI. In this regard, Yang et al.\textsuperscript{31} documented that HBO intervention reduced secondary SCI via nuclear factor-κB (NF-κB) and high-mobility group protein B1 (HMGB1) downregulation in rats with acute SCI. In regard to the other neuroprotective mechanism of HBO on SCI, it was documented that hypoxia-inducible factor-1α (HIF-1α) reduction and VEGF elevation by HBO intervention may be inversely associated with spinal cord repair.\textsuperscript{32} Another study documented that HBO via Toll-like receptor (TLR)/NF-κB signaling induced protective effects against rat SCI.\textsuperscript{33} The researchers believe that HBOT reduces secondary SCI and promotes neurological outcome through TLR2/NF-κB signaling pathway. A research has shown that early HBOT (at the 1st hour after trauma) contributed to the biochemical and histopathological improvement of the rats after SCI.\textsuperscript{34} To determine the mechanisms of HBOT in SCI, a study measured the expression levels of connexin 43 and VEGF in the damaged part of the spinal cord.\textsuperscript{35} The results showed that VEGF significantly increased, while the level of connexin 43 significantly decreased after HBOT. Immunoreactive responses are like a double-edged sword in which the macrophages were considered as predominant inflammatory cells. In this regard, results of a study showed that HBOT by altering the macrophage M1 phenotype to the M2 phenotype modified the inflammatory environment, which promotes functional recovery and axonal extension.\textsuperscript{36} Liang et al.\textsuperscript{37} demonstrated that HBOT compromised NACHT leucine rich repeat and pyrin domain containing protein 3 (NALP-3) inflammasome, caspase 1 and adaptor molecule apoptosis-associated speck-like protein, in addition to mitigating IL-1β release in the damaged spinal tissue. HBOT has a protective effect on SCI by reducing neuronal cell apoptosis and MMP-9/2 gene expression in rats, so that improved motor function scores and increased myelinated nerve fibers.\textsuperscript{38} Studies emphasize the key role of endoplasmic reticulum stress in the induction of neuronal apoptosis following SCI. In this regard, it was documented that HBOT by inhibiting endoplasmic reticulum stress-induced apoptosis alleviated secondary SCI and thereby improved the neurological function.\textsuperscript{39} Another study tested the hypothesis that HBOT via regulation of c-Jun N-terminal kinase (JNK) and glucose-regulated protein 78 expression ameliorates secondary SCI.\textsuperscript{40} The results showed that HBOT increased glucose-regulated protein 78 level and decreased that of JNK which leads to tissue survival, differentiation, development, and homeostasis. It has been reported that regulation of autophagy improves neurological function after SCI.\textsuperscript{41} In this regard, it was documented that enhancement of autophagy expression and acceleration of cell repair rate after SCI may be another mechanism of action of HBOT.\textsuperscript{42} HBOT potentially by inhibiting receptor expression for monocyte chemoattractant protein 1 and advanced glycation end products recovers locomotor function.\textsuperscript{43} Results of another study which was investigated the mechanisms of HBOT following SCI, suggested that reducing lipid oxidation and oxygen free radicals is one of the mechanisms.\textsuperscript{35} Sun et al.\textsuperscript{46} documented that HBO significantly improved the recovery of neuronal function and fractional anisotropy compared to SCI group on days 7, 14, and 21 after SCI. Recently, it was documented that HBOT improves neurological disorders by amelioration of apoptosis and suppressing dendritic/synaptic degeneration through upregulating the brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B signaling pathways in the anterior horn of spinal cord after SCI.\textsuperscript{47} Also, another study revealed that HBO via stromal cell-derived factor-1/CXC chemokine receptor 4 axis activation and promotion of BDNF expression improves neurological function after SCI in rats.\textsuperscript{48} HBO improves functional recovery through inhibiting iNOS, cyclooxygenase-2, glial fibrillary acidic protein, and neuron-glial antigen 2; meanwhile this process may be due to inhibition of NF-κB and Akt pathways.\textsuperscript{49} Assessment of HBOT in rat model of SCI using diffusion tensor imaging showed that HBOT for 4 weeks is the more appropriate course.\textsuperscript{50}

**Brain injury**

Studies have shown that brain damages after stroke or trauma are due to a variety of pathophysiological processes such as nitrate and oxidative stress, disruption of the blood-brain barrier (BBB), excitotoxicity, neural cell death, inflammatory reactions, and deficits in angiogenesis.\textsuperscript{51,52} In this regard, Weinstein et al.\textsuperscript{53} showed that HBO conferred significant protection against death from untreated cerebral ischemia in anaesthetized gerbils, while histological examination showed that the extent of patchy bilateral ischemic neuronal damage was much less in surviving gerbils that received HBO. After that, a study was conducted to determine the effects of HBOT on free radical generation and lipid peroxidation following global cerebral ischemia.\textsuperscript{54} Results of this study showed that HBO elevated the level of oxygen free radicals after ischemia in the brain, but, this elevation was not accompanied with increased lipid peroxidation or decreased neurophysiological recovery. In fact, despite the initial increase in free radical generation, the amount of peroxidation was similar to control group, while the cortical somatosensory evoked potential recovery was more than 50-fold in the HBO-treated animals relative to the control group. Another study documented that HBO reduces blood flow and brain vascular permeability after global cerebral ischemia in rabbits, however, recovery of the somatosensory evoked potential was the same as control and HBO groups.\textsuperscript{55} While, HBO in another study had no beneficial effects on neurologic outcome after acute focal cerebral ischemia.\textsuperscript{56} It was reported that adult rats with middle cerebral artery occlusion which are exposed to HBO immediately or after a 60-minute delay showed improvement in motor impairment, as well as a reduced cerebral infarction compared to normal atmospheric pressure.\textsuperscript{57} Assessment of the role of neutrophils and prophyllactic HBO on cerebral injury revealed that HBO before ischemia at 2.8 atmosphere absolute (ATA; 1 ATA = 101.325 kPa) for 45 minutes reduces myeloperoxidase...
concentration, functional neurologic deficits, and cerebral infarct volume through inhibiting neutrophil sequestration. Results of an investigation revealed that altered excitatory amino acids and brain energy metabolites which occurred during brain ischemia were regulated with HBO at different times after ischemia. Neurotrophin-3 plays a protective role against neuronal cell death in response to brain ischemia. In this regard, it was documented that HBO decreases down-regulation of the post-ischemic neurotrophin-3 mRNA in the rat hippocampus. HBO has dual effect on cerebral infarction, and using HBO within 6 hours of ischemia-reperfusion injury can be beneficial but using HBO 12 hours or more after injury can be harmful, while tissue damage was not reduced by HBO during 4 hours of permanent focal cerebral ischemia. Yin et al. revealed that HBO can lead to an inhibition of cyclooxygenase-2 over-expression in cerebral cortex after cerebral ischemia. Hyperbaric oxygenation reduces focal brain damage and reduces striatal dopamine secretion after occlusion of middle cerebral artery. One of the molecular mechanisms of protection by HBO is the prevention of apoptosis which might preserve more tissue in the brain and improve neurologic function. In this regard, Yin et al. documented that HBO (7 days after reperfusion) reduced brain infarction and improved neurologic scores by preventing apoptotic death (abolished DNA fragmentation and reduced terminal deoxynucleotidyl transferase dUTP nick end labeling-positive cell number) in rat ischemic cortex. It is well known that cerebral ischemia causes significant changes in the Na⁺, K⁺-ATPase and SOD activities. In this regard, it was documented that preservation of Na⁺, K⁺-ATPase and reinforcement of SOD activity are the possible mechanisms of HBO in severe brain ischemia. Assessment of the apoptotic cell number revealed that HBO attenuated secondary brain damage in an experimental transient brain injury (TBI). To elucidate the timing and mechanisms of HBO protection following cerebral ischemia, Veltkamp et al. examined the early in vivo effects of HBO by repetitive magnetic resonance imaging and BBB permeability for sodium fluorescein 2 hours after transient focal ischemia. The results showed that HBO significantly decreased abnormal diffusion weighted imaging signal volume, lesion size on T2-weighted images, BBB permeability on T1-weighted images, and vasogenic edema assessed on T2-weighted images and histologic sections after 24 hours. Another study suggested that delayed, but multiple HBO (2.5 ATA, 2 hours per day for 6 consecutive days) can improve neurologic function and reduce cerebral infarction after transient focal ischemia. Recent data emphasize the key role of apoptosis in the spread of lesion after TBI. In this regard, Bel-xL, Bel-2 and Bax proteins immunostaining in the brain tissue showed a significant increase in Bel-2 and Bel-xL anti-apoptotic proteins after HBO, while staining for pro-apoptotic protein Bax did not significant. A study was conducted to assess HBO effects on intracranial pressure dynamics and survival in rat severe fluid percussion brain injury, concluding HBO during the early phase of injury significantly diminished intracranial pressure elevation rate and reduced mortality rate. In regard to BBB integrity preservation with HBO after cerebral ischemia, Veltkamp et al. documented that HBO decreases ischemic degradation of cerebral microvascular laminin-5 and blocks upregulation of postischemic plasma MMP. Calvert et al. tested the hypothesis that HBO alternates the expression of HIF-1α in neonatal hypoxia-ischemia. The results showed that HBO increased glucose transporter-1, glucose transporter-3, aldolase, and lactate dehydrogenase expression, while decreased p53 expression and HIF-1α-p53 interaction. Therefore, HIF-1α phenotype alternation is one of the underlying mechanisms of HBO neuroprotection following neonatal hypoxic-ischemic injury. Effectiveness of HBO is controversial in permanent ischemia models, so that in extensive focal ischemia HBO is only effect in early re-canalization. HBO can reduce neuronal apoptosis after TBI by reducing cytochrome c secretion and Bax dimers and over-regulation of Bcl-2 expression. The effects of HBO on inflammatory infiltration and expression of MMPs in rat dynamic cortical deformation have been evaluated. HBO showed a significant reduction in the number of terminal deoxynucleotidyl transferase dUTP nick end labeling-positive cells, neutrophilic inflammatory infiltration, and MMP-9 expression. The potential neuroprotective effects of HBO in a focal cerebral ischemia model proved with significant neuroprotection (reduction of infarct volume) at 5 hours after ischemia that lasted for 168 hours. A study revealed that early intra-ischemic HBO could reduce hemorrhagic transformation (hemoglobin content) in a rat model of focal transient cerebral ischemia. A 40-day series of 80 low-pressure HBOs following TBI increases vascular density in the damaged hippocampus and improves cognitive function. Zhou et al. tested the effects of HBO on mitochondrial function, as measured by cognitive improvement and cellular adenosine triphosphate after lateral fluid-percussion injury in rat. The results showed that HBO-treated animals had significantly higher levels of cerebral ATP and cognitive recovery and lower neuronal loss in the CA2/3 and hilar regions. In another study, cerebral partial pressure of oxygen was measured using electron paramagnetic resonance oximetry before and after occlusion of the middle cerebral artery and HBO exposure in rats. The results of the study revealed that measurements of the partial pressure of oxygen showed no increase in ischemic or normal hemispheres minutes after HBO exposure, despite decreasing the infarct size. Another study suggested that hyperoxia protection is due to a negative regulation of the proapoptotic function of mitochondrial translocator protein such as mitochondrial membrane potential conservation after cerebral contusion. Study on optimal dosing and timing of HBO in a rat model of transient ischemia/reperfusion revealed that oxygen is a highly neuroprotective molecule when used early and in high doses. Results of a study suggested that single HBO has a time limitation of 12 hours after TBI; meanwhile multiple HBOs have the ability to extend the delivery time window after TBI. Sun et al. found that HBO decreases infarct size and reduces post-thrombolytic intracerebral hemorrhage after thromboembolic occlusion of the middle cerebral artery in rats. Also, it was documented that hyperbaric oxygenation has neuroprotective effects in middle cerebral artery occlusion-induced brain injury through reducing hydroxyl free radical formation and glutamate release. Zhao et al. documented that HBO increases claudin-5 and claudin-1 expression, and decreases permeability of the BBB
via the suppression of MMP-2 and MMP-9 after cerebral ischemia–reperfusion in rats, respectively. HBOT stimulates IL-10 overproduction, neurogenesis, and angiogenesis, while reduces gliosis following TBI in rat.\textsuperscript{13} Also, HBOT reduced TBI-induced TNF-α expression and microglial activation during the acute phase of TBI resulting in a neuroprotective effect.\textsuperscript{88} Data of another study showed that HBOT through promoting axonal sprouting and synapse remodeling can intensify neuroplastic responses, which contributes to the improvement of locomotor function following cortical ablation in rat.\textsuperscript{89} Study on the effects of hyperbaric oxygenation on oxidative stress in acute transient focal cerebral ischemia in rats revealed significant reduction in infarct volume, activation of astrocite, and increasing glutathione level.\textsuperscript{90} Neonatal hypoxia-ischemia encephalopathy causes brain damage and neurodegeneration leading to cognitive and behavioral impairment. Liu et al.\textsuperscript{91} suggested that HBOT is effective in promotion of histological and long-term functional recovery after neonatal hypoxia-ischemia brain damage due to caspase-3 inhibition and apoptosis inducing factor-mediated pathways. In regard to the effects of delayed HBOT on cerebral ischemia and its potential mechanisms, it was documented that delayed HBOT promotes neurogenesis and improves neurofunctional recovery in the late-chronic phase of stroke probably due to reactive oxygen species/HIF-1α/β-catenin pathway.\textsuperscript{92} Despite the mentioned beneficial effects of HBOT in experimental models of stroke, Lu et al.\textsuperscript{93} documented that HBOT increases brain damage area by activation of extracellular signal-regulated kinase (ERK) 1,2, which interrupts autophagy flux in a transient cerebral ischemic rat model. IL-10 plays an important role in the neuroprotection of HBO on against TBI, so that IL-10 deficiency aggravates the brain damage and abrogates the beneficial effects of HBO on apoptosis, inflammation, and edema after injury.\textsuperscript{94} A study was conducted to investigate the effect of the different hyperbaric oxygenation manipulations based on morphological, molecular-biological, and behavioral tests at 4 hours, 15 days and 75 days after TBI in rats.\textsuperscript{95} The results showed that hyperbaric oxygenation inhibits cell apoptosis in the rat hippocampus and improves their physiological functions in the HBO-early group better than the HBO-delayed group. Another study demonstrated that HBO could enhance neuroprotection and improve prognosis through inhibiting cerebral edema, intensifying the metabolism of local neurons, reducing apoptosis, inhibiting the inflammatory reaction, and protecting BBB integrity in a blast-induced TBI model in rabbits.\textsuperscript{96} Kraitys et al.\textsuperscript{97} showed that the long-term protective effects of HBOT are provided by the cortex remyelination, which is demonstrated by the recovery of sensorimotor function. Also, using diffusion-weighted imaging and DCE–magnetic resonance imaging revealed that HBO improves cytotoxic edema and impaired BBB and promotes the recovery of neurofunction after experimental TBI.\textsuperscript{98} HBOT during the acute phase of TBI can attenuate TNF-α and transforming growth-interacting factor, and increase transforming growth factor β-1 which leads to decreased apoptosis in the affected cortex.\textsuperscript{14} Liu et al.\textsuperscript{99} found that daily HBOT significantly improved Morris water maze performance and attenuated edema in the ipsilateral hippocampus after TBI, suggesting that the therapeutic effect of HBO is at least partially mediated through reducing brain edema. The effects of HBO on cognitive dysfunction showed that HBOT, provided 5–7 days after craniocerebral trauma, improves cognitive function and neuroplasticity in a controlled cortical impact rat model.\textsuperscript{100} Study of the relative neuroprotective effects HBO and TLR4 knockout following temporary middle cerebral artery occlusion in mouse revealed that a single HBOT immediately after occlusion and after 24 hours reperfusion significantly reduces edema and improves perfusion, while, TLR4 knockout protects mice against ischemia but to a lesser extent than HBOT.\textsuperscript{101} It was documented that HBOT due to inhibition of the TLR4/NF-κB signaling pathway protects the neurons after traumatic injury in rat, so that significantly inhibits the activation of the TLR4/NF-κB signaling pathway, reduces TNF-α, caspase-3, IL-1β and IL-6 expression, and reduces neural apoptosis and improves the neurological function.\textsuperscript{102} HBOT increased expression of the heme oxygenase, nuclear factor erythroid 2-related factor 2 (Nrf2), and quinine oxidoreductase 1 in the brain tissue around the lesion and also improved neurofunctional effect after TBI.\textsuperscript{103} A study revealed that HBO reduces IL-1β and IL-18 and suppresses protein expression of inflammasome components, along with high-mobility group box 1 reduction after TBI in the brain and serum.\textsuperscript{104} In regard to repetitive mild TBI, it was found that HBOT significantly decreased the magnetic resonance imaging-identified abnormalities and tissue histopathology.\textsuperscript{105} HBOT ameliorates TBI-induced depression-like behavior by reducing neuroinflammation if early intervention is possible, suggesting a possible mechanism by which depression-like behavior recovery might occur.\textsuperscript{106} Results of a study showed that immediate and delayed HBOT for moderate TBI in mice have similar effects, so that displayed significant improvement in learning abilities, decreased neuronal loss and reactive astrocytes, and increased myelin basic protein.\textsuperscript{107} Recently, it was found that HBO promotes neural stem cell proliferation and migration to the lesion area by activating VEGF/ERK signaling on day 7 after TBI.\textsuperscript{108} It is well known that the nucleotide binding oligomerization domain like receptor family pyrin domain containing 3 (NLRP 3) inflammasome has been implicated in the secondary injury of TBI. In this regard, Qian et al.\textsuperscript{109} documented that HBO improves motor score and reduces brain edema following TBI, along with IL 1β, IL 18, and NLRP 3 inflammasome components reduction. The results revealed that HBO decreases inflammation via modulation of microglial NLRP-3 inflammasome signaling. HBOT following hyperglycemic middle cerebral artery occlusion in rat reduces hemorrhagic transformation and infarction volume via ATP/NAD+/Sirt1 pathway which may be a promising approach for diabetic patients with acute ischemic stroke.\textsuperscript{110} Multiple HBOT significantly decrease the expression of c-jun, c-fos, and Bax, while increase the expression of Bcl-2, neurotrophin-3, glial cell line-derived neurotrophic factor, BDNF, and nerve growth factor.\textsuperscript{111} Also, HBO exposure through increasing tight junction protein zonula occludens-1 and caveolin-1 improved BBB permeability following global cerebral ischemia/reperfusion injury in rat.\textsuperscript{112} He et al.\textsuperscript{113} found that HBOT attenuates neuronal apoptosis via Akt/GSK3β/β-catenin pathway after TBI.
Nerve injury

Muscle paralysis and neuropathic pain due to the destruction of motor and sensory neurons are among the most common symptoms of nerve injuries.114,115 Meanwhile, neuroinflammation, oxidative stress, excitotoxicity, apoptosis, and neurotrophic support deficit are some of the mechanisms involved in neural degeneration after nerve injury.116-118 In this regard, using the rat sciatic nerve model, the effect of HBO on peripheral nerve healing after destruction was evaluated.119 Results of this study suggested that HBOT for 1 week following microsurgical repair promotes functional recovery in transected peripheral nerves. Also, another study concluded that HBO effectively saves fibers from ischemia.120 Although, regard to rat peroneal nerve crush and transaction injury there were no HBO-related changes in nerve/muscle force measurements and edema.121,122

Whereas, a study on the regenerative effects of HBO on crushed sciatic nerve injury suggested that therapies consisting of 100% oxygen under pressure can improve the healing of peripheral nerve in rabbits.123 HBOT (first at 0, 4, and 8 hours postoperatively and then every 8 hours) stimulates axonal outgrowth following a sciatic nerve crush lesion in rat, evaluated using the pinch-reflex test and with neurofilament staining.124 Whereas, another study concluded that HBOT (twice daily for 3 consecutive days), had no influence on functional recovery after standard nerve crush injuries on sciatic nerves of rats using walking-track analysis.125 After that, some investigators studied the effect of HBOT on axonal outgrowth in cellular and acellular nerve grafts of sciatic nerves in rat. The axonal outgrowth was significantly longer in animals treated with HBO after cellular nerve grafting,126 in contrast to acellular nerve grafts with no beneficial effects on axonal outgrowth.127 Another study confirmed that HBOT could not restore the gait or the strength of muscle after 90 days with nerve transection and repair or with nerve crush injury in rats.128 Mrsic-Pelcić et al.129 found that HBOT prevented ischemia-induced changes in the Na⁺,K⁺-ATPase activity after HBO administration in the optic nerves of global cerebral ischemia-exposed rats, while the level of the SOD activity in the ischemic animals was not changed. Evaluation of long-lasting effects of hyperbaric oxygenation on transected sciatic nerve and repaired with microsurgery showed functional recovery after 7 weeks.130 Evaluation of the effects of HBOT on the histological pattern of damaged facial nerve in rabbits indicated an increase in the mean axon diameter 2 weeks after injury.131 In spite of protective effects of HBOT in peripheral nerve injury, some evidence revealed that the ERK1/2 and p38 have been differently activated in the dorsal root ganglion by prolonged HBO exposure.132 A study showed that HBOT reduces neuropathic pain and inhibits intraneuronal TNF-α production after chronic constrictive injury.133 Analysis of the thermal hyperalgesia, mechanical allodynia, and neurochemical changes of neuropathic pain in rat sciatic nerve injury showed that repetitive HBOT greatly inhibited behavioral signs of neuropathic pain and nerve injury-induced induction of c-Fos and activation of astrocytes, and increased phosphorylation of N-methyl-D-aspartate receptor subtype 2B receptor and the subsequent Ca²⁺-dependent signals in rats.134 Pre- and post-HBOT inhibits neuropathic pain following chronic constriction injury in rats through the regulation of neuronal and inducible NOS expression in the spinal cord, demonstrating that HBO has therapeutic effects on neuropathic pain.135 The role of brain opioid receptors in the anti-allodynic properties of HBO following crush-induced neuropathic pain in rats was investigated in another study.136 Data analysis of this study revealed that HBOT significantly decreased the nerve crush-induced allodynia, whereas, this anti-allodynic effect by the opioid antagonist naltrexone was reversed. Another study conducted to specify the effect of different times of HBOT application on transected-sciatic nerve regeneration using standard microsurgical techniques.137 The results showed the best gait analysis and less fibrosis with HBOT started at postoperative first hour compared to postoperative first and second week. In regard to the neuroprotective mechanism of HBOT on chronic constriction-induced neuropathic pain, it was revealed the microglial mitophagy involvement.138 Results of our laboratory revealed that pre- and post- HBOT had neuroprotective properties following sciatic nerve degeneration through decreasing lipid peroxidation, increasing SOD and catalase activities, attenuating caspase-3 and cyclooxygenase-2 expression, and increasing S100β expression.139 Recently, it was found that iNOS and neuronal NOS levels were significantly decreased with HBOT following chronic constriction injury in rats.140

Neurodegenerative disease

Neurodegenerative diseases are associated with progressive nerve cell damage and neuronal loss that impair motor or cognitive function.139 On the other hand, oxidative stress and inflammatory response play an important role in the pathogenesis of neurodegenerative diseases.140-142 Dave et al.143 found that HBOT in an experimental motor neuron disease significantly ameliorates mitochondrial dysfunction in the spinal cord and motor cortex, meanwhile greatly delays the disease onset. Chen et al.144 documented that HBO prevents cognitive impairments in D-galactose induced aging model in mice due to reducing oxidative stress and blocking NF-κB pathway. Attenuation of neuroinflammatory processes is another possible mechanism underlying the effect of HBO on Alzheimer’s disease through decreasing microgliosis, astrogliosis, TNF-α, and IL-1β and increasing scavenger receptor A, arginase1, IL-4, and IL-10 expression.145 Research on Parkinson’s disease has shown that 11-week exposure to mild HBO inhibits the decrease of dopaminergic neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson’s disease.146

Neurotoxic injury

For the first time, the effect of HBOT on the peripheral nerve disorder produced by administration of clioquinol, an antifungal and antiprotozoal drug which is neurotoxic in large doses, to rabbits was studied.147 The damage of myelin and axons, which was apparent after administration of clioquinol, decreased in grade with HBO. In another study, the effect of HBO on streptozotocin-induced diabetic neuropathy was investigated.148 The findings indicated that HBOT will partially reverse induced neuropathy in chronic diabetes. In contrast, Aydin et al.149 did not document any beneficial effects of HBOT on nerve regeneration in early diabetes. In regard to
the protective effects of HBOT following severe carbon monoxide neurotoxicity, it was found that HBO is not effective in preventing neurologic sequelae in mice following severe carbon monoxide neurotoxicity.\textsuperscript{150}

**In Vitro Studies**

A few numbers of *in vitro* studies regarding HBO neuroprotection and its basic molecular mechanisms began to accumulate (Additional Table 6). In spite of the results suggested that activation of N-methyl-D-aspartate receptors and nitric oxide production are involved in the neurotoxicity produced by prolonged HBO exposure (6 ATA for 30, 60, and 90 minutes) in primary rat cortical cultures,\textsuperscript{151} Günther et al.\textsuperscript{152} found that HBO had neither favorable nor unfavorable effects on the early morphological and functional restitution of ischämically damaged primary corticencephalic cell cultures of rats under Hypoxia and glucose-deprivation (*in vitro* ischemia). β-Catenin, a protein involved in Wnt signaling and cell adhesion, plays an important role in the development of nervous system. In this regard, it was documented that HBOT intensifies the neural stem cell proliferation and neurogenesis by β-catenin-induced activated Neurogenin 1 gene and suppresses astrocytogenesis by β-catenin-induced down-regulated bone morphogenetic protein 4 gene.\textsuperscript{153} An *in vitro* study revealed that HBO via the induction of heat shock protein 32 protected cultured spinal neurons from oxidative and oxygen glucose deprivation injury, while HBO through reactive oxygen species/p38 mitogen-activated protein kinase/Nrf2 pathway induced the expression of heat shock protein 32.\textsuperscript{154} Another study documented that *in vitro* HBO after cell injury significantly accelerated neural stem cell proliferation and the VEGF/phospho-ERK pathway.\textsuperscript{108} Examination of the effect of HBOT on the neuroprotective factor secretion, proliferation, and BDNF-release in fibroblasts and mesenchymal stem cells showed a significant increased proliferation of fibroblasts and altered the protein expression pattern in mesenchymal stem cells after 5 days of HBOT.\textsuperscript{155} Also, it was found that HBOT promotes differentiation of neural stem cells into oligodendrocytes and neurons and reduces the number of astrocytes via regulation of Wnt3/β-catenin and BMP-2 signaling pathways.\textsuperscript{156}

**Clinical Trials**

Despite the growing body of preclinical evidence confirming HBOT neuroprotection, few clinical studies have been performed and therefore limited information is currently available, which are summarized in Additional Table 7. In regard to the neuroprotective effects of HBOT against spinal cord injuries, results of a clinical trial study indicated that 8 weeks of HBOT can significantly improve nerve function and consequently promote daily life activities in the patients with incomplete SCI.\textsuperscript{157} Another randomized clinical trial studied the effect of HBO in 79 patients with acute SCI.\textsuperscript{158} Results of this study showed that plasma HMGB1 and NF-kB expression down-regulated with HBOT in patients on days 3, 7, 10 and 30, and meanwhile F-wave chronodispersion decreased with HBOT on days 10 and 30. Also, American Spinal Injury Association and Franklin Grade motor/pain scores on day 30 were significantly improved in the treatment group. In regard to brain injuries, results of a prospective randomized trial showed that HBOT did not increase the number of patients in the favorable outcome categories following severely brain injury.\textsuperscript{172} A double-blind pilot study suggested that HBO improves outcome after acute ischemic stroke.\textsuperscript{159} Rockswold et al.\textsuperscript{160} for the first time demonstrated a prolonged effect of HBOT on cerebral blood flow and cerebral metabolism in severely brain injured patients, while, the increased cerebral metabolic rate of oxygen and decreased ventricular cerebrospinal fluid lactate levels after therapy indicated that HBO may improve aerobic metabolism in these patients. Another study documented that HBOT could improve obviously brain electric activity mapping, Glasgow coma and outcome scales in patients with severe brain injury, and decrease the morbidity and mortality.\textsuperscript{161} A study was designed to investigate the efficacy, safety, and feasibility of HBO (60 minutes with 100% oxygen to 2.5 ATA) in 33 ischemic stroke patients.\textsuperscript{173} Compared to medication treatment alone, HBOT was more effective in controlling epilepsy, improving clinical symptoms, and relieving hydrocephalus in patients with post-brain injury neural status.\textsuperscript{162} Treatment of chronic brain injury with HBOT significantly improved motor skills, daily living, communication, and socialization.\textsuperscript{140} Results of a study on the metabolism and cerebral circulation of patients in the subacute phase of head injury showed that HBOT significantly decreased both pulsatility index and jugular venous lactate after HBO.\textsuperscript{144} To assess the beneficial effects of HBOT on the prognosis of patients with subacute TBI, the clinical status of the patients were assessed before and 3 to 6 months after HBOT with the Glasgow outcome and Glasgow coma scales.\textsuperscript{11} The Glasgow coma and outcome scales of the HBOT group were improved 6 months after HBOT, with minimal adverse side effects. Meanwhile, another study revealed that HBOT (2.4 ATA) following mild TBI had no effect on post-concussive symptoms.\textsuperscript{174} Evaluation of the whether elevated dissolved oxygen by HBO could activate neuromplasticity after stroke, revealed that HBOT significantly improves neurological outcome even in the late chronic stage.\textsuperscript{163} A prospective, randomized phase II clinical trial revealed that combined hyperbaric hyperoxia/normobaric hyperoxia therapies after severe TBI significantly improved oxidative metabolism markers, decreased intracranial hypertension, and improved markers of cerebral toxicity, while the mortality significantly reduced.\textsuperscript{166} Boussi-Gross et al.\textsuperscript{167} tested the effect of HBOT on brain function and quality of life in patients with mild TBI. Results of this study revealed that HBOT induces neuroplasticity and improves quality of life with prolonged post-concussion syndrome. However, another studies demonstrated that HBO at either 1.5, 2.0 or 2.4 ATA equivalent had no effect on postconcussion symptoms after TBI.\textsuperscript{175-178} A study conducted to evaluate the safety and potential long-term neurological consequences of HBOT on intracerebral hemorrhage in diabetic patients.\textsuperscript{168} Results of this study showed that early HBOT is safe and effective in terms of long-term neurological outcome in diabetic patients suffering from intracerebral hemorrhage. Recently, a retrospective analysis was performed on 62 consecutive patients prescribed for HBOT after stroke.\textsuperscript{169} Results of this study showed that some patients (n = 24) significantly benefitted from HBOT by...
improving their clinical neurological status and quality of life.

In regard to nerve injuries, a clinical trial conducted in patients with idiopathic trigeminal neuralgia suggested that one course of HBOT (10 consecutive days) is an effective approach for treating neuropathic pain in human with produced a long-lasting, rapid-onset, and dose-dependent analgesic effects.8

In regard to neurodegenerative disease, a phase I safety study and a phase II efficacy study of HBOT in patients with ALS did not recommend HBOT in ALS patients.179,180 Some studies conducted on hyperbaric-oxygen therapy of multiple sclerosis. Results of a randomized, placebo-controlled, double-blind study suggested a positive effect of HBO on advanced multiple sclerosis.170 In contrast, short-term results of a placebo-controlled, double-blind trial did not support the claims made for HBO in the management of multiple sclerosis,181 similar to some other studies.182-187

In regard to neurotoxic injury, results of a study suggested that repetition of HBOT prevents the delayed neuropsychiatric sequelae of carbon monoxide poisoning when applied individually with monitoring of quantitative electroencephalography as an indicator of efficacy.171

CONCLUSION

In recent years, HBOT has attracted considerable attention because of its biological properties. Neuroprotection benefits of HBOT, as a therapeutic option, confirmed with a lot of preclinical in vivo and in vitro studies. These beneficial effects have been mainly attributed to anti-oxidative, anti-inflammatory, and anti-apoptotic properties, in addition to improvement of oxygen supply and neural metabolism and stimulating autophagy. The evidence presented in this review indicates the potential of HBOT in treatment and prevention of a variety of injuries to the nervous system. Meanwhile, because limited data is available to demonstrate the neuroprotective effects of HBOT in humans, newly designed clinical trials are needed on HBOT’s neuroprotection and its possible mechanisms as well as the course and dose of HBOT.

Author contributions
FA and ARK designed and wrote the manuscript. Both authors read and approved the final manuscript.

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Additional files

Additional Table 1: Summary of studies regarding the effects of HBOT against spinal cord injury.

Additional Table 2: Summary of studies regarding the effects of HBOT against brain injury.

Additional Table 3: Summary of studies of the effects of HBOT against nerve injury.

Additional Table 4: Summary of studies of the effects of HBOT against neurodegenerative diseases.

Additional Table 5: Summary of studies of the effects of HBOT against neurotoxic injury.

Additional Table 6: Summary of in vitro studies on neuroprotective effects of HBOT.

Additional Table 7: Summary of clinical trials on neuroprotective effects of HBOT.

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| Author         | Year  | Model of injury | Therapy schedule | Finding                                                                 | Possible mechanism                                                                 |
|---------------|-------|-----------------|------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Higgins et al. | 1981  | Transdural impact injury in cat | 2 ATA for a period of 3 hours | Preservation of marginally injured neuronal elements of the spinal cord long tracts | Reversal of focal tissue hypoxia or reduction of tissue edema                      |
| Murakami et al. | 2001  | Ischemia in rabbit | 3 ATA for 1 h at 30 min after reperfusion | Attenuation of the selective motor neuron death and improvement of neurofunctional outcomes | Without providing possible mechanisms                                              |
| Huang et al. | 2003  | Contusion in rat | 2.8 ATA for 1 h/day for 1 wk starting at 6 h following injury | Retained more sparing tissue and improved neurological outcome | Without providing possible mechanisms                                              |
| Dahman et al. | 2007  | Clip compression in rat | 2.8 atmospheres twice daily for a total of eight 90 min-sessions | Diminished TBARS, SOD and GSH-Px | Prevention of oxidative stress                                                  |
| Tai et al. | 2010  | Clip compression in rat | 2.5 ATA for 2 h immediately after SCI | Attenuating overproduction of IL-1β and TNF-α, stimulating production of GDNF, VEGF, and IL-10, attenuating hindlimb dysfunction | Upregulation of growth factors                                                  |
| Dayan et al. | 2012  | Clip compression in rat | 2.80 ATA for 60 min daily for 5 d | Decreasing SOD, NOS and NO, improving functional recovery | Without providing possible mechanisms                                              |
| Yang et al. | 2013  | Contusion in rat | 2.5 ATA, twice daily at 12 h intervals | Reduced spinal cord edema, stabilized the blood-spinal cord barrier, and promoted recovery of neuronal function | Down regulation of IL-6, MMP-2, and MMP-9 and up regulation of expression of VEGF |
| Huang et al. | 2013  | Contusion in rat | 2.0 ATA, 30 min after SCI for 80 min once daily for consecutive 24 d | Reduced the mRNA and protein expression of iNOS and the serum NO content, improved motor evoked potential and locomotor recovery | Through the iNOS mRNA-iNOS-NO signaling pathway                                   |
| Yang et al. | 2013  | Contusion in rat | 2.5 ATA, twice daily in the first 3 d at intervals of 8 h, and reduced to once daily thereafter | Down regulated HMGB1 and NF-αB | Anti-inflammatory activity                                                        |
| Zhou et al. | 2013  | Contusion in rat | 2.0 ATA for 60 min twice daily for the first 3 d and once daily for the following days | Repair of damage spinal cord, improved the hind limb functional recovery | Upregulation of VEGF and downregulation of HIF-1α                                |
| Tan et al. | 2014  | Contusion in rat | 2.0 ATA, 6 h after surgery for a 60 min once a day | Decreased TLR2 and NF-αB expression and histological scores as well as IL-1β and TNF-α levels | Inhibiting inflammatory responses                                                 |
| Yaman et al. | 2014  | Contusion in rat | 2.4 ATA in two 90-min sessions for 5 d | Improved motor recovery, diminished nitrite levels | Without providing possible mechanisms                                              |
| Liu et al. | 2014  | Contusion in rat | 2.0 ATA twice per day for 3 d and then daily for the following days consecutively after surgery | Improved hindlimb motor function, decreased histochemistry scores | Changing VEGF and CX43 expression level                                           |
| Geng et al. | 2015  | Contusion in rat | 2.8 atm for 90 min every 12 h | Increased IL-4 and IL-13 levels, reduced TNF-α and IFN-γ levels, shifting the macrophage phenotype from M1 to M2 | Macrophage polarization                                                          |
| Liang et al. | 2015  | Contusion in rat | 2.0 ATA for 60 min twice per day at 8 h intervals for the first 3 d and daily thereafter immediately after injury | Compromised NALP-3, ASC and caspase-1, mitigated IL-1β release | Inactivating NALP-3 inflammasome                                                 |
| Hou et al. | 2015  | Contusion in rat | 0.2 MPa at 0.01 MPa/min for 4 h after SCI, for four times daily for 3 d | Improved motor function scores and increased myelinated nerve fibers | Reducing apoptosis and expression of MMP-9/2                                      |
| Liu et al. | 2015  | Contusion in rat | 2.0 ATA 6 h after surgery for 60 min once a day | Decreased CHOP and caspase-12 and caspase-3, improved neurological function | Inhibiting ER stress induced apoptosis                                            |
| Liu et al. | 2015  | Contusion in rat | 2.0 ATA 6 h after surgery, once every 60 minutes | Increased GRP78 level, decreased INK and suppressed caspase-3 activation, improved hind limb motor function | Inhibiting the ERS response                                                       |
| Kang et al. | 2015  | Contusion in rat | 2.5 ATA once daily, 24 h after the injury | Reduced HMGB1, TLR4, and NF-αB, improved locomotor function | Decreasing inflammatory process                                                  |
| Sun et al. | 2016  | Contusion in rat | 2.0 ATA for 90–100 min with inter-vaules of 15 min, once per day | Uregulated Beclin-1 and LC3II, improved locomotor function | Enhancing autophagy expression                                                   |
| Wang et al. | 2016  | Contusion in rat | 2.0 ATA 60 min once daily | Inhibited RAGE and MCP-1, improved locomotor function | Relieving secondary inflammatory responses                                        |
| Sun et al. | 2016  | Contusion in rat | 3.0 ATA for 60 min, began at 2 h after SCI, once a day for 5 d | Increased SOD activities and decreased MDA levels, improved locomotor function, less cystic degeneration | Increasing oxygen-free radical scavenging and reducing lipid oxidation           |
| Sun et al. | 2016  | Contusion in rat | 2.0 ATA immediately after surgery for 1 h | Improved neuronal function and FA | Without providing possible mechanisms                                              |
| Ying et al. | 2017  | Contusion in rat | 2.0 ATA at 6 h after surgery for 90 min | Ameliorated neurological impairment, decreased TUNEL reaction, suppressed dendritic/synaptic degeneration | Upregulating the BDNF/Tbr2 signaling pathways                                     |
| Meng et al. | 2019  | Contusion in rat | 2.0 ATA for twice a day at 12 h intervals for 3 consecutive days and thereafter once a day | Improved functional recovery | Activating SDF-1/CXCR4 axis and promoting BDNF expression                        |
| Zhou et al. | 2019  | Contusion in rat | 2.0 ATA for 60 min, three consecutive courses and each course lasted 10 d, once a day | Improved functional recovery, inhibited iNOS, COX-2, GFAP and NG2 | Inhibiting inflammation and glial scar formation                                  |
| Liu et al. | 2019  | Contusion in rat | 2.0 ATA for 60 min, 6 h after injury twice per week for 8 h intervals for the first 3 d and then daily for the consecutive days | Recovery of locomotor function | Without providing possible mechanisms                                              |

Note: 1 ATA = 101.325 kPa. ASC: Apoptosis-associated speck-like protein; ATLAS: atmosphere absolute; BDNF: brain-derived neurotrophic factor; CHOP: CCAAT-enhancer-binding protein homologous protein; COX-2: cyclooxygenase-2; CX43: connexin 43; CXCR4: CXC chemokine receptor 4; ERS: endoplasmic reticulum stress; FA: fractional anisotropy; GDNF: glial cell line-derived neurotrophic factor; GFAP: glial fibrillary acidic protein; GRP78: glucose-regulated protein 78; GST-Px: glutathione peroxidase; HBT: hyperbaric oxygen therapy; HIF-1α: hypoxia-inducible factor 1α; HMGB1: high mobility group protein B1; IFN-γ: interferon-γ; IL: interleukin; iNOS: inducible nitric oxide synthase; JNK: c-Jun N-terminal kinase; LC3II: Microtubule-associated proteins 1A/1B light chain 3B II; MCP 1: monocyte chemotactic protein 1; MDA: malondialdehyde; MMP: matrix metalloproteinase; NALP-3: NACHT, LRR and PYD domains-containing protein 3; NF-κB: nuclear factor κB; NG2: neuron-glial antigen 2; NO: nitric oxide; NOS: nitric oxide synthase; RAGE: receptor for advanced glycation end products; SCI: spinal cord injury; SDF-1: stromal cell-derived factor-1; SOD: superoxide dismutase; TBA:rs: Thrombin activatable fibrinolysis inhibitor; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling; VEGF: vascular endothelial growth factor.
## Additional Table 2: Summary of studies regarding the effects of HBOT against brain injury

| Author                  | Year  | Model of injury                  | Therapy schedule | Finding                                                                 | Possible mechanism                                                                 |
|-------------------------|-------|----------------------------------|------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Weinstein et al.         | 1986  | Cerebral ischemia in gerbil      | 1.5 ATA for 15 min | Decreased ischemic neuronal damage and mortality rate                    | Without providing possible mechanisms                                                |
| Mink et al.              | 1995  | Global cerebral ischemia in rabbit | 2.8 ATA for 75 min | Increased oxidized glutathione and the ratio of oxidized glutathione to reduced glutathione, promoted cortical somatosensory evoked potential recovery | Without providing possible mechanisms                                                |
| Mink et al.              | 1995  | Global cerebral ischemia in rabbit | 2.8 ATA for five cycles of oxygen and air, each for 20 and 5 min | Reduced brain vascular permeability and cerebral blood flow                | Without providing possible mechanisms                                                |
| Chang et al.             | 2000  | Cerebral ischemia in rat         | 3 atm, 2 × 90 min at a 24-h intervals | Reduced ischemic brain damage and behavioral dysfunctions                | Without providing possible mechanisms                                                |
| Atochin et al.           | 2000  | Temporary MACO                  | 2.8 atm for 45 min before ischemia | Reduced MPO concentration, functional neurologic deficits, and cerebral infarct volume | Inhibiting neutrophil sequestration                                                  |
| Badr et al.              | 2001  | Temporary MACO                  | 3 ATA for 1 h     | Decreased glucose, pyruvate, and glutamate                              | Regulating brain energy metabolites and excitatory amino acids                      |
| Yang et al.              | 2001  | Transient forebrain ischemia in rat | 2.5 ATA for 2 h  | Increased cell survival                                                  | Reducing down-regulation of the NT-3 mRNA level                                    |
| Yang et al.              | 2001  | Transient MACO                  | 3 ATA for 1 h     | Decreased infarcted area in the 3- and 6-h HBOT groups, increased infarcted area in the 12- and 23-h therapy groups | Without providing possible mechanisms                                                |
| Yin et al.               | 2002  | Transient focal cerebral ischemia in rat | 3 ATA for 1 h, at 6 h after reperfusion | Reduces infarct area                                                    | Inhibition of COX-2 over-expression                                                |
| Yin et al.               | 2002  | Transient focal cerebral ischemia in rat | 2.8 ATA during ischemia | Reduced edema and neuronal shrinkage                                      | Reduction of dopamine                                                               |
| Yin et al.               | 2003  | Focal cerebral ischemia in rat   | 2.5 ATA for 2 h, at 6 h after reperfusion | Reduced brain infarction and improved neurologic scores                  | Preventing apoptotic death                                                         |
| Mrsić-Peleći et al.      | 2004  | Global cerebral ischemia in rat  | Not available     | Enhanced SOD activity and preserved Na+,K+-ATPase activity               | Without providing possible mechanisms                                                |
| Palzur et al.            | 2004  | Brain contusion in rat           | 2.8 ATA for two consecutive sessions of 45 min each, 3 h after injury and thereafter twice every day for 3 consecutive days | Reduced the number of TUNEL positive cells and the volume of the lesion          | Without providing possible mechanisms                                                |
| Veltkamp et al. [37,38]  | 2005  | Focal cerebral ischemia in rat   | 3.0 ATA for 1 h  | Reduced volume of abnormal DWI signal and lesion size on T2w, increased BBB permeability and vasogenic edema | Without providing possible mechanisms                                                |
| Yin and Zhang            | 2005  | Transient focal ischemia in rat  | 2.5 ATA for 2 h per day, repeated daily for 6 d | Decreased infarct ratio and ameliorated neurological deficits           | Increasing Bcl-2 and Bcl-xL                                                          |
| Vlodavsky et al.         | 2005  | Cerebral contusion in rat        | Not available     | Decreased apoptosis and TUNEL-positive cells                            | Increasing Bcl-2 and Bcl-xL                                                          |
| Rogatsky et al.          | 2005  | Severe traumatic brain injury in rat | 1.5 ATA for 60 min beginning 2 h after FPIH | Diminished ICP elevation rate and decreased mortality level              | Without providing possible mechanisms                                                |
| Veltkamp et al.          | 2006  | Transient focal cerebral ischemia in rat | 3.0 ATA for 1 h With a delay of 45 min after filament introduction | Preserved integrity of the BBB                                         | Attenuating degradation of laminin-5 and blocked MPP-9 upregulation                |
| Calvert et al.           | 2006  | Hypoxia-ischemia in rat          | 2.5 ATA for 2 h  | Increased GLUT-1, GLUT-3, LDH, and Ald, decreased HIF-1α,p53 interaction and p53 expression | Alteration of the HIF-1α phenotype                                                  |
| Liu et al.               | 2006  | Traumatic brain injury in rat    | Not available     | Alleviated neuronal apoptosis                                           | Reducing Cyt C and Bax and up-regulating Bcl-1                                       |
| Vlodavsky et al.         | 2006  | Traumatic brain injury in rat    | 2.8 ATA, two sessions of 45 min each | Decreased neutrophil inflammatory infiltration, MMP-9 expression, and TUNEL-positive cells | Without providing possible mechanisms                                                |
| Henninger et al.         | 2006  | Embolic model of focal cerebral ischemia with partially spontaneous reperfusion | 2.5 ATA for 60 min beginning 180 min after MCAO | Reduced infarct volume                                                  | Without providing possible mechanisms                                                |
| Qin et al.               | 2007  | Focal transient cerebral ischemia in rat | 3.0 ATA for 1 h, 30 min after MCAO | Reduces BBB disruption, hemorhagic transformation, mortality, and infarct volume and swelling | Without providing possible mechanisms                                                |
| Harch et al.             | 2007  | Chronic traumatic brain injury in rat | 1.5 ATA, 7 d/wk | Improved cognitive function                                           | Increasing hippocampus vascular density                                              |
| Zhou et al.              | 2007  | Lateral fluid-perfusion injury   | 1 h of hyperbaric oxygen plus 3 h of normobaric 100% oxygen | Increased cerebral ATP, improved cognitive recovery and reduced hippocampal neuronal cell loss | Without providing possible mechanisms                                                |
| Hou et al.               | 2007  | Middle cerebral artery occlusion in rat | 2.0 ATA for 60 min | pO(2) not show an increase in the ischemic or normal hemispheres despite decreasing the infarct size | Negative regulation of the proapoptotic function of mitochondrial TSPO               |
| Soustiel et al.          | 2008  | Cortical contusion in rat        | Not available     | Reduced TSPO expressing and TUNEL positive cells                       | Without providing possible mechanisms                                                |
| Yang et al.              | 2010  | Middle cerebral artery occlusion in rat | 2.8 ATA for 1 h during ischemia | Alleviated brain injury                                                | Reducing hydroxyl free radical formation and glutamate release                     |
| Zhao et al.              | 2011  | Cerebral ischemia-reperfusion in rat | 0.25 MPa for 60 min and ventilated with pure oxygen for 10 min at intervals | Decreased permeability of the BBB                                       | Reducing MMPs activity and augmenting claudins expression                           |
| Lin et al.               | 2012  | Traumatic brain injury in rat    | 2.0 ATA for 1 h/d for three consecutive days | Reduced motor and cognitive dysfunction, cerebral infarction and apoptosis | Inhibiting activated inflammation and gliosis, stimulating both angiogenesis and neurogenesis |
| Author          | Year | Model of injury | Therapy schedule | Finding                                                                                                                                           | Possible mechanism                                                                 |
|-----------------|------|-----------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Lim et al.      | 2013 | Traumatic brain injury in rat | 2.0 ATA at 1 h or 8 h after TBI | Attenuated cerebral infarction, reduced microglial activation, TNF-α expression, and neuronal apoptosis expression                                  | Attenuating microgliosis and proinflammatory cytokine expression                        |
| Brkic et al.    | 2012 | Cortical ablation in rat     | 2.5 ATA for 60 min, once a day for 10 d | Recovered motor functions, enhanced recovery of muscle strength, induced over-expression of GAP43 and SYP                                           | Intensifying neuroplastic responses by promoting axonal sprouting and synapse remodeling |
| Wang et al.     | 2012 | Acute transient focal cerebral ischemia in rat | 3 ATA for 1 h, starting at 3 h post brain ischemia | Reduced infarct volume and activated astrocyte, increased glutathione level                                                                | Decreasing oxidative stress                                                                                                                   |
| Li et al.       | 2013 | Neonatal hypoxia-ischemia in rat | 2.5 ATA for 90 min, 1 h after hypoxia exposure | Improved neurobehavioral functions especially for cognitive performances, reduced lesion size, decreased expression of caspase-3-positive cells and nuclear AIF translocation | Suppression of apoptosis                                                                                                                        |
| Hu et al.       | 2014 | Middle cerebral artery occlusion in rat | 2.5 ATA starting at 7 d after MCAO for 3 sessions, each session was 1.5 h daily for consecutive 7 d followed with 5 d break | Promoted neurogenesis and improved neurofunctional recovery, increased ROS and HIF-1α, and up-regulated neurogenin-1, doublecortin and synapsin-1 | Mediated by ROS/HIF-1α/β-catenin pathway                                                   |
| Chen et al.     | 2014 | Traumatic brain injury in mice | 2.0 ATA for 1 h | Reduced lesion volume and cerebral edema, improved neurological status, attenuated apoptosis and inflammation, improved BBB | Enhancing neuronal and cellular IL-10 protein levels                                      |
| Zhang et al.    | 2014 | Blast-induced traumatic brain injury model in rabbit | 2.0 ATA once, 12 h after injury | Promoted metabolism of local neurons, inhibited brain edema, protected BBB integrity, decreased cell apoptosis, and inhibited inflammatory response | Without providing possible mechanisms                                                   |
| Krajsy et al.   | 2014 | Traumatic brain injury in rat | Repeated 2.2 atm for 1 h at days 1–21 following trauma induction | Regressed neurological impairment, increased myelin basic protein isoforms, PLP expression and myelin synthesis | Pronounced remyelination                                                               |
| Wei et al.      | 2015 | Traumatic brain injury in rats | 2.0 ATA for 1 h immediately after TBI | Reduced TNF-α, neuronal damage, and neuronal apoptosis, attenuated TGIF and increased TGF-β1                                                | Decreasing proinflammatory cytokine and TGIF, and increasing TGIF-β1 leading to decreased neuronal apoptosis |
| Liu et al.      | 2015 | Traumatic brain injury in rats | 2 ATA for 60 min, 6 h after injury once per day for 2 wk | Improved post-TBI MWM performance                                                                                                           | Reducing edema                                                                            |
| Pushkov et al.  | 2016 | Temporary middle cerebral artery occlusion in mouse | 2.5 atmospheres pressure for 60 min | Reduced edema and improved perfusion better than TLR4 knockout                                                                                     | Without providing possible mechanisms                                                   |
| Meng et al.     | 2016 | Traumatic brain injury in rat | 0.12 MPa for 60 min, 2 h after TBI, twice with a 10 h interval | Reduced caspase-3, TNF-α, IL-10 and IL-1β, reduced apoptosis, improved neurological function                                                   | Inhibition of the TLR4/NF-κB signaling pathway                                           |
| Meng et al.     | 2016 | Traumatic brain injury in rats | 0.12 MPa for 60 min, two therapies were a 10 h period | Increased Nrf2, HO-1, and NQO-1, reduced the number of apoptotic and injured nerve cells, improved functional neurological scores | Up-regulation of the Nrf2 signaling pathway                                              |
| Geng et al.     | 2016 | Traumatic brain injury in mice | Not available | Improved motor score and reduced brain edema, suppressed protein expression of inflammasome components, reduced IL-1β, IL-18, and HMGBl | Inhibiting the activation of inflammasome signaling                                     |
| Huang et al.    | 2016 | Repetitive mild traumatic brain injury in rat | 1 h/d for 3 d at 2 ATA consecutively, starting at 1 d after initial injury | Improved cumulative tissue damage                                                                                                             | Without providing possible mechanisms                                                   |
| Lim et al.      | 2017 | Traumatic brain injury in rats | 2.0 ATA for 60 min immediately after TBI for 3 d | Attenuated TBI-induced depression-like behavior, reduced neuronal apoptosis, marker OX42 activation, and TNF-α expression | Attenuating neuroinflammation                                                            |
| Baratza-Goldstein et al. | 2017 | Traumatic brain injury in mice | HBOT for 4 consecutive days, at 3 h and 7 d post-injury | Improved learning abilities, decreased neuronal loss and reactive astrocytes, increased myelin basic protein | Without providing possible mechanisms                                                   |
| Yang et al.     | 2017 | Traumatic brain injury in rats | 3 atmospheres for 1 h, once daily for 7 consecutive days | Improved neurological function, promoted NSE proliferation and migration, increased VEGF, VEGFR2, Ras-1, MEK1/2, and ERK 1/2 protein expression | Activating VEGF/ERK signaling                                                             |
| Qian et al.     | 2017 | Traumatic brain injury in mice | 2.0 ATA for 1 h, once daily for 7 consecutive days | Improved motor score and reduced brain edema, reduced IL-1β and IL-18, suppressed NLRP3-3-inflammasome components | Without providing possible mechanisms                                                    |
| Hu et al.       | 2017 | Middle cerebral artery ischemia-reperfusion in rat | 2 ATA for 1 h immediately after ischemia | Increased ATP, and NAD+, and Sirt1, attenuated hemorrhagic transformation and brain infarction, improved neurological function | Activation of ATP/NAD+/Sirt1 pathway                                                     |
| Xing et al.     | 2018 | Traumatic brain injury in rats | 3 atmospheres ATA for 1 h in 12 h interval for the following 3 d and a total of six therapies | Reduced c-fos, c-jun, Bax and weakened the activation of Caspase-3, alleviated the decrease of Bcl-2, promoted the expression of NFG, HIFN, GDNF, and NT-3 | Without providing possible mechanisms                                                    |
| Li et al.       | 2018 | Global cerebral ischemia-reperfusion in rat | 2.5 atm for 60 min | Improved BBB permeability                                                                                                                     | Increasing caveolin-1 and tight junction protein ZO-1                                 |
| He et al.       | 2019 | Traumatic brain injury in mice | 2.8 ATA for 90 min | Attenuated neuronal apoptosis                                                                                                                  | Akt/GSK3β/β-catenin pathway                                                             |

Note:1 ATA (atm) = 101.325 kPa, AIF: Apoptosis Inducing Factor; Akt: protein kinase B, Ald: aldolase; ATP: adenosine triphosphate, BBB: blood-brain barrier; BDNF: brain-derived neurotrophic factor; COX-2: cyclooxygenase-2; Cyt C: cytochrome C; DWI: diffusion weighted imaging; ERK: extracellular signal-regulated kinase; FBPI: percussion brain injury; GAP43: growth Associated Protein 43; GDNF: glial cell line-derived neurotrophic factor; GLOUT: glucose transporter; GSK3β: glycogen synthase kinase 3β; HBF: hypoxia inducible factor; HMGBl: high mobility group protein 1; HO-1: heme oxygenase 1; iC3P: intracranial pressure; IL-1: interleukin; LDH: lactic dehydrogenase; MACO: middle cerebral artery occlusion; MEK1/2: mitogen-activated protein kinase 1/2; MMP: matrix metalloproteinase; MPO: myeloperoxidase; MWM: Morris water maze; NALP3: NACHT, LRR and PYD domains-containing protein 3; NF-κB: nuclear factor-κB; NGF: nerve growth factor; NQO-1: quinine oxidoreductase 1; Nrf2: nuclear factor erythroid 2-related factor 2; NCS: neural stem cell; NT-3: neurotrophin-3; P2X2 partial pressure of oxygen; ROS: reactive oxygen species; SOD: superoxide dismutase; SYT: synaptophysin; TBI: traumatic brain injury; T2w: T2-weighted; TGF-β1: transforming growth factor-β1; TLR: Toll-like receptor; TNF-α: tumor necrosis factor-α; TGF-β1: transforming growth factor-β1; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling; VEGF: vascular endothelial growth factor; VEGFR2: vascular endothelial growth factor receptor 2; ZO-1: zona occludens-1.
Additional Table 3: Summary of studies of the effects of HBOT against nerve injury

| Author            | Year | Model of injury          | Therapy schedule                                      | Finding                           | Possible mechanism                     |
|-------------------|------|--------------------------|-------------------------------------------------------|-----------------------------------|----------------------------------------|
| Zamboni et al.    | 1995 | Transsected-devascularized sciatic nerve in rat | 2.5 ATA, twice daily for 1 wk                        | Improved sciatic function index   | Without providing possible mechanisms |
| Kihara et al.     | 1995 | Ischemic sciatic nerve injury in rat | 2.5 atm for 2 h/d for 7 d beginning within 30 min of ischemia | Rescued fibers from ischemic degeneration | Without providing possible mechanisms |
| Bradshaw et al.   | 1996 | Crushed sciatic nerve in rabbit | 202, 242, and 303 kPa initiated 4 d post injury       | Improved nerve morphology         | Without providing possible mechanisms |
| Haapaniemi et al. | 1998 | Crushed sciatic nerve in rat | A series of 45-min exposures at 3 ATA at 0, 4, and 8 h postoperatively and then every 8 h | Stimulated axonal outgrowth        | Without providing possible mechanisms |
|                   |      |                          | 3.2 ATA for 45 min repeated at 4 and 8 h postoperatively and then every 8 h until evaluation | Longer axonal outgrowth           | Without providing possible mechanisms |
| Mrsić-Pelić et al.| 2004 | Global cerebral ischemia | Not available                                         | Prevented ischemia-induced changes in the Na⁺,K⁺-ATPase activity | Without providing possible mechanisms |
| Eguiluz-Ordoñez et al.| 2006 | Sciatic nerve transaction in rat | Not available                                        | Increased axons and blood vessel number | Without providing possible mechanisms |
| Vilela et al.     | 2008 | Facial nerve crush injury in rabbit | Not available                                      | Promoted the mean axonal diameter  | Without providing possible mechanisms |
| Li et al.         | 2011 | Chronic constrictive injury in rat | For 1 hat 2.4 atm once a day                        | Alleviated CCI-induced neuropathic pain | Reducing TNF-α production |
| Han et al.        | 2013 | Chronic constriction injury in rat | Pre-HBO or post-HBO 12 h before or after CCI at 0.25 MPa at a rate of 0.0125 MPa/min for 60 min | Increased mechanical withdrawal threshold, extended thermal withdrawal latency, decreased nNOS and iNOS | Regulation of spinal NOS expression |
| Gibbons et al.    | 2013 | Sciatic nerve crush injury in rat | 3.5 ATA for 60 min                                   | Reduced allodynia                  | Through opioid receptors               |
| Ince et al.       | 2016 | Sciatic nerve transaction in rat | Not available                                      | Best gait analysis and less fibrosis at postoperative first hour | Without providing possible mechanisms |
| Han et al.        | 2017 | Chronic constriction injury in rat | 0.25 MPa for 60 min, five times at a frequency of once per day | Ameliorated pain-related behaviors, decreased mitochondrial membrane potential indexes, upregulated NIX and BNIP3 expression | Upregulating microglial mitophagy |
| Shams et al.      | 2017 | Sciatic nerve transaction in rat | 2.0 ATA, 60 min/d for 5 consecutive days beginning on 1 d before and immediately after nerve transaction | Decreased MDA, increased SOD and CAT, attenuated caspase-3 and COX-2, increased S100β | Antioxidative, anti-inflammatory, and anti-apoptotic activity |
| Ding et al.       | 2018 | Chronic constriction injury in rat | 2.5 ATA for 60 min one day after CCI for 5 consecutive days | Improved hyperalgesia              | Decreasing iNOS and nNOS               |

Note: 1 ATA (atm) = 101.325 kPa. ATA: Atmosphere absolute; atm: atmospheric pressure; ATP: adenosine triphosphate; BNIP3: Bcl2 interacting protein 3; CAT: catalase; CCI: chronic constrictive injury; COX-2: cyclooxygenase-2; HBO: hyperbaric oxygen; HBOT: hyperbaric oxygen therapy; iNOS: inducible nitric oxide synthase; MDA: cyclooxygenase-2; NIX: Bcl2 interacting protein 3-like; NOS: neuronal nitric oxide synthase; NOX: nitric oxide synthase; NR2B: N-methyl D-aspartate receptor subtype 2B; S100β: S100 calcium-binding protein B; SOD: superoxide dismutase; TNF-α: tumor necrosis factor-α.

Additional Table 4: Summary of studies of the effects of HBOT against neurodegenerative diseases

| Author            | Year | Model of injury          | Therapy schedule                                      | Finding                                                   | Possible mechanism                     |
|-------------------|------|--------------------------|-------------------------------------------------------|-----------------------------------------------------------|----------------------------------------|
| Dave et al.       | 2003 | Wobbler mice             | 2 ATA for 1 h/d for 30 d 0.25 MPa for 60 min          | Delayed the onset of disease, improved the rate of respiration for complex IV in mitochondria | Without providing possible mechanisms |
| Chen et al.       | 2017 | D-galactose induced aging model in mice | Not available                                      | Improved behavioral performance                            | Reducing oxidative stress and blocking nuclear factor-κB pathway |
| Shapira et al.    | 2018 | 3xTg-induced Alzheimer’s disease in mice | Not available                                      | Reduced astrogliosis, microgliosis, IL-1β, and TNF-α, increased scavenger receptor A, arginase 1, IL-4 , and IL-10, reduced hypoxia, amloid burden, and tau phosphorylation, ameliorated behavioral deficits | Attenuating neuroinflammation |
| Kusuda et al.     | 2018 | MPTP-induced Parkinson’s disease in mice | 1317 hPa with 43% oxygen for 3 h, three times a week | Decreased dopaminergic neuron loss                         | Without providing possible mechanisms |

Note: 1 ATA = 101.325 kPa. ATA: Atmosphere absolute; HBOT: hyperbaric oxygen therapy; IL: interleukin; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TNF-α: tumor necrosis factor-α.
Additional Table 5: Summary of studies of the effects of HBOT against neurotoxic injury

| Author               | Year | Model of injury                          | Therapy schedule                      | Finding                                                                 | Possible mechanism                                                                 |
|----------------------|------|------------------------------------------|----------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Mukoyama et al.147    | 1975 | Clioquinol-induced peripheral nerve damage | Not available                          | Decreased damage of myelin and axons                                    | Without providing possible mechanisms                                              |
| Low et al.148         | 1988 | Streptozotocin-induced diabetic neuropathy in rat | 2 atm for 2 h, 5 d/wk for 4 wk         | Increased albumin blood-nerve barrier index, normalized caudal nerve action potential | Without providing possible mechanisms                                              |

Note: 1 ATA = 101.325 kPa. ATA: atmosphere absolute; HBO: hyperbaric oxygen; HBOT: hyperbaric oxygen therapy; HMGB1: high mobility group protein B1; NF-κB: nuclear factor-κB.

Additional Table 6: Summary of in vitro studies on neuroprotective effects of HBOT

| Author               | Year | Model of induction | Cell type                | Finding                          | Possible mechanism                                                                 |
|----------------------|------|--------------------|--------------------------|----------------------------------|-----------------------------------------------------------------------------------|
| Zhang et al.153      | 2011 | HBO-induced neurogenesis | Neural stem cells         | Promoted neural stem cells proliferation | β-Catenin signaling pathway                                                      |
| Huang et al.154      | 2016 | HBO exposure       | Spinal neurons           | Induced HSP32 expression          | ROS/p38 MAPK/Nrf2 pathway                                                        |
| Yang et al.155       | 2017 | Cell injury controller II system | Neural stem cell          | Accelerated NSC proliferation and the levels of proteins related to cell cycle| Activating VEGF/ERK signaling                                                   |
| Chen et al.156       | 2019 | HBO exposure       | Neural stem cells         | Promoted differentiation of NSCs into neurons and oligodendrocytes and reduced the number of astrocytes | Regulation of Wnt3/β-catenin and HMP2 signaling pathways |

Note: ERK: Extracellular signal-regulated kinase; HBO: hyperbaric oxygen; HBOT: hyperbaric oxygen therapy; HSP32: heat shock protein 32; Nrf2: nuclear factor erythroid 2-related factor 2; NSC: neural stem cell; p38 MAPK: p38 mitogen-activated protein kinase; ROS: reactive oxygen species; VEGF: vascular endothelial growth factor.

Additional Table 7: Summary of clinical trials on neuroprotective effects of HBOT

| Author               | Year | Model of injury                          | Therapy schedule                      | Finding                                                                 | Possible mechanism                                                                 |
|----------------------|------|------------------------------------------|----------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Feng et al.157       | 2017 | Incomplete spinal cord injury            | 2.0 ATA once a day and 6 days per week for a total of 8 weeks | Higher American spinal injury association and functional independence measure scores, lower depression and anxiety | Prolonged effect on cerebral blood flow and cerebral metabolism, increased cerebral metabolic rate of oxygen and decreased ventricular cerebrospinal fluid lactate levels |
| Sun et al.158        | 2019 | Acute spinal cord injury                 | Not available                          | Down-regulated HMGB1 and NF-κB expression, decreased F-wave chronodispersion, improved American Spinal Injury Association and Frankel grade motor/pain scores | Improved Glasgow coma scale, brain electric activity mapping and Glasgow outcome scale, reduced mortality and morbidity |
| Nighoghossian et al.159 | 1995 | Middle cerebral artery occlusion         | Daily to 40 min at 1.5 ATA for a total of 10 dives | Detected an outcome trend favoring HBOT | Decreased both pulsatility index and jugular venous lactate |
| Rockswold et al.160   | 2001 | Severely brain injury                    | 1.5 ATA for 60 min every 24 h          | Prolonged effect on cerebral blood flow and cerebral metabolism, increased cerebral metabolic rate of oxygen and decreased ventricular cerebrospinal fluid lactate levels | Improved living, socialization, communication, and motor skills |
| Ren et al.161        | 2001 | Severe brain injury                      | Not available                          | HBOT was superior to medication treatment alone in the recovery of clinical symptoms, control of epilepsy, and resolution of hydrocephalus | Improved Glasgow coma scale and Glasgow outcome scale 6 mon after HBOT |
| Shi et al.162        | 2003 | Postbrain injury                         | 2 to 4 courses of HBO                | HBOT was superior to medication treatment alone in the recovery of clinical symptoms, control of epilepsy, and resolution of hydrocephalus | Decreased both pulsatility index and jugular venous lactate |
| Golden et al.163     | 2006 | Chronic brain injury                     | Not available                          | Improved daily living, socialization, communication, and motor skills | Improved Glasgow coma scale and Glasgow outcome scale 6 mon after HBOT |
| Nakamura et al.164   | 2008 | Head injury in the subacute phase        | 2.7 ATA for 60 min every 24 h          | Decreased both pulsatility index and jugular venous lactate | Increased both pulsatility index and jugular venous lactate |
| Lin et al.11         | 2008 | Traumatic brain injury                   | Not available                          | Improved Glasgow coma scale and Glasgow outcome scale 6 mon after HBOT | Improved Glasgow coma scale and Glasgow outcome scale 6 mon after HBOT |
| Efrati et al.165     | 2013 | Stroke                                   | Two months of 40 sessions (5 d/wk), 90 min each at 2 ATA | Improved neurological functions and life quality | Improved Glasgow coma scale and Glasgow outcome scale 6 mon after HBOT |
| Rockswold et al.166   | 2013 | Severe traumatic brain injury            | 1.5 ATA for 60 min followed by normobaric hyperoxia, 3 h of 100% fraction of inspired oxygen at 1.0 ATA | Improved markers of oxidative metabolism, reduced intracranial hypertension, improved in markers of cerebral toxicity, reduced mortality and improved clinical outcome | Improved markers of oxidative metabolism, reduced intracranial hypertension, improved in markers of cerebral toxicity, reduced mortality and improved clinical outcome |
| Boussi-Grosset et al.167 | 2013 | Mild traumatic brain injury              | 1.5 ATA for 60 min at 40 therapy sessions (5 d/wk) | Induced neuroplasticity and improved quality of life | Improved markers of oxidative metabolism, reduced intracranial hypertension, improved in markers of cerebral toxicity, reduced mortality and improved clinical outcome |
| Xu et al.168         | 2018 | Intracerebral hemorrhage                 | 2.5 ATA for 60 min                 | Early HBOT was safe and effective with regards to the long-term neurological outcome | Improved markers of oxidative metabolism, reduced intracranial hypertension, improved in markers of cerebral toxicity, reduced mortality and improved clinical outcome |
| Golan et al.169      | 2020 | Ischemic stroke                          | 60 daily sessions consisting of 90 min of exposure at 0.2 MPa | Improvement of clinical neurologic status and quality of life in some patients | Improved markers of oxidative metabolism, reduced intracranial hypertension, improved in markers of cerebral toxicity, reduced mortality and improved clinical outcome |
| Fischer et al.170    | 1983 | Multiple sclerosis                       | 2 ATA for 90 min once daily for a total of 20 exposures | A positive, though transient, effect with minor side effects | Improved markers of oxidative metabolism, reduced intracranial hypertension, improved in markers of cerebral toxicity, reduced mortality and improved clinical outcome |
| Murata et al.171     | 2005 | Carbon monoxide poisoning                | Repetitive HBOT five times a week     | Delayed neuropsychiatric sequelae of carbon monoxide poisoning | Delayed neuropsychiatric sequelae of carbon monoxide poisoning |

Note: 1 ATA = 101.325 kPa. ATA: atmosphere absolute; HBO: hyperbaric oxygen; HBOT: hyperbaric oxygen therapy; HMGB1: high mobility group protein B1; NF-κB: nuclear factor-κB; p38 MAPK: p38 mitogen-activated protein kinase; ROS: reactive oxygen species; VEGF: vascular endothelial growth factor.