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# Application of hyperbaric oxygen therapy in the treatment of spinal cord injury: insights from preclinical to clinical evidence

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### *From the Contents*



## Abstract

Spinal cord injury (SCI) is a severe trauma that leads to significant motor, sensory, and autonomic dysfunction, imposing a substantial disease burden and economic costs globally. The pathophysiology of SCI involves primary and secondary injury stages, with the latter characterized by inflammatory responses, apoptosis, and tissue necrosis. Current therapeutic interventions, including pharmacological treatments and stem cell therapies, provide limited benefits and do not fully address the therapeutic effects on SCI. Hyperbaric oxygen therapy (HBOT), which delivers 100% oxygen at pressures exceeding 1 atmosphere absolute, has shown potential in SCI animal models due to its antiapoptotic, antioxidant, anti-inflammatory, and angiogenesis-promoting effects, thereby limiting secondary injury. Clinical studies have also demonstrated some efficacy of HBOT in treating SCI; however, the optimal timing, duration, and treatment cycles of HBOT remain contentious, and long-term efficacy has yet to be assessed. This review synthesizes the basic research and clinical practice of HBOT for SCI, thereby summarizing the main mechanistic pathways and demonstrating its clinical effects. Future large-scale, multicenter clinical studies are warranted to determine the efficacy and safety of HBOT in treating SCI and explore combined therapeutic modalities for a more comprehensive treatment approach.

**Key Words:** antiapoptotic; anti-inflammatory; antioxidant; clinical efficacy; hyperbaric oxygen therapy; literature review; neuroprotection; prospect; spinal cord injury; theoretical models

## Introduction

Spinal cord injury (SCI) represents a severe form of trauma that can lead to motor, sensory, and autonomic dysfunction. The global annual incidence rate of SCI ranges from 10.4–83 cases per million individuals, imposing a significant disease burden and economic cost on patients and society.[1,2] The pathophysiology of SCI can be divided into two stages: primary and secondary injury. Primary injury is typically caused by direct external forces acting on the spinal cord, such as contusion, laceration, and microhemorrhage. Secondary injury, on the other hand, is a complex biological process involving inflammatory responses, apoptosis, and tissue necrosis, which continues to inflict damage to the spinal cord following primary injury.[3] Current therapeutic interventions, including pharmacological treatments, neural implants, and stem cell therapies, aim to reduce neuroinflammation, promote axonal growth, increase myelination, and decrease cavity size. However, existing treatment strategies provide only limited short-term benefits and do not fully overcome the detrimental effects of SCI[1,4,5] (**Figures 1** and **2**).

Hyperbaric oxygen (HBO) therapy (HBOT) is a medical intervention in which 100% oxygen is administered at pressures exceeding 1 atmosphere absolute (ATA; 1 ATA = 101.325 kPa) to treat a variety of conditions. This therapeutic modality significantly enhances the dissolved oxygen content in the blood, thereby augmenting tissue oxygenation.[6-8] The application of HBOT in the medical field is extensive and includes treatments for decompression sickness, wound healing, carbon monoxide poisoning, and other conditions. Additionally, HBOT has demonstrated unique therapeutic effects in promoting wound healing, exerting antimicrobial effects, and modulating immune responses.[9,10] HBOT also has considerable potential in the treatment of neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. Through mechanisms that include reducing neuroinflammation, modulating apoptosis, and activating neuroprotective pathways, as well as potential epigenetic mechanisms, HBOT positively impacts these conditions.[9] However, HBOT is not without side effects and contraindications. Prolonged exposure to HBO environments may lead to oxygen toxicity, lung damage, and vision problems, among other conditions.[11] Therefore, stringent patient assessment and monitoring are required during HBOT to ensure the safety and efficacy of the treatment.

HBOT for SCI is an exploratory treatment approach that has garnered significant attention in recent years. Studies have indicated that HBOT exerts neuroprotective effects through various mechanisms, such as reducing apoptosis, lowering oxidative stress, decreasing inflammation, promoting angiogenesis, reducing spinal edema, and enhancing autophagy, potentially limiting secondary injury.[12-14] Currently, there is a lack of consensus on the optimal timing, duration, and number of treatment cycles for HBOT, which restricts the generalizability of the outcomes. This

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review aims to further delineate the basic research and clinical application of HBOT for SCI, thereby providing novel insights for the clinical application of HBOT in the treatment of SCI.

## Search Strategy

To accomplish this goal, we performed an exhaustive literature search via PubMed to identify pertinent articles published between 2000 and 2024. The search was conducted via the terms "hyperbaric oxygen," "hyperbaric oxygen therapy" and "spinal cord injury." The retrieved articles included original research, review articles, and meta-analyses. The inclusion criteria were as follows: the literature must be directly pertinent to the research topic. The exclusion criteria were as follows: 1) studies with lower quality scores using the AMSTAR 2 tool[15] and 2) studies for which the full text was inaccessible. Furthermore, we also conducted a review of the references within the selected literature.

## Theoretical Models of Spinal Cord Injury and Hyperbaric Oxygen Therapy

Animal models of SCI, including various types, such as impingement, compression, crushing, and laceration models, are fundamental to SCI research. The modified Allen method, which uses a spinal cord impactor to induce injury, is a prevalent choice for SCI model preparation. However, a modified aneurysm is also used to simulate SCI formation. Literature reviews have identified several methods for preparing SCI models, including aneurysm clip compression, calibrated clamp compression, pneumatic compression, and weight–drop compression.[16-28] Among these methods, the modified Allen's weight loss method stands out for its reproducibility and clinical relevance, offering a stable modeling approach with a fixed point, height, and weight and a mechanism of injury that closely mirrors that observed in clinical SCI patients. The selection of a mild injury model is strategic, as severe injuries may result in complete paraplegia, thereby obscuring the potential therapeutic effects of treatments such as hyperthermia. The evidence suggests that utilizing mild rather than moderate injuries can yield more reliable and uniform lesion outcomes.[16-28] This facilitates standardized and enhanced analytical approaches for future SCI animal studies involving impingers.

In the context of animal experiments, HBOT parameters can vary on the basis of experimental conditions and facility capabilities. The key parameters in setting up an HBO chamber include the atmospheric pressure and oxygen concentration. The majority of studies reviewed have adopted 2 ATA for pressure, alongside the use of pure oxygen (100%) for concentration[16-28] (**Figure 3**).

## Mechanisms of Hyperbaric Oxygen Therapy for Spinal Cord Injury

### Anti-inflammatory effects of hyperbaric oxygen therapy

SCI triggers an intense inflammatory response, leading to a cascade of pathological reactions that inflict irreversible damage on the body.

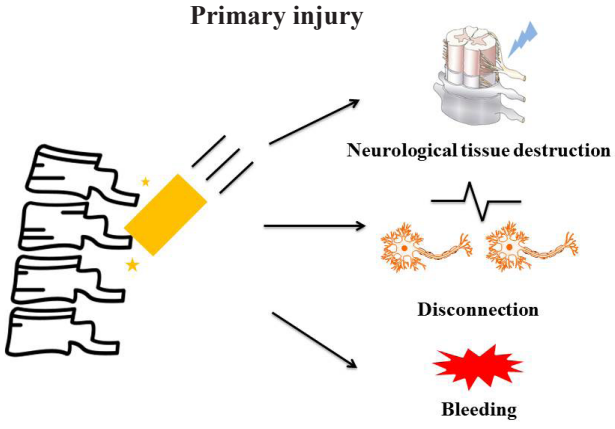


**Figure 1 | Pathophysiological mechanisms of primary injury following spinal cord injury.**
(1) Destruction of spinal cord neural tissue ensues. (2) Subsequently, neural cell connections within the spinal cord are disrupted. (3) Concurrently, vascular damage leads to the formation of hematomas. Created with Microsoft PowerPoint 2010.

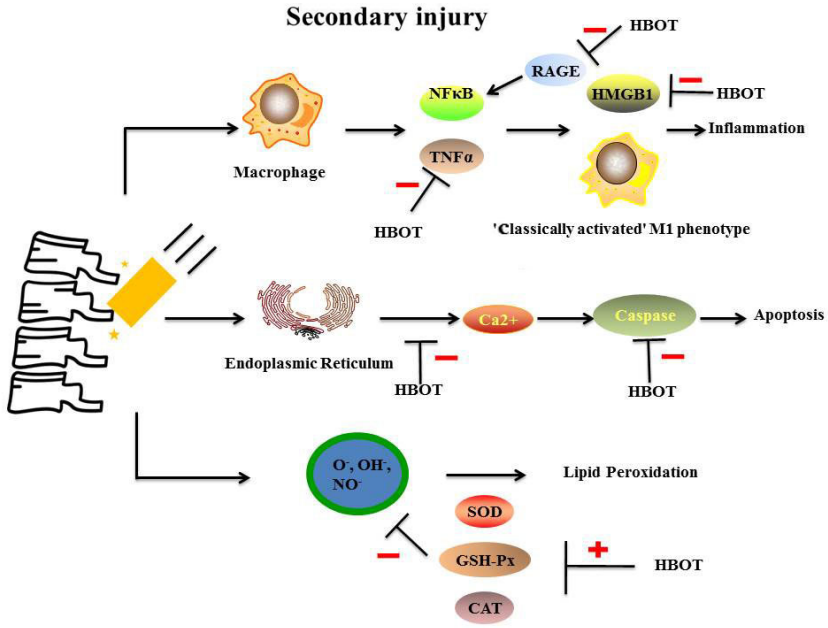


**Figure 2 | Pathophysiological mechanisms of secondary injury after spinal cord injury and the related targets of HBOT.**
(1) Macrophages release the proinflammatory cytokine TNFα and activate NFκB, further activating HMGB1 and the M1 phenotype, thereby inducing neuroinflammation. (2) Neurons release large amounts of $Ca^{2+}$ from the endoplasmic reticulum, activating the caspase pathway and leading to apoptosis. (3) Following spinal cord injury, a large amount of reactive oxygen species ($O^-$, $OH^-$, and $NO^-$) are released, causing lipid peroxidation reactions. Created with Microsoft PowerPoint 2010. CAT: Catalase; GAH-Px: glutathione peroxidase; HBOT: hyperbaric oxygen therapy; HMGB1: high mobility group box 1; NFκB: nuclear factor kappa B; NO: nitric oxide; RAGE: receptor for advanced glycosylation end products; SOD: superoxide dismutase; TNFα: tumor necrosis factor-α.

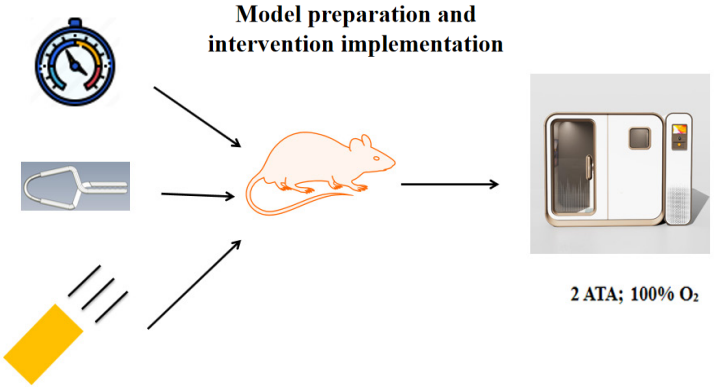


**Figure 3 | Preparation of animal models and implementation of interventions.**
The model preparation methods from top to bottom in the figure are as follows: pneumatic compression, aneurysm clip compression, calibrated clamp compression, and weight–drop compression. The majority of the intervention conditions for hyperbaric oxygen therapy are 2 ATA and 100% $O_2$. Created with Microsoft PowerPoint 2010. ATA: Atmosphere absolute.

Consequently, anti-inflammatory treatments after SCI have emerged as a prominent research focus. Yin et al.[16] revealed elevated expression of inflammatory markers (NADPH oxidase-1 and NADPH oxidase-2) post-SCI. They noted a reversal with concurrent HBOT, mirroring the pattern observed in upstream and downstream inflammatory signaling pathways, including Toll-like receptor (TLR)-4, myeloid differentiation primary response 88 adapter-like protein, myeloid differentiation primary response 88, tumor necrosis factor receptor associated factor 6, inhibitor of κB kinase α, inhibitor of kappa B kinase β, nuclear factor-κB (NF-κB), interleukin (IL)-1β, tumor necrosis factor-α (TNF-α), and substance P, among 10 other protein expression indicators. Further measurements of inflammatory indicators (CD68 and glial fibrillary acidic protein) in cellular samples on day 49 post-experiment indicated upregulation following injury and a subsequent decrease with HBOT. HBOT might modulate the aforementioned inflammatory factors, thereby mitigating the damage associated with neuroinflammation and oxidative stress. This study confirmed the anti-inflammatory therapeutic effects of HBOT; however, the research revealed only superficial aspects, and the underlying mechanistic pathways require further exploration.

In patients with SCI, the plasma levels of proinflammatory cytokines such as IL-6 and soluble IL-2 receptor are significantly increased, whereas the count and cytotoxic activity of natural killer cells are concurrently decreased. The upregulation of the T-cell regulatory protein SPTA1 may reverse these effects by promoting T-cell proliferation.[17] Ahmadi et al.[18] conducted immunohistochemical analysis of the inflammatory cytokine TNF-α in rats post-SCI and following intervention. These findings indicate that, in rats with SCI, HBOT diminishes the production of TNF-α by macrophages/monocytes during the acute inflammatory phase, thereby mitigating secondary SCI damage. The combination of HBOT and methylprednisolone synergistically led to a significant improvement in outcomes.

High mobility group box 1 (*HMGB1*) serves as a late mediator of inflammation in both aseptic injury and inflammatory processes. HMGB1 is typically located in the nucleus of nonactivated inflammatory cells, including monocytes and macrophages. Upon the activation of inflammatory cells by cytokines such as TNF-α due to injury or infection, HMGB1 translocates from the nucleus to the cytoplasm and is subsequently released. NF-κB is a pivotal component of the inflammatory response and is activated via a cascade of signaling pathways. Consequently, this activation triggers inflammatory factors, including TNF-α, IL-1, and other elements of the inflammatory response pathway.[29,30] A study indicated that HBOT decreases the peak expression of *HMGB1* mRNA on day 3 following injury, suggesting the potential for HBOT to attenuate inflammation by modulating HMGB1 expression levels. The therapeutic effects of HBOT on SCI have become increasingly apparent, particularly during the subacute phase at 3 days postinjury. The evidence suggests that the efficacy of HBOT in curbing excessive inflammatory responses is due to the downregulation of *HMGB1* and NF-κB expression, which in turn facilitates the injury repair process.[19] Furthermore, reducing extracellular HMGB1 levels may diminish interactions with its receptors, receptor for advanced glycation end products (RAGE) and TLR, potentially dampening inflammatory signaling.[19] Consistent with these findings, Kang et al.[20] also identified TLR4 as a potentially significant mediator in the inflammatory signaling pathway. This study investigated the role of *HMGB1* in HBOT treatment for SCI, raising the question of whether other anti-inflammatory pathways might also be involved in modulating its effects.

Among the numerous contributing factors, nitric oxide (NO) is particularly instrumental in the progression of inflammation and associated tissue damage. In SCI, excessive NO production is correlated with increased expression levels of the inducible NO synthase (iNOS) enzyme. Specific pathological triggers can increase iNOS mRNA transcription and protein expression, potentially contributing to NO overproduction. This cascade can initiate spinal cord inflammation and edema and intensify damage to peripheral neurons within the affected region. Neuronal damage is linked to the *iNOS* mRNA-iNOS-NO signaling cascade. The sequence of pathological changes likely involves spinal cord ischemia/hypoxia, which activates the *iNOS* mRNA-iNOS-NO signaling pathway. This activation augments NO production at the injury site, precipitating hypoxic neuronal dysfunction, neuroinflammation, and neuronal cell death or apoptosis. Concurrently, excessive NO production can increase local vascular permeability, intensify spinal cord edema, exacerbate ischemia/hypoxia, and perpetuate the activation of the *iNOS* mRNA-iNOS-NO signaling pathway. The subsequent application of HBOT results in significant decreases in both *iNOS* mRNA and protein expression, along with reduced serum NO levels. These findings elucidate the neuroprotective mechanism of HBOT post-SCI. By downregulating *iNOS* mRNA and protein expression in the spinal cord at an early stage, HBOT diminishes NO production at the injury site. This strategy circumvents neuronal death and apoptosis attributable to post-SCI neuroinflammation.[21] Huang et al.[21] examined the classical inflammatory pathway (*iNOS* mRNA-iNOS-NO) to elucidate one of the mechanisms by which HBOT can be used to treat SCI. It is pertinent to consider whether other canonical inflammatory signaling pathways might exert similar effects. Additionally, within the context of these classical inflammatory pathways, it is essential to explore whether there are any particularly potent pathways.

TLRs, a class of pivotal signaling molecules, mediate innate immune and inflammatory responses via NF-κB signaling pathways. Among the 13 identified TLRs in mice, TLR2 is linked to inflammation induced by SCI. Upon activation during pathological processes, NF-κB stimulates the production of reactive cytokines and translocates from the cytoplasm to the nucleus to activate the transcription of proinflammatory genes, including IL-1β and TNF-α.[31,32] Tan et al.[22] conducted SCI modeling and utilized real-time polymerase chain reaction and western blot assay to assess TLR2 and NF-κB expression levels, alongside enzyme-linked immunosorbent assays for quantifying IL-1β and TNF-α levels. Elevated TLR2 and NF-κB expression levels were observed concurrently with increased IL-1β and TNF-α levels. Compared with those in untreated control rats, the levels of TLR2, NF-κB, IL-1β, and TNF-α in SCI rats subjected to HBOT were downregulated. Consequently, post-SCI exposure to HBOT confers protection against secondary injury by suppressing TLR2/NF-κB-mediated inflammatory pathways, resulting in significant restoration of neurological function. Similarly, the signal molecule silent information regulator 1 also plays a significant role in the treatment of SCI with HBOT.[33]

After SCI, macrophages and microglia are pivotal in the neuroinflammatory response. They can polarize into either the "classically activated" M1 phenotype or the "alternatively activated" M2 phenotype based on signals from the affected microenvironment, a process termed macrophage polarization. Classically activated macrophages, which are induced by helper T-cell type 1 (Th1) cytokines such as interferon-α and TNF-α, produce superoxide and proinflammatory cytokines. These proteins are crucial for host defense and tumor cell elimination but can also inflict collateral damage on healthy cells and tissues. In contrast, alternatively activated macrophages, which are induced by T-cell type 2 cytokines such as IL-4, IL-10, and IL-13, promote healing and tissue repair. M2 macrophages, on the other hand, foster angiogenesis and matrix remodeling and suppress detrimental immune responses.[34,35] Geng et al.[23] assessed macrophage phenotypes and inflammatory mediators in rat spinal cord tissue following SCI and subsequently subjected to HBOT. They discovered that HBOT promoted the M2 phenotype while curbing the M1 phenotype. Additionally, HBOT was associated with reduced levels of interferon-α and TNF-α and elevated levels of IL-4 and IL-13. Furthermore, the microstructure of spinal cord neurons indicated signs of recovery. The hypothesis was that HBOT, when applied post-SCI, could decrease interferon-α and TNF-α levels while increasing IL-4 and IL-13 levels. This shift was predicted to enhance macrophage differentiation into the M2 phenotype, consequently diminishing the neuroinflammatory response and enhancing spinal cord neuron survival.

Connexin 43 (CX43) is a pivotal protein that facilitates gap junction formation within the central nervous system. Upregulated CX43 following central nervous system injury permits the propagation of death signals from damaged cells to adjacent healthy cells, which can result in the expansion of the lesion. Liu et al.[24] assessed CX43 expression in the spinal cord tissues of rats post-SCI and following HBOT and revealed a significant reduction in CX43 expression on postoperative days 3 and 7. Thus, the inhibition of CX43 upregulation through HBOT post-SCI in rats may prevent neutrophil infiltration, mitigate inflammation, and contribute to neuronal protection as well as regeneration. This study provides a novel perspective from which to investigate post-SCI vascular permeability, further exploring whether HBOT can ameliorate vascular permeability to exert its anti-inflammatory effects. The NACHT, LRR and PYD domain-containing protein 3 (NALP3) inflammasome, a

multimeric protein complex that mediates the release of the proinflammatory cytokine IL-1β and contains a NACHT structural domain, leucine-rich repeat sequence, and pyrin structural domain, has garnered significant attention in the context of SCI. Compared with NALP3, the adaptor molecule apoptosis-associated speck-like protein (ASC), and caspase-1, the inflammasome assembles through these components. NALP3 recruits the adaptor molecule ASC via an N-terminal interaction within the pyrin domain. Subsequently, ASC activates caspase-1 via its C-terminal domain, triggering the release of mature IL-1β. Notably, NALP3 plays a crucial role in initiating the inflammatory response. The study by Liang et al.[25] found that following spinal cord injury in rats, the expression levels of NALP3, caspase-1, and ASC at both the protein and mRNA levels were significantly elevated. Subsequent treatment with HBO resulted in a significant reduction in the mRNA and protein expression levels of NALP3, ASC, and caspase-1. Investigators have also quantified the inflammatory cytokine IL-1β and identified a significant correlation with caspase-1 activity. These findings indicate that HBOT mitigates secondary damage in SCI by inhibiting the transcription of IL-1β and the activation of the NALP3 inflammasome pathway, which is crucial for IL-1β production.

RAGE interacts with various ligands, such as HMGB1 and the S100 family of calcium-binding proteins. The binding of these ligands to RAGE initiates a cascade of cellular signaling events, including the activation of NF-κB, which subsequently results in the production of proinflammatory cytokines and induces inflammation. Monocyte chemotactic protein-1 (MCP-1), a β-chemokine family member, activates and recruits mononuclear phagocytes, T cells, and B cells, which are induced by various central nervous system injuries. Wang et al.[26] assessed the expression levels of RAGE and MCP-1 using immunohistochemistry, reverse transcription-quantitative polymerase chain reaction, and western blotting. Additionally, they evaluated neutrophil infiltration through myeloperoxidase activity assays, an indirect measure of inflammation. These findings indicated that RAGE and MCP-1 expression levels were increased and myeloperoxidase activity was increased in rats post-SCI. Conversely, after HBOT, both RAGE and MCP-1 levels decreased, as did myeloperoxidase activity. Thus, HBOT was demonstrated to mitigate the secondary inflammatory response, potentially through the inhibition of RAGE and MCP-1 expression, leading to significant motor function recovery. Turner et al.[27] conducted a genomic screen via the Gene Set Enrichment Analysis database, revealing that the pathways most significantly downregulated after HBOT were associated with inflammatory processes—encompassing cytokines and NF-κB—as well as apoptotic signaling.

Wang et al.[28] proposed that HBOT can downregulate the expression of aquaporin 4/9 genes and proteins, thereby attenuating the inflammatory response in the injured spinal cord. This study offers a fresh perspective on the use of HBOT for SCI treatment, suggesting that HBOT may modulate vascular permeability within the spinal cord to exert its anti-inflammatory effects. Inflammation serves a 'double-edged sword' role within the body, being both protective and potentially harmful. Key inflammatory mediators, including iNOS and cyclooxygenase-2 (COX-2), participate in inflammatory responses following traumatic injury; however, their reduced expression can inhibit inflammatory processes. Reduced levels of iNOS and COX-2 expression contribute to the suppression of the inflammatory response. Zhou et al.[36] The expression of the inflammation-related factors iNOS and COX-2 was detected via immunohistochemistry and western blot analysis. These findings revealed a lower number of iNOS- and COX-2-positive cells in the HBOT group than in the SCI group and a significant reduction in the relative protein expression levels of iNOS and COX-2 after 7 days of HBOT. Investigations into the upstream signaling pathways of protein kinase B (AKT) and NF-κB revealed that these molecules were upregulated following SCI and subsequently downregulated with HBOT. Consequently, researchers have proposed that the AKT and NF-κB pathways play a role in the inflammatory response after SCI and that HBO treatment may suppress their activation, thereby potentially facilitating SCI recovery.

### Antiapoptotic effects of hyperbaric oxygen therapy

Following SCI, ischemia and hypoxia constitute significant elements of secondary injury, leading to apoptosis. NO and neurotrophic factors both play important roles in the process of spinal cord neuronal cell apoptosis. Yu et al.[37] investigated the impact of HBOT on SCI-induced apoptosis in a rat model. They discovered that HBOT administered 30 minutes posttrauma for 90 minutes significantly decreased the number of apoptotic cells and the expression of *iNOS* genes in the affected area, suggesting a potential long-term role for neurotrophic factors in disease progression. They suggested that HBOT could have significant long-term implications in disease management. Additionally, neurotrophic factors may influence the chronic phase of the disease. Furthermore, they proposed that the improvement in neuronal apoptosis following HBOT is potentially linked to elevated blood oxygen levels and ameliorated hypoxic conditions. Unfortunately, this study did not delve further into the underlying mechanisms; however, subsequent research has filled this gap. Ying et al.[38] investigated the antiapoptotic effects of HBOT following SCI, employing ANA-12, a specific inhibitor targeting the brain-derived neurotrophic factor (BDNF)/TrkB signaling pathway. HBOT mitigated apoptosis, which correlated with elevated BDNF and TrkB expression levels and enhanced neural recovery. In contrast, the application of inhibitors led to increased degeneration and apoptosis, opposing the positive effects of HBOT. Furthermore, the HBOT-mediated protective effects were significantly diminished by the inhibitors, which was associated with reduced BDNF/TrkB expression and a deteriorated neurobehavioral status. These findings suggest that HBOT may ameliorate neurological impairment induced by SCI through upregulation of the BDNF/TrkB signaling pathway, thereby exerting antiapoptotic effects. Apoptosis is significantly influenced by the Caspase gene family and disruptions in cellular calcium homeostasis. Pan et al.[39] examined the effects of HBO pretreatment on neuronal apoptosis, the calcium ion concentration, and Caspase-3/7/8/12 expression in a rat SCI model. They discovered that while *caspase* mRNA expression increased post-SCI, no significant difference was observed between HBOT-pretreated rats and the blank control group. These findings indicate that activation of the Caspase pathway post-SCI induces neuronal cell apoptosis in the spinal cord of rats. Furthermore, HBOT preconditioning (HBO-PC) mitigated neuronal cell apoptosis in SCI-afflicted rats via the caspase pathway. Further analysis of caspase subclasses revealed that HBO-PC could partially obstruct the endoplasmic reticulum signaling pathway, thereby reducing downstream caspase expression and the extent of neuronal apoptosis. Consistent with these findings, Liu et al.[40] demonstrated that HBOT suppresses the endoplasmic reticulum stress response and diminishes neuronal apoptosis in the spinal cord by downregulating caspase-12 and caspase-3, consequently facilitating the recovery of hindlimb motor function. Related research has identified the adaptor molecule apoptosis-associated speck-like protein as a potential upstream signaling molecule for caspase-3.[41] At normal concentrations, intracellular $Ca^{2+}$ is essential for maintaining neuronal excitability; however, an overload of $Ca^{2+}$ can decrease the excitability threshold, resulting in neuronal apoptosis. Similarly, Pan et al.[39] observed a significant increase in the intracellular $Ca^{2+}$ concentration in the cytoplasm of rats post-SCI, but HBO-PC-treated rats did not exhibit significant calcium overload. In spinal cord surgeries, factors such as lesion location and nature, surgeon skill, and operation duration can cause varying degrees of spinal cord damage, potentially leading to postoperative complications. Given the findings from the aforementioned studies, it is plausible to consider the potential benefits of HBOT administered before spinal cord surgery. Consistent with these findings, Lu et al.[42] observed varying degrees of improvement in the neurobehavioral function of rats following SCI when they were pretreated with HBO, possibly due to the role of HBO-PCs in promoting endogenous neural stem cell proliferation. In the context of central nervous system diseases, the matrix metalloproteinases matrix metalloproteinase (MMP)-2 and MMP-9 contribute to vasogenic edema by hydrolyzing proteins and disrupting the integrity of capillary tight junctions, basement membranes, and the blood–brain barrier. Long et al.[43] investigated the role of these enzymes in neuronal apoptosis following SCI. They discovered that HBOT can decrease the expression of both MMP-2 and MMP-9 at the genetic and protein levels, which in turn leads to a significant reduction in neuronal cell apoptosis in the affected region. These studies revealed that the antiapoptotic effect of HBO in SCI may be related to iron. Despite these findings, the precise regulatory mechanisms underlying this process remain to be elucidated and warrant further investigation.

### Antioxidant effects of hyperbaric oxygen therapy

Oxidative stress, which is induced in the spinal cord medulla following SCI, negatively impacts the tissue and intensifies secondary injury. Consequently, antioxidants are being explored to effectively shield these tissues. Malondialdehyde (MDA), a product of lipid peroxidation, indicates lipid oxidation. Lipid-rich membrane structures in spinal cord neurons are susceptible to oxidative damage during SCI, which further exacerbates neuronal injury. SOD neutralizes superoxide radicals, sustaining the balance between cellular oxidation and antioxidant mechanisms, thereby mitigating free radical-induced cellular damage and preserving normal cellular function. Sun et al.[44] reported that HBOT enhanced neuromotor function in rats after stroke, as evidenced by increased serum superoxide dismutase activity and decreased MDA levels. This suggests that the neuroprotective effect of HBOT may be attributed to the inhibition of oxygen free radicals. Liu et al.[45] reported a similar conclusion: the combination of HBO and hypothermia plays a significant role in the treatment of SCI. Their study, which involved measuring MDA and antioxidant enzymes—superoxide dismutase, glutathione peroxidase, and catalase—in rat spinal cord tissues, demonstrated that the combination of HBO with hypothermia effectively prevented the increase in MDA levels. Furthermore, the efficacy of antioxidant enzymes in the combined therapy is significantly higher than that in other therapies such as hormonal therapy, hypothermia therapy, and HBOT, indicating a potential method to prevent lipid peroxidation and reduce free radical levels.[46] Pretreatment of primary spinal cord neurons with HBOT resulted in the upregulation of heme oxygenase-1 expression, a mechanism that has been evaluated for its capacity to combat oxidative stress and was found to confer a protective effect against oxidative damage.[47] A rat experiment revealed that HBOT induces heat shock protein 32 expression via the ROS/p38 mitogen-activated protein kinase/nuclear factor-erythroid factor 2-related factor 2 pathway, thereby increasing the cellular antioxidant capacity through the upregulation of ferritin.[48] Huang et al.[49] arrived at a similar conclusion. Fundamental research on mid-cervical SCI suggests that the antioxidant effects of HBOT may be attributed to the maintenance of septal redox homeostasis and the prevention of increased atrogene transcription through the reduction of protein hydrolysis via the ubiquitin–proteasome pathway (**Table 1**).[19,21,22,25,38,39,44,50,51]

## Clinical Effects of Hyperbaric Oxygen Therapy in Spinal Cord Injury

HBOT has widespread application in clinical practice. In a retrospective analysis conducted by the Department of Neurosurgery at Tokyo Metropolitan Ebara Hospital in Tokyo, Japan, the efficacy of HBOT in treating patients with cervical spinal cord injuries was evaluated. The HBOT group was compared with the non-HBOT group, and the Neurocervical Spine Scale was used to assess pre- and posttreatment improvements. The analysis revealed a significantly greater improvement rate in the HBOT group than in the non-HBOT group ($P < 0.05$), indicating better clinical symptom improvement.[52] Huang et al.[53] conducted a meta-analysis to examine the impact of HBOT on post-SCI motor, sensory, and psychological functions. After a thorough selection process, 11 studies were included in the meta-analysis. The primary outcomes were the American Spinal Injury Association motor and sensory scores, whereas the secondary outcomes included the modified Barthel index and the Hamilton scales for depression and anxiety. The results indicated that HBOT positively influenced motor and sensory functions, enhanced daily life self-care abilities, and mitigated depression and anxiety among SCI patients. A study with similar findings was also reported by Feng and Li.[54] Marrosu et al.[55] reported improvements in sensory–motor deficits in a 45-year-old male with cervical SCI following HBO cycling. Corresponding electroencephalography recordings, which were conducted with consistent instrumentation, revealed that these improvements corresponded to significant remodeling within the hierarchical framework of frontal-temporal-parietal lobe connections. The study by Marrosu et al.[55] could not definitively attribute the observed cortical connectivity changes to HBOT rather than an incidental phenomenon, and the temporal correlation between the modulation of connectivity in the frontal-temporal-parietal region and the HBO cycle suggests a potential link. A review of the literature by the authors indicates that HBOT might restore connectivity in the frontal region via a positive feedback mechanism originating from the lower levels. Based on this feedback, it is hypothesized that hyperbaric oxygenation could initially influence the interneuronal networks of the spinal cord, thereby enhancing frontal region connectivity. This process may initiate the restoration and

**Table 1 | Representative animal studies of HBOT in SCI**

| Study | Year | Animal | Model preparation | HBOT parameter | Main conclusion |
|---|---|---|---|---|---|
| Huang et al.[21] | 2013 | SD rats | Modified Allen's method | 2.0 ATA, 80–85% $O_2$, 80 min, once daily, for 24 consecutive days | HBOT can promote neuroprotection after SCI, which may be related to the anti-inflammatory effect of HBOT on the *iNOS* mRNA-iNOS-NO signaling pathway. |
| Yang et al.[19] | 2013 | SD rats | Modified Allen's method | 2.5 ATA, over 95% $O_2$, twice daily for 3 d, each session 90 min, then once daily | HBOT reduce secondary injury-induced cell apoptosis in SCI by downregulating the expression of HMGB1/NF-κB, thus promoting neural function repair. |
| Tan et al.[22] | 2014 | SD rats | T10 laminectomy + modified Allen's method | 2.0 ATA, 100% $O_2$, 60 min, once daily, for 14 d | HBOT may mitigate secondary SCI injury by inhibiting inflammatory responses mediated by the TLR2/NF-κB signaling pathway, thus promoting functional recovery. |
| Hou et al.[50] | 2015 | SD rats | Modified Allen's method | 2.0 ATA, 30 min, with pure oxygen concentration maintained above 96.5%, four times daily for 3 d | HBOT may play a protective role in SCI rats by downregulating MMP9/2 gene and protein expression, thereby reducing neuronal apoptosis. |
| Liang et al.[25] | 2015 | SD rats | Modified Allen's method | 2 ATA, over 95% $O_2$, 60 min, twice daily for 3 d, then once daily | HBOT has a protective effect on SCI by inhibiting the activation of the NALP3 inflammasome and reducing the release of IL-1β after SCI. |
| Sun et al.[44] | 2017 | SD rats | Modified Allen's method | 3.0 ATA,80% $O_2$, 60 min, once daily, for 5 d | HBOT has therapeutic value in treating SCI, possibly by enhancing SOD activity and reducing MDA content, thus increasing the clearance of oxygen free radicals and reducing lipid oxidation to protect against neuronal functional damage. |
| Pan et al.[39] | 2018 | SD rats | Modified Allen's method | 2.0 ATA, 80–85% $O_2$ concentration, 80 min, for 10 consecutive days | HBO pretreatment can reduce motor function loss in SCI rats, possibly by inhibiting the expression of pro-apoptotic proteins (Caspase-3/7/8/12), reducing apoptosis, and protecting neurons. |
| Ying et al.[38] | 2019 | SD rats | Modified Allen's method | 2.0 ATA, over 96.5% $O_2$, 90 min, once daily, for 7 d | HBOT reduces apoptosis and dendritic/synaptic degeneration induced by SCI via the BDNF/TrkB signaling pathway, improving neurological deficits caused by SCI. |
| Smuder et al.[51] | 2020 | SD rats | Modified Allen's method | 3 ATA, 100% $O_2$, 1 h/d, for 10 consecutive days | HBOT protects diaphragm function by increasing antioxidant capacity and reducing atrogen expression, thereby reducing oxidative stress and inflammation. |

ATA: Atmospheric absolute; BDNF: brain-derived neurotrophic factor; HBOT: hyperbaric oxygen therapy; HMGB1: high mobility group box 1; IL-1β: interleukin-1β; iNOS: inducible nitric oxide synthase; MDA: malondialdehyde; MMP9/2: matrix metalloproteinase 9/2; NF-κB: nuclear factor-κB; NO: nitric oxide; NALP3: NLR family pyrin domain containing 3; $O_2$: oxygen; ROS: reactive oxygen species; SCI: spinal cord injury; SD: Sprague–Dawley; SOD: superoxide dismutase; TLR2: Toll-like receptor 2; TrkB: tropomyosin-related kinase B.

remodeling of intercortical connectivity across the brain, fine-tuning the overall circuitry to optimally respond to the wiring requirements of the spinal network. Furthermore, Tan et al.[56] conducted a review of 40 SCI patients and compared MRI and electrophysiological examination changes before and after treatment between the HBOT and control groups. Compared with the control group, the HBOT group exhibited a notably reduced incidence of Grade III injuries on MRI—characterized by a complete loss of gray matter encircled by incomplete white matter. Additionally, the HBOT group demonstrated increased peak amplitudes and shortened latencies in somatosensory-evoked potential and motor-evoked potential assessments. Moreover, the sensory nerve conduction velocity and motor nerve conduction velocity were significantly higher in the HBOT group than in the control group ($P < 0.05$) (**Table 2**).[52,54-56]

The assessment of the safety of HBOT, which includes adverse reactions and therapeutic effects, has garnered widespread attention in the treatment of diseases. Currently, clinical studies on the adverse reactions to HBOT in individuals with SCI are limited, and these studies rely primarily on adverse reactions to HBO in other diseases as a reference. Scholars have reported the following points. First, oxygen toxicity is caused by prolonged inhalation of oxygen at high partial pressures or high pressures. Should this occur, one must immediately leave the hyperbaric environment and actively implement preventive measures, such as intermittent exposure to air[57,58]; second, barotrauma, which occurs when the pressure within air-containing cavities such as the lungs, middle ear, and paranasal sinuses is not balanced with external pressures, leading to mechanical forces that cause tissue displacement, deformation, and tearing; third, decompression sickness, which can arise if exposure to high pressure for an extended period, is followed by rapid and excessive decompression, causing the ratio of dissolved nitrogen tension in body tissues to the ambient pressure after decompression to exceed the saturation limit of inert gases, resulting in the formation of gas bubbles; fourth, fire hazard, which poses the greatest threat and has the most severe consequences in HBOT; and fifth, other issues such as cross-infection and gas embolism. To prevent the aforementioned incidents, enhancing the quality of professionals, reinforcing the concept of safety first, strictly selecting indications to prevent the misuse of HBOT, adhering to equipment maintenance and repair regulations, prohibiting the operation of equipment with malfunctions, strengthening scientific management and improving rules and regulations are imperative.[59-62]

In the clinical application of HBOT, experts have clearly defined absolute and relative contraindications. The absolute contraindications are included in **Table 3**.

Clinical studies on the application of HBOT in SCI have predominantly reported beneficial outcomes; however, the use of HBOT for SCI remains a contentious issue in clinical practice. The selection of patients with SCI focuses predominantly on those with cervical SCI, and there are comparatively few clinical studies on HBOT for thoracolumbar SCI, which introduces certain limitations in evaluating the efficacy of HBOT in SCI. Furthermore, concerning treatment protocols, a review of the clinical applications of HBO in other diseases has been conducted. For example, in wound treatment, diabetic foot

**Table 2 | Representative clinical studies of HBOT in SCI**

| Study | Year | Study type | SCI segment | HBOT parameter | Main conclusion |
|---|---|---|---|---|---|
| Feng and Li[54] | 2017 | Randomized controlled trial | Cervical, thoracic, and lumbar spinal cord | HBOT chamber pressure reached 0.2 MPa (2.0 ATA) uniformly within 20 min, with two sessions lasting 30 min each. Once daily, 6 d a week for 8 wk. | HBOT can improve functional impairment; alleviate depression, anxiety, and other negative emotions; strengthen patients' determination to overcome the disease; and encourage patients to actively participate in rehabilitation training, forming a virtuous cycle. |
| Tan et al.[56] | 2017 | Retrospective study | Not specified | Patients stayed in a chamber pressurized to 2 ATA for 45 min, with oxygen mask for 90 min. | HBOT once daily for 30 consecutive days can promote recovery of motor and neurological functions, thus achieving therapeutic effects for spinal cord injury. |
| Asamoto et al.[52] | 2000 | Retrospective study | Cervical spinal cord | 2.0 ATA for 85 min (compression for 10 min, normoxia for 60 min, decompression for 15 min), once daily for 10 d. | HBOT has a significant improvement effect in acute traumatic cervical spinal cord injury and can be used as an adjunctive therapy. |
| Marrosu et al.[55] | 2021 | Case report | Cervical spinal cord | 1.5 ATA, each session lasting 30 min, additional information not provided | HBOT may play a key role in restoring connectivity in the frontal lobe areas. |

ATA: Atmospheric absolute; HBOT: hyperbaric oxygen therapy; SCI: spinal cord injury.

**Table 3 | Absolute and relative contraindications of HBOT**

| Category | No. | Contraindication | Detailed description |
|---|---|---|---|
| Absolute contraindications | 1 | Untreated pneumothorax | The presence of abnormally accumulated gas in the pleural cavity can exacerbate the progression of pneumothorax and even cause severe respiratory distress under hyperbaric conditions. |
| | 2 | Concurrent use of disulfiram | Disulfiram affects the production of oxidase, thereby significantly weakening the body's antioxidant damage effects, and the administration of HBOT can lead to oxidative damage. |
| | 3 | Concurrent use of anticancer drugs (bleomycin, cisplatin, doxorubicin) | Bleomycin can cause adverse reactions leading to restrictive lung disease, and HBOT can exacerbate these adverse effects. HBOT can enhance the toxic effects of cisplatin in tissues, delaying wound healing and thus affecting the efficacy of HBOT. |
| | 4 | Premature and/or low birth weight newborns | – |
| Relative contraindications | 1 | Perioperative period of thoracic surgery | HBOT after thoracic surgery may lead to secondary damage to the surgical site. |
| | 2 | Respiratory viral infections | The presence of viral infections can lead to the possibility of virus transmission. |
| | 3 | Perioperative period of middle ear surgery | The pressure inside the hyperbaric chamber is higher than atmospheric pressure, leading to increased pressure in the middle ear. |
| | 4 | Uncontrolled epilepsy | HBOT has adverse reactions such as oxygen toxicity, which can induce seizures. If epilepsy is not controlled, it may increase the likelihood of seizure occurrence. |
| | 5 | High fever | – |
| | 6 | Claustrophobia | – |
| | 7 | Skull base fracture with cerebrospinal fluid leak | – |
| | 8 | Uncontrolled hypertension | – |
| | 9 | Pulmonary bullae | – |
| | 10 | Severe emphysema | – |

HBOT: Hyperbaric oxygen therapy.

ulcers may be treated with 2.0–2.4 ATA, 90–120 minutes, 1–2 times daily, for a total of 20–40 sessions; compromised flaps and grafts may be treated with 2.0–2.4 ATA, 90–120 minutes, starting with 2–3 times daily and reducing to 1–2 times daily once the condition stabilizes; compartment syndrome and crush injuries may be treated with 2.0–2.4 ATA or 2.5 ATA, initially 2–3 times daily, then once daily after stabilization; in postresuscitation cerebral resuscitation, 2.0–2.5 ATA may be administered, starting with 1–2 times daily for 2–3 days, each session lasting 60–90 minutes, followed by once daily for approximately 30 sessions; in cases of cranial brain injury, 0.15–0.25 MPa may be administered once daily for 5–10 sessions as one course of treatment, with a total of 30–60 sessions.[63-65] The included studies in this review set the pressure approximately 2 ATA, which is considered reasonable compared with the parameters used for other diseases, but there is no consensus on the duration and frequency of treatment, and the need for intermittent oxygenation remains a contentious issue. Currently, the clinical follow-up period for HBOT in patients with SCI is relatively short, preventing the assessment of long-term effects. Future large-scale, multicenter, double-blind prospective studies are needed to address these issues.[52,54-56,59,60]

## Future Prospection

SCI is a catastrophic event that has profound implications for patients and their families. HBOT has emerged as a potential neuroprotective and reparative intervention that has positive effects on SCI in both animal models and clinical practice. However, to fully harness the potential of HBOT in the treatment of SCI, future research must delve deeper and innovate across multiple dimensions.

1) Animal models constitute the fundamental basis for investigating the efficacy of HBOT. Currently, there are various animal models for SCI, yet a unified standard is lacking.[66] Future research should focus on further optimizing and standardizing these models to ensure the comparability of experimental results and their clinical relevance. For example, refining methods such as Allen's experiment could achieve precise control over the degree of injury, providing a stable foundation for the assessment of HBOT efficacy. In future animal experiments, the development of animal models that more closely mimic the pathophysiology of human SCI could be pursued, and gene-editing technologies (such as clustered regularly interspaced short palindromic repeats) could be utilized to create precise disease models.

2) HBOT has demonstrated significant anti-inflammatory and antiapoptotic effects; however, it remains unclear whether the microscale biochemical modifications and macroscale general network connectivity induced by HBOT are targeted to act on a specific mesoscale represented by particular neural populations, such as interneurons or excitatory/inhibitory cells. In-depth studies on how HBOT regulates inflammatory factors, apoptosis-related proteins, and signaling pathways, as well as its relationship with upstream and downstream molecular signals, will aid in the development of novel therapeutic strategies. Additionally, the efficacy of HBOT in SCI can be observed through the assessment of behavioral changes posttreatment. In recent years, traumatic hemorrhage resulting from SCI has emerged as a research hotspot, revealing a series of pathophysiological reactions due to hematomas, thus providing new insights into the treatment of SCI-related bleeding.

3) Although HBOT has shown potential in the clinical treatment of SCI and has also demonstrated promising therapeutic effects in animal experiments, there are still numerous challenges in translating animal experimental results to clinical practice, such as whether the neuroprotective pathways of HBOT in rodents and in vitro experiments are equally applicable to humans; the rigor and controllability of animal experimental study designs are higher than those in clinical studies, which may lead to unreliable clinical study outcomes; and medical ethical requirements in clinical studies may prevent the translation of some animal experimental results. Concurrently, HBOT is still limited by a comprehensive assessment of its efficacy and safety. Future clinical studies should expand sample sizes and conduct multicenter, randomized controlled trials to verify the long-term efficacy and safety of HBOT. A comparative design can be employed using hyperbaric air therapy or standard treatment. Regarding the blinding procedure, HBO and control treatments can be administered through separate double-blind conduits into the chamber, effectively implementing a double-blind setup.[67-71] Furthermore, exploring the combined application of HBOT with other therapeutic modalities, such as pharmacotherapy and cell therapy, may offer a more holistic treatment plan for SCI patients.

HBOT plays a significant role in the treatment of SCI. HBOT protects spinal cord neurons through anti-inflammatory, antioxidant, and antiapoptotic mechanisms, thereby maintaining spinal cord neural function. In clinical practice, HBOT has demonstrated certain therapeutic effects in treating SCI, but it also has some side effects. Therefore, contraindications should be noted in clinical applications. This article is a retrospective literature review. Although a scale was used to evaluate the literature selection, there is still a lack of unified standards for data acquisition and analysis, which may lead to certain biases in the results. In clinical studies of HBOT for SCI, the sample size is usually small, making it difficult to prove the significant correlation of the research content with limited data.

HBOT offers new perspectives and hope for the treatment of SCI. Future research is warranted to explore aspects such as the standardization of animal models, mechanistic research, and the expansion of clinical applications. Through these efforts, we anticipate that HBOT will play an increasingly significant role in the treatment of SCI, improving patient prognosis and quality of life.

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