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The role of hyperbaric oxygen therapy in the management of peripheral nerve injury

Summary of available data and clinical recommendations

February 2024

Peripheral nerve injuries (PNI) encompass a diverse range of conditions, from traumatic accidents to chronic neuropathies, affecting significant amount individuals each year. Understanding the causes and mechanisms behind PNI is crucial for improving treatment outcomes and enhancing the quality of life for affected individuals. Among the emerging therapies, hyperbaric oxygen therapy (HBOT) has shown promise as a potential intervention to promote nerve regeneration and recovery. This document explores the multifaceted landscape of peripheral nerve injuries, delving into their causes, pathophysiology, and the use of HBOT as a therapeutic approach. The latest clinical evidence is reviewed and recommendations regarding the application of HBOT in the management of PNI.

1. Causes and classification of PNI

Peripheral nerve injuries can occur due to a variety of causes, and they can range from mild to severe. Some common causes of **acute** PNI include:

I. Trauma: Physical trauma, such as accidents, falls, sports injuries, gunshot or other direct blows to a nerve, can lead to nerve damage or injury. This is often referred to as traumatic nerve injury.

II. Compression: Prolonged pressure or compression on a nerve can cause injury. Conditions like carpal tunnel syndrome, where the median nerve in the wrist is compressed, are examples of compression-related nerve injuries.

III. Stretching: Overstretching or excessive tension on a nerve can result in injury. This can occur during activities that involve sudden, forceful movements or stretching beyond the nerve's normal range.

IV. Lacerations: Cuts or wounds that damage or sever peripheral nerves can cause injury. Surgical procedures also carry a risk of accidental nerve damage.

V. Repetitive Motion: Repeated and prolonged movements or activities that put stress on specific nerves can lead to overuse injuries. Conditions like ulnar neuropathy or radial tunnel syndrome can result from repetitive motion.

VI. Infections: Certain infections, such as viral or bacterial infections, can affect peripheral nerves. Conditions like Guillain-Barré syndrome are autoimmune disorders where the body's immune system mistakenly attacks peripheral nerves.

Other causes of more slowly developed PNI may include:

I. Inflammatory Conditions: such as chronic inflammatory demyelinating polyneuropathy (CIDP) involve chronic inflammation of the peripheral nerves.
II. Systemic Diseases: Some systemic diseases, including diabetes, can lead to neuropathy (peripheral nerve damage) as a secondary complication.
III. Toxic Substances: Exposure to certain toxins or chemicals, such as heavy metals, can result in nerve damage.
IV. Genetic Factors: In some cases, genetic factors can predispose individuals to certain types of peripheral nerve disorders or neuropathies.
V. Tumors: Tumors or growths can compress or infiltrate peripheral nerves, leading to nerve damage.
VI. Medications: Some medications, particularly chemotherapy drugs, may have peripheral neuropathy as a side effect.

It's important to note that the symptoms and severity of PNI can vary widely depending on the cause and location of the injury. Common symptoms include numbness, tingling, weakness, pain, and changes in sensation or muscle function. The treatment of PNI often depends on the underlying cause and the extent of the damage, and it may include physical therapy, medications, surgery, or other interventions tailored to the individual's specific condition. Early diagnosis and appropriate management are essential for better outcomes in cases of PNI.

For the estimated 18,700 individuals annually in the United States who experience a traumatic peripheral nerve injury, a substantial fraction will endure lifelong pain or loss of function[1].

The classic Seddon grading scheme classifies PNI based on clinical outcomes and / three grades:

1. Neurapraxia, a temporary conduction block;
2. Axonotmesis, muscular atrophy consistent with axonal discontinuity;
3. Neurotmesis, a complete disruption of the nerve.

Sunderland expanded on this system in 1951[2] to add greater scientific and microanatomical basis and to further differentiate the highly variable recovery potential seen clinically. To

expand and explain variable outcomes in axonotmetic injuries, a third-degree injury was described as internal disorganization of the endoneurium with intact perineurium, fascicular architecture, and epineurium that leads to nerve recovery; a fourth-degree injury as disruption of the perineurium and fascicular architecture with intact epineurium which does not regenerate; and fifth-degree injury as complete loss of nerve trunk continuity. Although Sunderland's nerve injury grades provided a finer distinction, evidence for their specific mechanistic description is questionable; particularly the intact epineurium of fourth-degree injury.

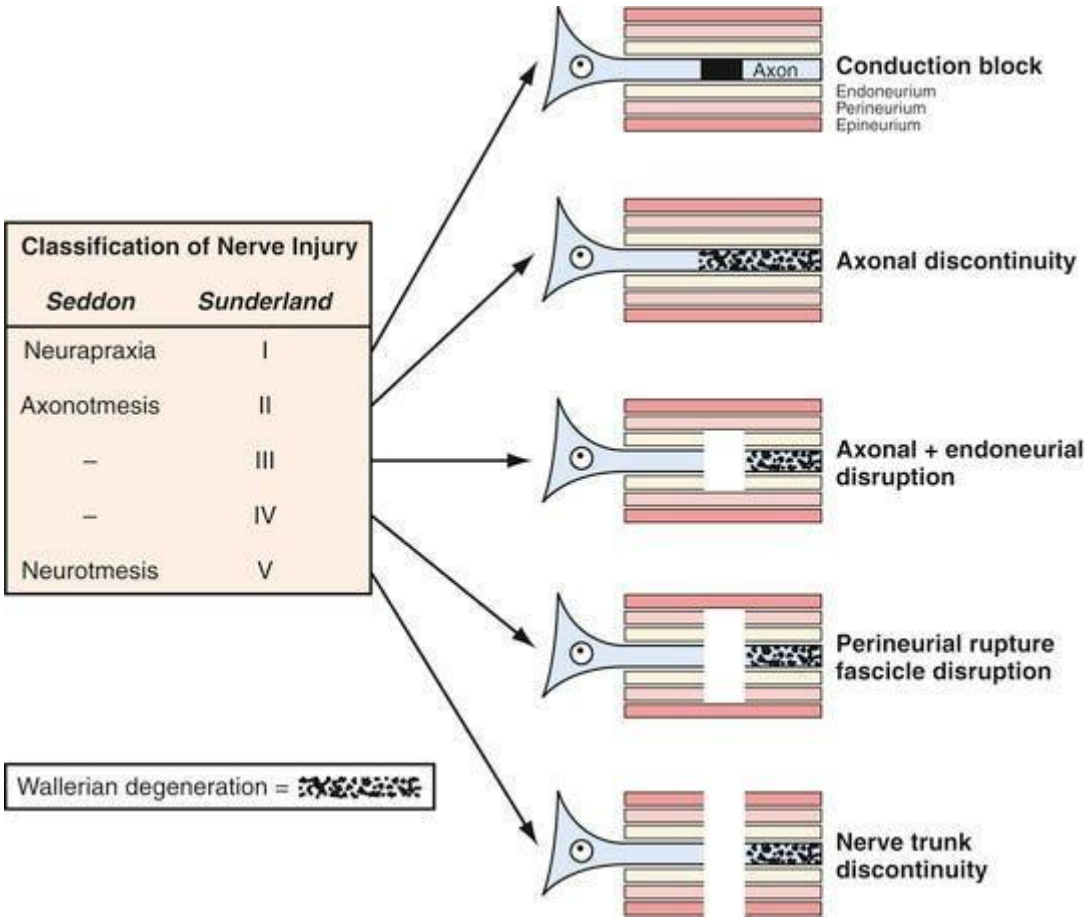


Figure 1. Classification of peripheral nerve injury (https://medium.com/@TheraspOT/peripheral-nerve-injury-1-46cbe18a0940)

2. Peripheral nerve basic structure and blood supply

Blood vessels and peripheral nerves are often found running parallel to each other in the body, share many analogous mechanisms during development and regrowth, and serve as structural guidance cues during regeneration, as blood vessels can direct neurite outgrowth in the

absence of intact basal lamina tubes[1,4]. The peripheral nerve is depicted, demonstrating the axon protected by the endoneurium. The nerve fascicle is enveloped by the perineurium. Groups of fascicles are surrounded by the epineurium. Each fascicle of endoneurium contains up to several thousands of axons. Blood is supplied by a network of capillary-like microvessels derived from arterioles and venules, which are branches of major limb vessels. The zoomed image depicts the close relationship of vessels and axons.

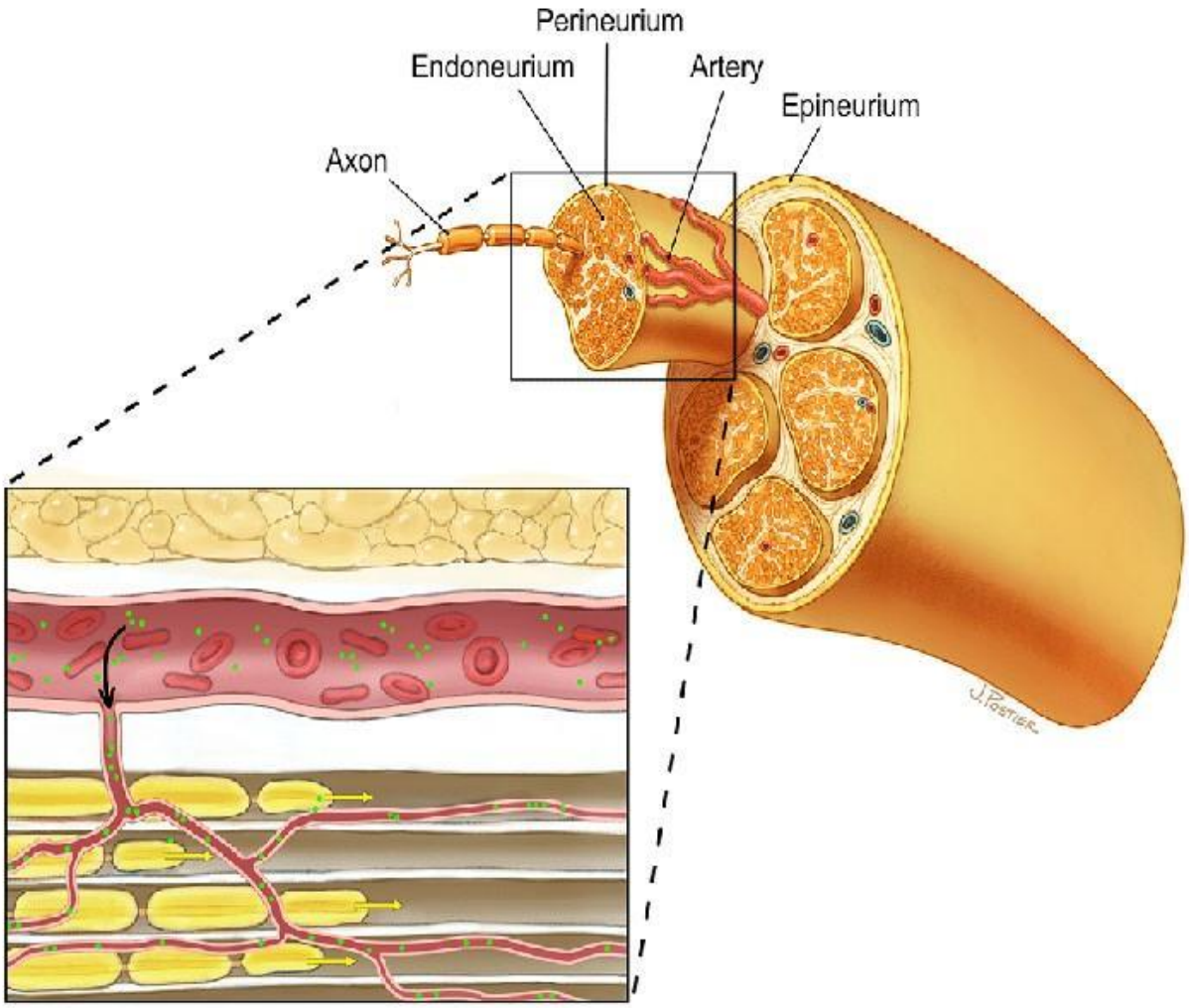


Figure 2. Schematic illustration of a peripheral nerve[3].

A substantial amount of knowledge concerning peripheral nerve injuries (PNI) has been gained in a surgical context, as the direct cause and ensuing pathophysiological cascade are easier to understand in these settings. It's worth noting that approximately 0.03%–0.1% of patients undergoing surgery with general anesthesia will experience perioperative PNI[5]. Fortunately, the majority of perioperative PNI symptoms resolve spontaneously or with conservative management alone[6]. For those patients who do suffer persistent neurological symptoms for

longer than 3 months postoperatively, or for whom electrophysiological studies report significant axonal loss, experts—along with ASRA—recommend surgical referral[6]. However, it is difficult to predict individual likelihood of benefit from surgical treatment, and only one quarter of patients who undergo surgical repair will derive significant improvements in pain or function[7,8].

Because of their high metabolic demands, peripheral nerves are highly vascularized tissue, with two separate but interconnected supply networks: intrinsic and extrinsic vessels[1]. The extrinsic supply originates from nearby large arteries and veins in adjacent tissue, which connect / the intraneural intrinsic system via coiled, tortuous vessels that allow relative movement and stretching of the nerve[1]. The intrinsic system is comprised of the arterioles and venules of the epineurial, perineurial, and endoneurial plexuses that run longitudinally along the nerve, along with perpendicular communicating vessels, anastomoses, and arteriovenular shunts. These highly interconnected and redundant networks have each been shown to provide adequate supply to maintain nerve function, even when the alternate system is completely ligated[1]. Although nerves are resilient to ischemia, sufficient mobilization or disruption of the extrinsic system along the length of the nerve has been shown to cause ischemic injury.

While the cause of perioperative PNI is often multifactorial, nerve ischemia has been proposed as a central feature underpinning different types of injury [9,10]. Limiting ischemia and restoring tissue oxygen delivery are therefore important factors to mediate nerve repair[1].

3. Perfusion and Ischemia in Nerve Injury

Ischemia has been implicated as an important mechanism leading to failed regeneration after nerve trauma, primarily as a promoter of a proinflammatory environment through cellular necrosis, macrophage activation and polarization, and endothelial upregulation of adhesive molecules, such as ICAMs and selectins, that recruit circulating leukocytes and lead to further inflammation and cell death[1]. Extended periods of ischemia causes damage to endothelial cells, resulting in a long-term reduction in perfusion, termed “no-reflow,” which has been seen long after vessel compression[1,11].

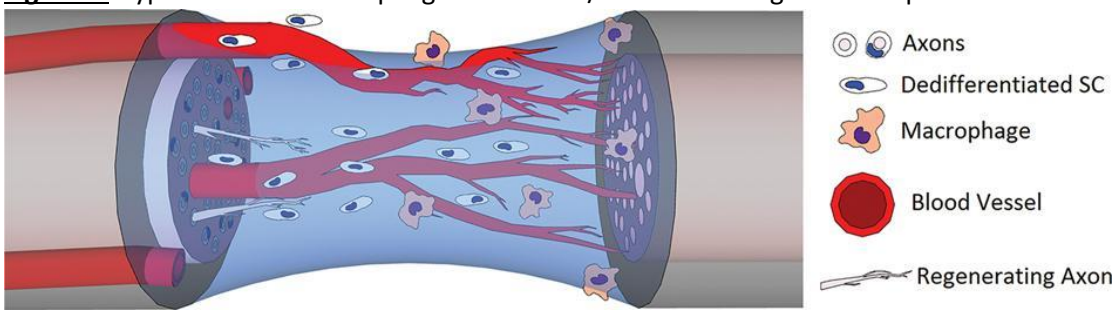
Both Stretch and compression injuries models are associated with impaired neuronal blood flow that affects nerve function. Transient nerve compression of 50 mmHg reduces nerve conduction velocity and increases epineurial vascular permeability[12], while more severe crush

models using clamps or forceps create a focal injury that can result in axonal degeneration[1]. Blood flow measurements of crush-injured nerves found a 30% reduction in perfusion 24 h after crush injury, followed by significant hyperemia at 48 h after injury[13]. Nerve stretch results in acute reduction in blood flow beginning at 8% elongation, with complete cessation of flow around 15%[14].

4. The Dual Influence of Hypoxia on Nerve Regeneration

As previously discussed in details, both ischemia and hypoxia are major co-factors preventing peripheral nerve regeneration. However, hypoxia, at least intermittent or relative hypoxia is also needed to induce the repair/regenerative mechanism including induction of HIF, VEGF, endothelial stem cells proliferation and migration, angiogensis. growth factors, including insulin-like growth factor-1 (IGF-1), glial cell–derived neurotrophic factor (GDNF) and nerve growth factor (NGF)[1]. In addition, there is a fundamental duality to hypoxia for nerve regeneration. Physiologic hypoxia-driven macrophage activity and angiogenesis, which guide and promote axonal regrowth, reside in tension with pathophysiologic chronic inflammation resulting from prolonged hypoxic conditions[1].

Figure 3. Hypoxia-driven macrophage infiltration / the fibrin bridge leads to p



olarized angiogenesis via VEGF and other growth factor expression, which then guides Schwann cell migration and neurite outgrowth[1].

Bringing these factors into balance—leveraging the benefits of relative hypoxia while safeguarding against the risks of prolonged hypoxia—underscores the imperative for future therapeutic interventions to strike the right equilibrium. This equilibrium is achieved

through the modulation of oxygen levels and pressure, utilizing specialized hyperbaric oxygen protocols, ultimately leading to what is known as the "Hyperoxic-Hypoxic Paradox."

5. Hyperbaric Oxygen Therapy and the Hyperoxic-Hypoxic Paradox

The understanding that at the cellular level, oxygen fluctuations can trigger cellular cascade that is usually triggered by hypoxia opens the opportunity to use intermittent hyperoxia to stimulate tissue regeneration without the hazardous hypoxia - termed "**Hyperoxic-Hypoxic Paradoxes"[15].**

In the clinical practice, intermittent hyperoxia can be generated using Hyperbaric oxygen therapy (HBOT). HBOT includes the inhalation of 100% oxygen at pressures exceeding 1 atmosphere absolute (ATA) to enhance the amount of oxygen dissolved in the body tissues. During HBOT, the arterial O2 tension typically exceeds 1500 mmHg, and levels of 200–400 mmHg occur in tissues. In a normal individual, at a normal environment (20.8% oxygen at 1ATA), the hemoglobin is almost entirely saturated (94-99%). Accordingly, while being in hyperbaric environment the effect is only on the dissolved oxygen. As mentioned above, the dissolved oxygen is the fraction responsible for the diffusion gradient from the capillaries to the mitochondria. In the following part of the article we will review the cellular cascade induced following repeated transient hyperoxia.

HIF

It has been proposed that relative changes of oxygen availability rather than constant hypoxia or hyperoxia, have the dominant effects on HIF expression[16-18]. According to this hypothesis, the cell interprets the change from normoxia to hypoxia or the return to normoxia after a hyperoxic exposure similarly as an oxygen shortage, and induces HIF-1-regulated gene synthesis[16-18].

The proposed mechanisms for increase HIF availability at normoxia after hyperoxic exposure relates to reactive oxygen species (ROS) availability and scavengers such glutathione synthase enzyme and Superoxide Dismutase (SOD) [16-18]. The balance between Oxygen levels, ROS/scavenger balance and HIF is detailed in figure 4.

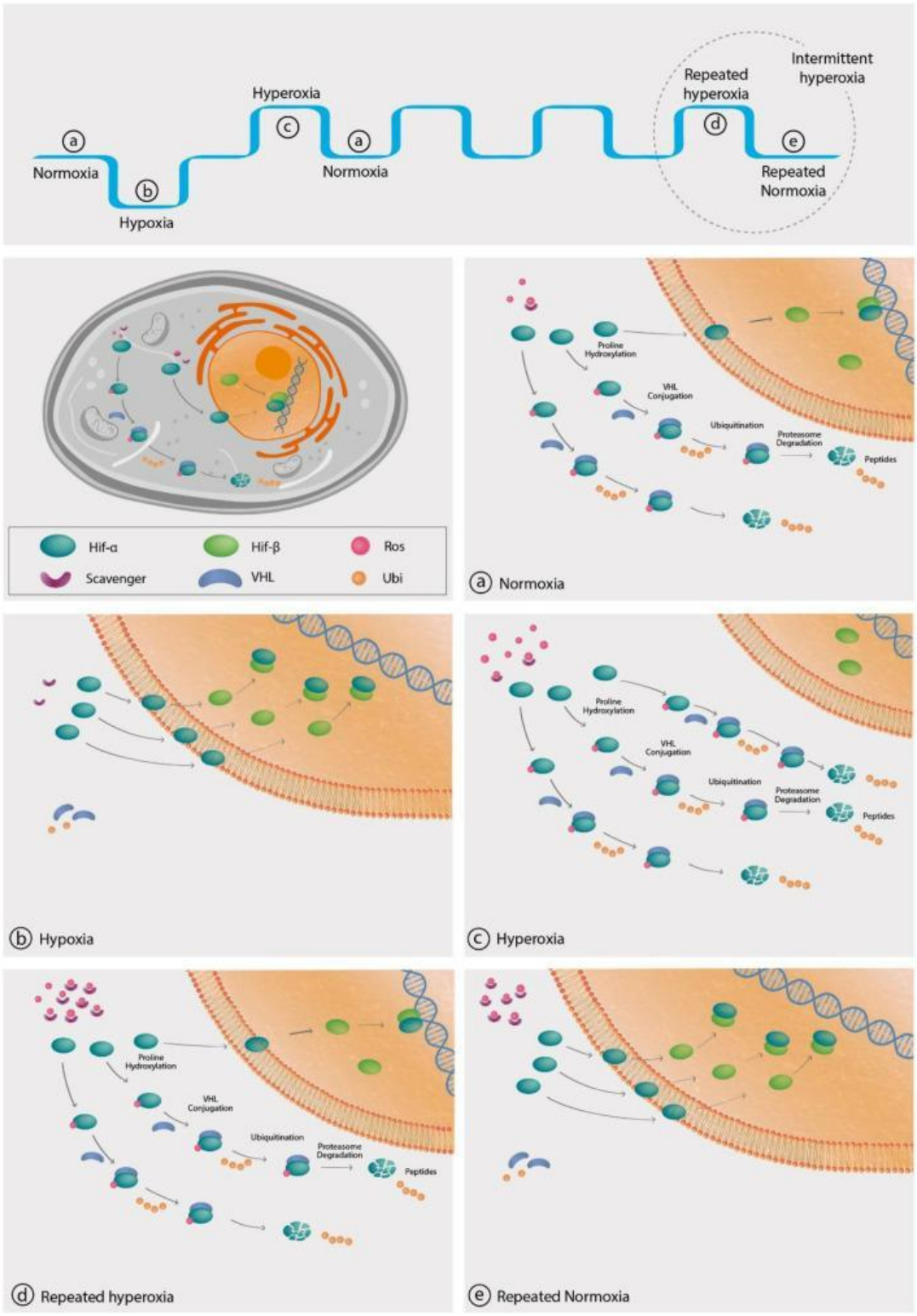


Figure 4. The intracellular cascade of HIF-1 alpha. Legend: HIF-1 is a heterodimer composed of cytoplasmatic HIF-1α and the nuclear HIF-1β subunits[15]. (a) Under normal oxygen environments, the ratio of ROS/scavenger is high and the free ROS molecules initiate HIF-1α hydroxylation, HIF-1α subunits become a target for VHLp (von Hippel–Lindau protein) protein which facilitates HIF-1α subunits ubiquitination and degradation. (b) Under hypoxic conditions, less oxygen and

ROS molecules are available, HIF-1α subunits are not hydrolyzed, and more HIF-1α subunits penetrate the nucleus to conjugate with HIF-1β subunits and generate the active HIF transcription factor. (c) At the hyperoxic environment, more ROS and oxygen are available; thus more HIF-1α subunits are hydrolyzed and degraded. (d) The adaptive response to repeated hyperoxia includes increases in the production of scavengers that adjust to the increased ROS generation. Thus, the ROS/scavenger ratio gradually becomes similar to the ratio under normal oxygen environment prior to initiating repeated hyperoxic exposures. (e) Upon return to normoxia, following repeated hyperoxic exposures, the ratio of ROS/scavenger is low due to the fact scavengers elimination half-life ($T_{1/2}$) is significantly longer than the $T_{1/2}$ of ROS. Accordingly, less HIF-1α subunits are hydroxylated, and more of them penetrate the nucleus, conjugate with HIF-1β to generate the active HIF, similar to the hypoxic state.

VEGF and angiogenesis

VEGF production is being induced by HIF-1 and once produced it stimulates the cellular processes needed for both angiogenesis and arteriogenesis. Utilizing the HHP, VEGF is significantly increased following intermittent hyperoxic exposures. There is growing evidence from pre-clinical as well as from clinical studies demonstrating that repeated HBOT sessions induce the crucial elements for angiogenesis: VEGF expression and endothelial progenitor cells (EPCs) [19-22]. Though, unlike VEGF induced under ischemic conditions, the induction of VEGF with hyperoxic stimuli can facilitate angiogenesis at tissues that are hypoxic/ischemic while breathing normal air. Clinical studies confirmed that repeated daily HBOT sessions augment the circulating levels of VEGF, EPCs, and improve the blood flow in the ischemic area of patients with chronic peripheral arterial occlusive disease with or without non-healing wounds [19-21,23].

With regards to PNI, it was shown that HBOT. It was demonstrated that HBOT accelerate peripheral nerve regeneration is related to HBOT induce angiogenesis as seen in the following figure from Raquel Eguiluz-Ordon˜ez et al. rat model of sciatic nerve injury after transection and repair with microsurgery in the nerve model[24].

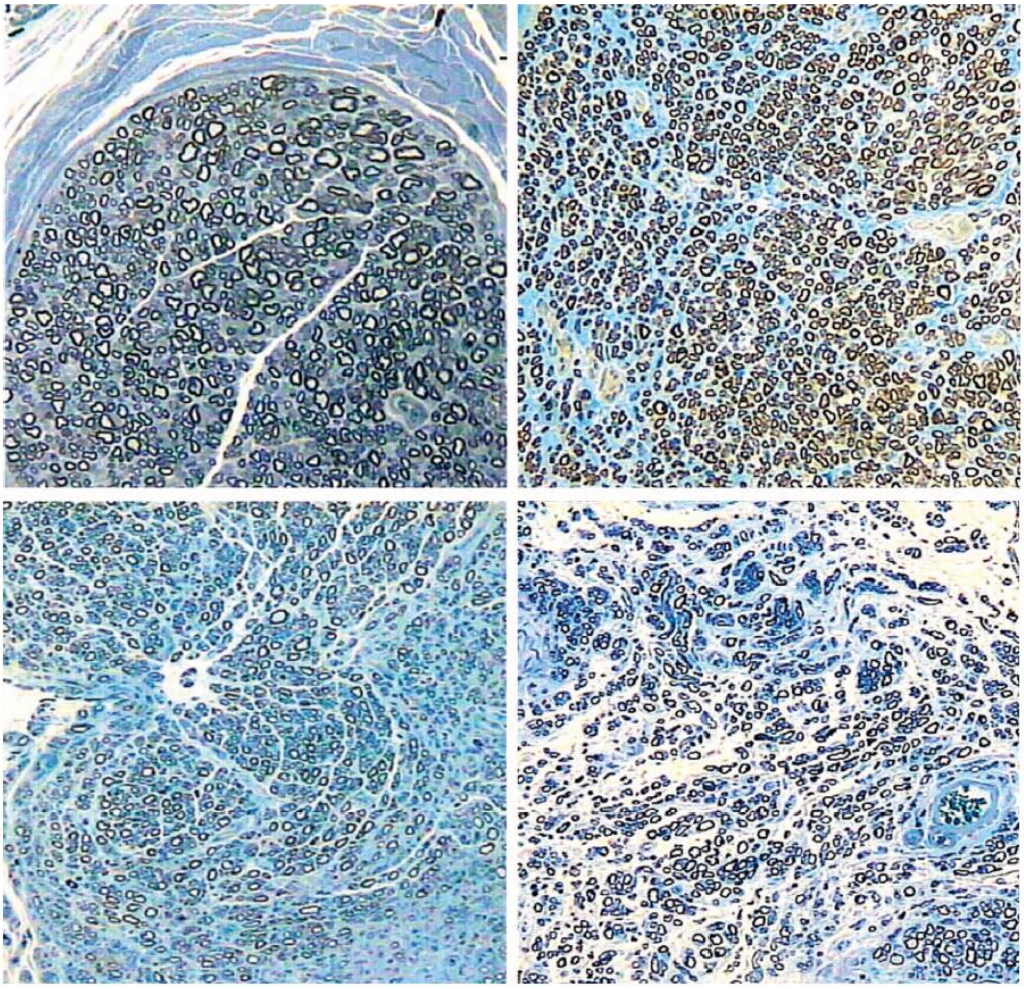


Figure 5[24]. Representative histologic features from transversal sections of sciatic nerves in HBOT and nontreated rats after transection and surgical repair. (*Above*, *left*) Numerous midsize axon covered by myelin (*black rings*) and occasional small blood vessels from rat sciatic nerve at 7 weeks without treatment. (*Above*, *right*) Sciatic nerve from an animal after 7 weeks of transection and repair treated with hyperbaric oxygen showing numerous small axons and small blood vessels. (*Below*, *left*) An apparent lower number of axons and blood vessels is shown in the sciatic nerve from a rat that was not treated with hyperbaric oxygen after 14 weeks of transection and surgical repair. (*Below*, *right*) Hyperbaric oxygen–treated rats, at 14 weeks, showing an increase in axons (toluidine blue; original magnification, _ 200).

Mitochondria

Any change in the free dissolved oxygen generates a diffusion gradient that directly affect the oxygen delivered and sensed by the mitochondria through the production of signaling molecules, the ROS. Thus, intermittent increase in the dissolved oxygen, generated by HBOT, can be compared to "intense interval training" with expected cumulative effect along repeated exposures. In a well-designed mice model study, it was demonstrated that adding intermittent hyperbaric exposure to exercise training further improves endurance performance by facilitating oxidative and glycolytic

capacities and by increasing the expression of proteins involved in mitochondrial biogenesis in striated muscles [25]. In humans, combining HBOT to exercise training regimen induced better cardiorespiratory fitness compared to exercise training alone [26].

In recent years there is growing evidence about the possibility and the important of mitochondrial transfer between astrocytes and neurons for proper maintenance of neuronal function and as cell-cell signaling [28,29]. Neurons can release and transfer damaged mitochondria to astrocytes for disposal and recycling [28] and astrocytes can release functional mitochondria that enter into neurons [29]. In a study done by Borlongan and Lippert, it was demonstrated that HBOT can facilitate the transfer of resilient mitochondria from astrocytes to neuronal cells who are more susceptible to inflammation[30]. The mitochondrial transfer from astrocytes to neurons made the neurons more resilience to inflammatory insult. These findings suggest a new mitochondrial mechanism of neuroglial crosstalk that may contribute to endogenous neuro-protective and neuro-recovery mechanisms induced by HBOT.

With regards peripheral nerves related injuries, it was shown that mitochondrial dysfunction has a crucial role for example in peripheral neuropathic pain by mediating neuroinflammation and neuromodulation[27]. Strikingly, HBOT reduce neuroinflammation and protect mitochondrial function, consequently preventing continuous neuronal damage[27].

Stem cells

As detailed above hypoxia and intermittent hyperoxia both increase HIF and its downstream gene expression including stem cell factor (SCF) [31]. The growing data from pre-clinical and clinical studies demonstrate the cumulative effect of repeated intermittent hyperoxia by HBOT on proliferation and mobilization of stem cells [32-49]. Clinical studies on patients suffering from diabetic wounds and post traumatic brain injury demonstrated that repeated HBOT sessions increase circulating (mobilization) stem cells in correlation with the clinical improvement [32-34].
With regards to subtypes of stem cells it was demonstrated that:

- HBOT promoted neuronal stem cell proliferation [35-41]
- HBOT stimulates vasculogenic stem cell growth and differentiation [42,43]
- HBOT stimulates colonic stem cells and induces mucosal healing [44]
- HBOT improves the osteogenic properties of mesenchymal stem cells [45,46].
- HBOT increases myoblast growth rate and enhance muscle regeneration [47-49].

The main advantage of stimulating stem cells by intermittent hyperoxia instead of hypoxia, is that stem cells proliferation and differentiation, just like any other regenerative process, is energy dependent – regeneration cannot be accomplished in hypoxic environment. The fact that oxygen is crucial for stem cells related regenerative effects can be learned from different studies that compared the results of stem cells injections with or without HBOT. The potential added value of using HBOT in addition to stem cells injections was evaluated in variety of tissues including: brain [50,51], spinal

cord and peripheral nerves [52,53], myocardium [54,55]. and diabetic wounds [56]. In all those studies, adding HBOT to stem cells injection had synergistic beneficial effect.

6. The current available data on the use of Hyperbaric Oxygen Therapy for peripheral neuronal injuries

The available data on the use of HBOT for PNI was meticulously summarized and published by Brenna et al. from the University of Toronto in November 2022[5]. Their comprehensive review encompassed six trials that explored HBOT as a treatment for PNI in human subjects, comprising two prospective cohort studies and four randomized controlled trials. These trials were conducted across various countries and involved diverse patient demographics, collectively involving 148 adult participants. Additionally, the review incorporated five case reports. Furthermore, the research included 40 studies conducted in a rat model, with two exceptions that employed a rabbit model. These studies collectively encompassed over 800 animal models of HBOT for PNI treatment. For more detailed information on these studies, please refer to the attached synopsis accompanying this working document.

In the original review article[5], it was observed that five out of the six human trials reported positive outcomes from HBOT, while one trial did not. It's noteworthy that the sole human trial which did not observe benefit from HBOT initiated treatment approximately 11 years, on average, after the initial nerve injury, which is considered a considerably late time point for any intervention. The assessment of nerve function, as described in the table, included parameters such as electroneuromyography, motor and sensory latencies/amplitudes and thresholds, and pain assessments. Similarly, four out of five case reports reported positive results with HBOT, with one case report not reporting benefit. Among the combined 51 animal and human studies, a significant majority (45 out of 51, constituting 88%) attributed primary outcome benefit to HBOT in the treatment of PNI.

Table 4 Overview of hyperbaric oxygen therapy protocols applied among human trials included in the review, including outcomes of nerve injury treatment

Study	Elapsed time from injury to hyperbaric oxygen therapy	Hyperbaric oxygen therapy protocol	Complications	Follow-up duration	Outcomes	Benefit (yes/no)
Ince, 2022[24]	Acute (within 96 hours)	5×120 min sessions at 2.0 ATA, over 5 days	Not reported	12 months (select cases followed 36 months)	Primary: Electromyography (conduction velocity)	Yes
					Secondary: Nerve-related muscle strength	Yes
					Secondary: Two-point discrimination (fingertip)	Yes
					Secondary: Two-point discrimination (thenar, hypothenar surfaces)	No
Elshinnawy, 2021[25]	Delayed (average 7.92 years)	10×60 min sessions at 100% O2 and 2.5 ATA, over 2 weeks	None	Two weeks	Primary: Motor and sensory latencies	Yes
					Secondary: Michigan Neuropathy Questionnaire	Yes
Kiralp, 2004[26]	Acute (approximately 1.5 months)	15×90 min sessions at 100% O2 and 2.4 ATA over 3 weeks	Not reported	45 days	Primary: Pain	Yes
					Secondary: wrist range of motion	Yes
					Secondary: wrist edema (circumference)	Yes
Cundall, 2003[27]	Delayed (2 years or more)	30×90 min sessions at 100% O2 and 2.4 ATA, over 6 weeks	Reversible myopia in one patient, severe sinus pain in another	6 months	Primary: Pudendal nerve terminal motor latency	Yes
					Secondary: Fecal incontinence quality of life scale	No (after 1 month)
					Secondary: Anal sphincter resting and squeeze pressures	No
Pritchard, 2001[28]	Delayed (11 years after insult)	30×100 min sessions, each with two 5 min air breaks, at 100% O2 and 2.4 ATA, over 6 weeks	Not reported	12–24 months	Primary: Warm and cold sensory threshold	No
					Secondary: Arm lymphoedema	Yes
Jordan, 1998[29]	Acute (0 to 3 months)	24×120 min sessions at 100% O2 and 2.0 ATA, over 3 months	Not reported	6 months	Primary: Frequency of neuropathy	Yes
					Secondary: Karnofsky functional impairment score	Yes
					Secondary: Patient subjective assessment scores	Yes

ATA, atmosphere absolute.

The prospective randomized study involving 74 patients with upper extremity injuries and the application of HBOT to facilitate peripheral nerve recovery is a particularly noteworthy and relevant study in the context of traumatic peripheral nerve injuries (PNI) [57]. This study sheds valuable light on the potential benefits of HBOT in the treatment of such injuries, with a specific focus on ulnar and median nerve injuries. In this study, patients with ulnar and median nerve injuries were subjected to a randomized allocation process based on the dates of their applications, resulting in two distinct groups. Group 1 comprised patients who received HBOT in addition to the standard epineural nerve repair procedure, while Group 2 consisted of patients who underwent epineural nerve repair without HBOT. The patients from both groups underwent regular follow-up assessments at 3, 6, and 12 months post-treatment. These assessments were comprehensive and included electroneuromyography (ENMG) analysis of the traumatized nerves, evaluations of muscle strength related to the injured nerves, and a two-point discrimination test.

The study's findings were highly promising and highlighted the potential advantages of incorporating HBOT into the treatment regimen for traumatic peripheral nerve injuries in the upper extremities. Specifically:

1. **Enhanced Impulse Transmission**: Patients in Group 1, who received HBOT in conjunction with nerve repair, exhibited notably faster impulse transmission.
2. **Faster Nerve Recovery**: The ENMG parameters consistently demonstrated that patients in Group 1 experienced a more rapid recovery of their injured nerves compared to those in Group 2.
3. **Improved Muscle Strength and Motor Recovery**: Patients in Group 1 not only achieved higher power scores but also demonstrated significantly more rapid motor recovery when compared to patients in Group 2.

In conclusion, the systematic review conducted by Brenna et al. provides a comprehensive and compelling overview of the use of hyperbaric oxygen therapy (HBOT) for peripheral nerve injuries (PNI) [5]. The review encompasses various types of studies, including human trials, case reports, and animal studies, to evaluate the efficacy and safety of HBOT in the context of PNI.The key findings from the review are as follows:

- **Human Trials:** Among the six human trials included in the review, HBOT was reported as beneficial in the majority of cases, with a positive outcome observed in 83% of these trials. This highlights the potential therapeutic value of HBOT in the treatment of PNI in human subjects.
- **Human Case Reports:** Similarly, the majority of human case reports (80%) described beneficial effects of HBOT when used as a treatment for PNI. These case reports contribute to the growing body of evidence supporting the efficacy of HBOT in clinical practice.
- **Animal Studies:** Animal studies, comprising 40 experiments, yielded particularly promising results, with HBOT demonstrating a positive effect in 90% of these studies. These experiments covered a range of PNI mechanisms, including transection, crush injuries, constriction/ligation, and even chemotherapy-induced and radiation-induced neuropathies.

Importantly, none of the studies, whether involving human subjects or animal models, reported worse outcomes following the administration of HBOT for PNI. This suggests that HBOT is a safe intervention with a favorable risk-benefit profile in the context of peripheral

nerve injuries. Furthermore, the absence of major complications reported after HBOT treatment is reassuring and underscores its safety as a therapeutic option.

The additional research findings published after the Brenna et al. systematic review in November 2022 further contribute to our understanding of the potential benefits of HBOT for PNI. These studies provide additional valuable insights into the mechanisms and clinical applications of HBOT in the context of nerve injuries[27,58] [^27^][^58^]. Here's a brief summary of the key findings from these additional studies:

1. **Awad-Igbaria et al. - Modulating Pain and Mitochondrial Function**: In a study conducted by Awad-Igbaria et al., using a rat model, it was observed that HBOT administered during the critical period following sciatic nerve injury had several positive effects[27]. These effects included:
    - Enhanced motor function.
    - Modulation of the transition from acute to chronic pain.
    - Reduction in neuroinflammation.
    - Improve of mitochondrial function.
    - Prevention of neuronal apoptosis in the dorsal root ganglion and spinal cord.

    These findings highlight the potential of HBOT not only in improving motor function but also in mitigating chronic pain development by targeting neuroinflammation and mitochondrial function. This study sheds light on the mechanisms through which HBOT may exert its therapeutic effects in nerve injury cases.

2. **Case Report - Salvage Therapy for Neurologic Deficit**: In a case report titled "Successful treatment of neurologic injury after complex spinal surgery with hyperbaric oxygen therapy," HBOT was used as a salvage therapy for a persistent postoperative neurologic deficit[58]. The report documented rapid and sustained improvement in the patient's condition following HBOT. This case report demonstrates that HBOT can be considered as a viable option in the management of neurologic injuries that may arise following complex surgical procedures, emphasizing its potential for neurologic recovery.

7. Conclusion and clinical recommendations

In conclusion, the existing body of evidence, encompassing preclinical studies, clinical trials, and case reports, strongly supports the use of hyperbaric oxygen therapy (HBOT) as an

effective intervention to enhance the recovery of peripheral nerve injuries (PNI). The application of dedicated HBOT protocols, utilizing the Hyperoxic-Hypoxic Paradox (HHP), has demonstrated the potential to augment the fundamental biological mechanisms required for neuronal growth and regeneration in individuals with PNI.

Key points to consider regarding the use of HBOT for PNI are as follows:

- **Safety and Efficacy:** The available data consistently indicate that HBOT for PNI is a safe and effective therapeutic approach. It has shown positive outcomes in terms of nerve recovery and symptom improvement in numerous studies.
- **Degree of nerve injury:** in clinical daily practice recommendation for HBOT can be based on Seddon classification. Grad III injuries (Neurotmesis, a complete disruption of the nerve) should not be treated by HBOT. HBOT can be considered in grade II injuries. Grade I is usually reversible so there is no need for HBOT.
- **Early Initiation:** To maximize the benefits of HBOT, it is advisable to initiate treatment as soon as possible following acute injury or nerve repair. Early intervention can contribute to better outcomes in PNI cases.
- **Treatment Protocol:** Based on the cumulative clinical data from PNI and other neurological indications, it is recommended that hyperbaric sessions involve the use of 100% oxygen at 2-2.5 atmospheres absolute (ATA) for 90 minutes. These sessions should include 5-minute air breaks either every 20 45 minutes to optimize both safety and therapeutic effects.
- **Individualized Approach:** The number of HBOT sessions needed to achieve maximal benefit should be individualized based on the patient's specific condition and response to treatment. Tailoring the treatment plan to the patient's needs is essential for optimizing outcomes.

Overall, HBOT has emerged as a valuable therapeutic option for individuals with PNI, offering the potential for improved nerve function and enhanced quality of life. This recommendation underscores the importance of considering HBOT as part of a comprehensive treatment approach for PNI and highlights the significance of early intervention and individualized care.

As medical research continues to advance, ongoing studies and clinical trials may further refine treatment protocols and expand our understanding of the full range of applications for HBOT in neurological and peripheral nerve conditions.

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