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Mechanism of action of hyperbaric oxygen in chronic pain in adult and pediatric patients: a literature review

M. Ciuffreda[1], A. Monacelli[2], S. Sorrenti[1], E. Pisello[1], G. Di Serafino[3], C. Piangatelli[1], D. Galante[4]

[1]Anesthesia, Resuscitation, and Pain Management Unit - AST ANCONA, Fabriano (AN), Italy.
[2]Specialization School in Anesthesia, Resuscitation, and Pain Management - Polytechnic University of Marche, Ancona (AN), Italy.
[3]Pain Management and Palliative Care Unit, AST Macerata (MC).
[4]Anesthesia, Resuscitation, and Pain Management Unit - Cerignola (FG), Italy.

Corresponding author: M. Ciuffreda, Medical executive in Anaesthesia, Resuscitation, Intensive Care and Pain Management Unit, AST Ancona, Fabriano, Italy. Email: ciuffredamat@libero.it

Keypoints

Biological and biochemical actions during hyperbaric oxygen therapy represent a valuable, albeit controversial, tool in the management of chronic pain.

Abstract

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."

To be classified as chronic pain, the condition must persist for more than three months. Its management requires a multimodal and multidisciplinary approach, in which hyperbaric oxygen therapy (HBOT), although still a subject of debate, represents a promising therapeutic opportunity.

There are multiple biological and biochemical mechanisms through which hyperbaric oxygen acts in the treatment of various pain syndromes.

Keywords

Hyperbaric oxygen, pain syndrome, hyperbaric chamber, chronic pain, hyperbaric therapy, pain treatment.

Introduction

In 2020, the International Association for the Study of Pain (IASP) revised the definition of pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."

This definition was further refined and expanded through six key notes:

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are distinct phenomena. Pain cannot be inferred solely from sensory neuron activity.
- Individuals learn the concept of pain through their life experiences.
- A person's report of an experience as painful should be respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a non-human animal experiences pain.

The six points within these notes emphasize the three dimensions of the painful experience: biological, psychological, and social. Furthermore, they highlight how pain can exert negative effects on physical function as well as social and psychological well-being.

From a chronological perspective, pain can be classified as: acute, persistent, or chronic.

Acute Pain: of short duration and attributable to tissue damage, its purpose is to alert the body to the presence of dangerous or potentially harmful stimuli. In this type of pain, the cause-and-effect relationship regarding its etiopathogenesis is clearly evident; it resolves once the stimulus is removed or the underlying damage is repaired.

Persistent Pain: resulting from the permanence or recurrence of an algetic stimulus, it retains the characteristics of acute pain but must be distinguished from chronic pain (e.g., pain from coxarthrosis).

Chronic Pain: the persistence of pain for more than 3 months, despite the healing of the causal pathology. It may involve a loss of connection to the initial cause, to the extent that the pain itself becomes the "disease."

This condition can lead to severe consequences on social life and the psychological and social aspects of the individual, potentially causing:

- Reduced physical activity, leading to immobilization.
- Inadequate nutrition and weight loss.
- Sleep disorders.
- Drug dependency.
- Social isolation (marital problems, unemployment, financial difficulties, anxiety, fear, and depression, potentially leading to suicide in some cases).

Pain as a Disease

Pain is therefore much more than a symptom: it can be considered a disease in its own right that must be managed, as it can create a vicious cycle that prolongs and exacerbates the pain itself.

The latest definition proposed in the journal *Pain* (April 2015), subsequently introduced into the new International Classification of Diseases (ICD-11) which came into effect in 2022, considers any pain lasting at least 3 months as chronic and introduces a distinction between:

- Primary chronic pain: where no clear causal correlation with a lesion is evident.
- Secondary chronic pain: where a clear cause-and-effect correlation is present.

The IASP categorizes chronic pain into seven clinico-etiological categories:

- Chronic primary pain
- Chronic cancer-related secondary pain
- Chronic postsurgical and posttraumatic secondary pain
- Chronic neuropathic secondary pain
- Chronic secondary headache and orofacial pain
- Chronic secondary visceral pain
- Chronic secondary musculoskeletal pain

The etiopathogenetic classification of pain distinguishes between:

- Nociceptive pain: defined by the IASP as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors." A variant of nociceptive pain is inflammatory pain, a process in which a noxious stimulus activates and sensitizes nociceptors (which are no longer in their basal state). This type of pain can be further subdivided into:
  1. Somatic: Caused by the stimulation of superficial nociceptors (skin and mucous membranes) or deep nociceptors (joints, bones, muscles). The stimulus causing the pain is identifiable (e.g., trauma).
  2. Visceral: Caused by the stimulation of nociceptors in internal organs; it presents with a vague distribution and is less localizable than somatic pain.
- Neuropathic pain: defined in 2012 by the IASP as "pain caused by a lesion or disease of the

somatosensory nervous system," involving either its central or peripheral components.

- Nociplastic pain: Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing peripheral nociceptor activation, or evidence for disease or lesion of the somatosensory system causing the pain. This definition also encompasses so-called dysfunctional pain.

Approximately 10% of the global population suffers from chronic pain, with 1.1% being classified as disabled. In Europe, the prevalence of chronic pain ranges between 16% and 46%, while in Italy, it affects 26% of the population (approximately 13 million people).

Italy ranks third, after Norway and Belgium, regarding the prevalence of chronic pain, and ranks first for the prevalence of severe chronic pain, which accounts for 13% of the total.

On a national level, the highest percentage is found in the North-West (27.7%), while the lowest is in the South (21.7%).

On average, individuals affected by chronic pain live in a state of continuous suffering for at least 7 years; for nearly one-fifth of them, this period extends beyond 20 years. It is estimated that at least 22% of the chronic pain population suffers from depression and anxiety due to the limitations imposed by daily suffering.

Treatment requires a multimodal approach where hyperbaric oxygen therapy, though still controversial, certainly represents a therapeutic opportunity.

Methods

A systematic review was conducted in accordance with the PRISMA statement across major databases (PubMed, Cochrane, Scopus, and Web of Science).

Studies published between January 1, 2015, and December 31, 2025, were included if they evaluated or investigated the biological and biochemical mechanisms of hyperbaric oxygen therapy (HBOT) in major chronic pain syndromes.

These include: diabetic neuropathy, complex regional pain syndrome (CRPS), post-traumatic and post-surgical pain syndromes, chronic ulcers and non-healing wounds, osteoarticular pathologies (e.g., osteonecrosis, chronic osteomyelitis), headaches (specifically cluster headaches).

The selection criteria targeted both adult and pediatric patients (individuals over 12 years of age). A total of 55 articles were analyzed in this review.

Discussion

The analgesic effects of hyperbaric oxygen have been investigated in models of nociceptive, inflammatory, and neuropathic pain.

The use of hyperbaric oxygen therapy (HBOT) has proven effective in the treatment of various pain syndromes.

Preclinical evidence suggests that impairments in tissue oxygenation and redox homeostasis may contribute to the pathophysiology of pain syndromes. Indeed, hypoxia and reactive oxygen species (ROS), which may result from microvascular dysfunction, inflammation, and reduced perfusion, can contribute to both peripheral and central sensitization.

At the peripheral level, the reduction in tissue oxygen can lead to the accumulation of hypoxia-inducible factor 1α (HIF-1α). This factor has been shown to induce the upregulation of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α) and interleukin-11β (IL-1β), thereby potentially increasing nociceptor excitability.

Hypoxia can also drive a metabolic shift toward anaerobic glycolysis, resulting in the accumulation of lactate and local acidosis. This environment, in turn, can activate proton-sensitive channels such as acid-sensing ion channels (ASICs) and the transient receptor potential vanilloid 1 (TRPV1), potentially facilitating prolonged nociceptive signaling.

In parallel, it has been observed that excessive ROS production can cause oxidative modifications to ion channels and signaling proteins, lowering nociceptor activation

thresholds and promoting ectopic discharges within peripheral pain pathways. The resulting amplification of peripheral nociceptive input can ultimately alter pain processing within the central nervous system. In the dorsal horn of the spinal cord, sustained afferent signaling has been shown to increase glutamate release and trigger the activation of the N-methyl-D-aspartate (NMDA) receptor, initiating synaptic plasticity that favors hyperexcitability.

Hypoxia- and ROS-driven signals can also activate microglia and astrocytes, leading to the production of pro-inflammatory mediators (e.g., IL-1β, TNF-α, IL-6). These glia-derived mediators can amplify excitatory transmission while simultaneously compromising gamma-aminobutyric acid (GABA) inhibitory pathways. This ultimately disrupts the balance between excitation and inhibition within pain pathways, with the combined final effect of establishing a state of sustained neuronal hyperexcitability in both peripheral nociceptors and central nociceptive pathways.

This dual sensitization provides a potential neurobiological basis for clinical manifestations such as hyperalgesia and allodynia, which are cardinal characteristics observed in chronic pain syndromes.

Hyperbaric oxygen therapy (HBOT), which involves the administration of 100% oxygen at pressures exceeding atmospheric levels, is capable of significantly increasing the amount of dissolved oxygen in the plasma, thereby improving tissue oxygenation—particularly in ischemic or inflamed areas. The physiological effects are believed to include the reversal of hypoxia, the suppression of HIF-1α-driven inflammatory pathways, the reduction of excessive ROS production, the stimulation of angiogenesis and the promotion of tissue repair. Collectively, these mechanisms can contribute to the restoration of local homeostasis and interrupt the self-perpetuating cycles of hypoxia, oxidative stress, and inflammation.

Consequently, hyperbaric oxygen represents a valuable tool in the multidisciplinary and multimodal management of both acute and chronic pain.

The primary mechanisms of action of hyperbaric oxygen on pain syndromes include:

- **Action on the Central Nervous System (CNS):** neuroimaging studies of patients undergoing HBOT have demonstrated alterations in the metabolic activity of cortical, frontal, and thalamic regions, along with variations in white matter microstructure, suggesting neuroplastic adaptation. At the central level, HBOT promotes neuroplasticity, increases the expression of Brain-Derived Neurotrophic Factor (BDNF), and reduces both oxidative stress and neuroinflammation. At the central level, hyperbaric oxygen modulates the release of neuronal dynorphins, leading to an increased release of nitric oxide (NO)-dependent endogenous opioids. Furthermore, it promotes the activation of μ and κ opioid receptors located in the spinal cord, thereby potentially reducing both nociceptive hypersensitivity and neuroinflammatory responses.
- **Mitochondrial action:** hyperbaric oxygen has demonstrated the ability to preserve mitochondrial function by decreasing apoptotic activity. Furthermore, it appears to counteract transmembrane defects and dysfunctions within the respiratory chain.
- **Anti-inflammatory action:** This effect is achieved through the down-regulation of pro-inflammatory cytokines (TNF-, IL-, IL-6) and the up-regulation of anti-inflammatory ones (IL-10). This anti-inflammatory action contributes to the reduction of both central and peripheral sensitization.
- **Antioxidant action:** facilitated by the enhancement of endogenous antioxidant defense mechanisms, such as increased levels of superoxide dismutase (SOD), catalase, and glutathione peroxidase, this action contributes to the desensitization of nociceptors, counteracting the maintenance of chronic pain states.
- **Modulation of transcription factors:** HBOT induces the inhibition of NF-kB (pro-inflammatory) and the activation of Nrf2 (cytoprotective). NF-kB is a transcription factor that stimulates the production

of pro-inflammatory cytokines; conversely, Nrf2 regulates the expression of genes encoding antioxidant enzymes and detoxification systems, protecting cells from oxidative and chemical damage.

- **Anti-edematous action:** through its vasoconstrictive effect, HBOT helps reduce post-traumatic and/or post-surgical edema.
- **Induction of neoangiogenesis in ischemic areas:** angiogenesis is a complex process occurring in response to hypoxia, redox stress, and lactate concentration, triggering the production and release of growth factors. This occurs via two processes:
  1. regional angiogenic stimuli, which influence the efficiency of new vessel growth from local endothelial cells;
  2. recruitment and differentiation of circulating stem/progenitor cells (SPCs) to form *de novo* vessels, a process known as vasculogenesis.
- **Optimization of healing processes:** hyperbaric oxygen promotes wound healing by stimulating collagen synthesis through increased cellular metabolism and fibroblast reactivation. By facilitating lesion repair, it contributes to the reduction or elimination of the underlying noxious stimulus (noxa) driving the pain syndrome.

Conclusion

In scientific literature, hyperbaric oxygen therapy is not indicated as a standalone or first-line therapy for pain syndromes.

Its biological and biochemical actions certainly represent a valuable, albeit controversial, tool in the management of chronic pain. As reported in the primary clinical guidelines, its use is recommended within a multidisciplinary and multimodal framework.

Furthermore, the implementation of HBOT must not cause a delay in, nor be a reason for the exclusion of, standard therapies that are established and accepted by the scientific community.

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