

# Therapeutic effects of hyperbaric oxygen: integrated review

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## Abstract

Hyperbaric oxygen therapy refers to inhalation of pure oxygen in a closed chamber. Hyperbaric oxygen has a therapeutic effect in numerous pathological conditions, such as decompression sickness, arterial gas embolism, carbon monoxide poisoning and smoke inhalation, osteomyelitis, osteoradionecrosis and wound healing. Hyperbaric oxygen therapy is used for treating underlying hypoxia. This review indicates the action of hyperbaric oxygen on biochemical and various physiological changes in cellular level. Narrative review covers the current indications and contraindications of hyperbaric oxygen therapy. The review also focuses on the therapeutic effects of hyperbaric oxygen pretreatment and precondition in different pathological conditions. The complications and side effects of hyperbaric oxygen therapy are discussed.

**Key words:** carbon monoxide poisoning; decompression sickness; hyperbaric oxygen therapy; osteomyelitis; osteoradionecrosis; wound healing

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## INTRODUCTION

The prefix “hyper” means increased while “baric” refers to pressure. During hyperbaric oxygen therapy (HBOT) a patient inhales 100% pure oxygen greater than normal atmospheric pressure inside a highly pressured chamber. Inside this chamber, the oxygen pressure is usually 1.5–3 times than that at sea level. In 1620, Drebbel developed a one-atmosphere diving bell.<sup>1</sup> Use of hyperbaric therapy was first documented in 1662. Nathaniel Henshaw, a British clergy and physician, used a system of organ bellows with unidirectional valves to change the atmospheric pressure in a sealed air tight chamber called domicilium in which oxygen is compressed and decompressed. In 1937, Behnke and Shaw for the first time used hyperbaric chamber in treating patients with decompression sickness. Since 1955, HBOT has been used for the management of various medical conditions.<sup>2</sup>

Oxygen (O<sub>2</sub>) transportation in blood is mainly by hemoglobin that has an oxygen saturation of about 97% while plasma contains 0.32% of dissolved oxygen under normal atmospheric pressure.<sup>3</sup> The blood circulation helps to delivery of oxygen and other nutrients to the tissues and to remove the products of metabolism including carbon dioxide.<sup>4</sup> Oxygen delivery is dependent on oxygen availability, the ability of arterial blood to transport oxygen and tissue perfusion.<sup>5</sup> Normal concentration of oxygen in blood at sea level is 3 mL/L. Tissues of a healthy individual during rest need around 60 mL of oxygen per 1 L of blood flow that helps in metabolism of cells. At atmospheric pressure of 304 kPa dissolved oxygen approaches 60 mL/L plasma, that is the total oxygen needed by tissues at rest.<sup>6</sup> During the HBOT procedure, the oxygen pressure in arterial blood can increase to 2000 mmHg (~266.6 kPa), and the high blood-to-tissue oxygen pressure gradient increases the tissue oxygen pressure to 500 mmHg (~66.7 kPa).<sup>7</sup> This has a positive

effect on the healing of inflammatory and microcirculatory disorders under ischemic conditions.

In the HBOT the individual is placed in a closed chamber and breathes pure oxygen. The oxygen pressure inside the chamber and the duration are increased depending on individual pathological conditions. The HBOT duration varies from 3 minutes to 2 hours till the pressure inside the chamber becomes normal. There may be little discomfort and ear pain during the alteration of oxygen pressure inside the chamber.<sup>6</sup>

## MECHANISMS UNDERLYING THE THERAPEUTIC EFFECTS

At cellular level around 80% of oxygen is utilized by mitochondria which is a power house of cells while remaining 20% is used by other organelles. Mitochondria require oxygen to receive the electrons at the end of the electron transport chain to utilize that energy to make adenosine triphosphate. Hypoxia leads to increase the oxidative stress that results in generation of reactive free radicals of oxygen and nitrogen.<sup>8</sup> Free radicals of oxygen and nitrogen are extremely toxic to cells and result in damage which induces cellular death and apoptosis.<sup>9</sup> The HBOT helps to correct hypoxic condition by increasing oxygen delivery leading antimicrobial activity and the attenuation of the hypoxia-inducible factor mediated effects. Its effects also reduce the formation of reduce oxidative stress, increasing the body’s ability to heal, vasoconstriction, and angiogenesis resulting in reduced inflammation.<sup>10</sup> Hyperbaric oxygen dissociates carbon monoxide from cytochrome C oxidase, improving electron transport and cellular energy state.<sup>6</sup> The therapeutic pressures used in HBOT are described in terms of atmospheres absolute pressure ranging from 1.5 to 3.0 atm (1 atm = 101.325 kPa). Biochemical changes in cellular level of HBOT are indicated in **Table 1**.

**Table 1: Biochemical changes in cellular level of hyperbaric oxygen**

No.	Biochemical changes
1	Hyperbaric oxygen therapy helps in angiogenesis that promotes healing wounds
2	Increase oxygen content kills anaerobic bacteria
3	Prevent the production of clostridial $\alpha$ toxin and pseudomonas species
4	It helps to restore neutrophil mediated killing of bacteria
5	Reduce leucocyte adhesion in reperfusion injury
6	Prevent the release of free radicals and proteases which causes vasoconstriction and cellular damage

## INDICATIONS AND CONTRADICTIONS TO HYPERBARIC OXYGEN THERAPY

The therapeutic uses of HBOT in various pathologic conditions are included in **Table 2**.<sup>6,11-13</sup> **Table 3** includes contraindication and limitations for the HBOT.<sup>6,11</sup>

During prolonged duration of HBOT oxygen poisoning can be prevented by giving short breaks and breathing normal air. This will lead to lessen the excessive oxygen taken by the tissues. During HBOT each individual will be given specific dose depending on their age, pathologic condition and the site of the disease to minimize the chance of toxicity and complications. The most common symptoms during HBOT include light headache and fatigue which are reversible as the individual are taken out of the hyperbaric oxygen chamber. The side effects of the HBOT are relatively less when the individual is placed less than 2 hours inside the chamber and when the pressure does not exceed 300 kPa compared to normal atmospheric pressure. Though the side effect is mild but can be life-threatening if not managed immediately. The common side effects that may be encountered are nausea, vomiting, myopia, feeling of claustrophobia, fatigue and headache. **Table 4** includes the complications and side effects that can be associated with HBOT.

## CLINICAL APPLICATION AS THERAPEUTIC USES OF HYPERBARIC OXYGEN

### Necrotizing infections

Soft infections caused by clostridial  $\alpha$  toxin production leads to myonecrosis and gas gangrene. Experimental evidence and clinical experience suggest that treatment with hyperbaric oxygen improves systemic illness and decreases tissue loss by demarcating the border between devitalized and healthy tissue. This reduces the extent of surgical amputation or debridement.<sup>14</sup> In necrotizing fasciitis studies suggest that hyperbaric oxygen plays an adjuvant role with surgical debridement. It enhances blood perfusion and improves innate immunity at the site of injury.<sup>15</sup>

### Osteomyelitis

Osteomyelitis is an infection of bone. Bacteria present in the bloodstream from infectious diseases spreads to the bone. HBOT also has a beneficial role in refractory osteomyelitis.<sup>16</sup> Osteomyelitis treatments mainly include extensive irrigation and debridement, intravenous antibiotics, and reconstruction.

**Table 2: Therapeutic indications and uses of hyperbaric oxygen therapy**

No.	Therapeutic indication and uses
1	Refractory osteomyelitis – infection caused in bones
2	Management of osteoradionecrosis–complication during radiotherapy
3	Carbon monoxide poisoning and during inhalation of excessive smoke
4	Cyanide poisoning
5	Gas gangrene, gangrene where the gas accumulates in tissues
6	Decompression sickness during deep water diving
7	Injury from crushing where there is sudden inadequate blood flow in the arteries and in ischemic injury
8	Delayed wound healing and improved skin graft and flap healing
9	Necrotizing bacterial soft tissue infections
10	Gas embolism caused in blood vessels due to air bubble entrapment
11	Brain trauma, chronic stroke and acute cerebral edema
12	Delayed healing of diabetic wounds
13	Adjuvant treatment in anemia due to blood loss
14	Hemorrhagic shock
15	Radiation induced injury
16	Infection caused due to clostridial myonecrosis and actinomycetes
17	Neuroblastoma stage IV
18	Post anorexia encephalopathy
19	Sudden deafness
20	Limb replantation, skin graft and flaps
21	Aggressive periodontitis
22	Pneumatosis cystoides intestinalis

HBOT helps osteogenesis, neovascularization, and collagen production.<sup>17-19</sup> HBOT increases the oxygen tension in ischemic wounds under conditions of adequate arterial inflow. This effect of HBOT on tissue oxygenation is obtained through formation of new vessels by neovascularization and increase in vascular endothelial growth factor.<sup>20,21</sup> Therapeutic effects of HBOT on infections can be made by direct suppression the growth of anaerobic bacteria such as clostridia and hyperoxygenation in tissues causes increase the fibroblasts and collagen proliferation, neovascularization of ischemic tissues and stimulation of bacterial lysis by leukocytes.<sup>22,23</sup> After surgical debridement of the osteolytic region, HBO at 2.4 to 2.5 atmospheres absolute pressure (ATA; 1 ATA = 101.325 kPa) for 5 to 7 times per week provides clinical efficacy by removing swelling and pain. A total of 30 to 40 treatments are required to get the clinical results.

### Carbon monoxide poisoning

Carbon monoxide has 200 times more binding capacity to hemoglobin in blood than oxygen thus reducing the oxygen content in blood. Hemoglobin sites that are free from binding have an increased affinity towards oxygen, and this reduces the availability of oxygen to the tissues leading to hypoxia. Hyperbaric oxygen gives an alternative source of tissue oxygenation through oxygen dissolved in the plasma.<sup>24</sup> HBOT acts by dissociation of carbon monoxide from the hemoglobin and

**Table 3: Contraindications of hyperbaric oxygen therapy**

No.	Contraindications and limitations
1	In lung conditions where there are chances of lung collapse
2	Ear injury and thoracic surgery
3	Upper respiratory tract infection
4	Pregnancy
5	Pneumothorax
6	Uncontrolled hypothermia
7	In claustrophobia individuals

myoglobin.<sup>25</sup> The symptoms associated with carbon monoxide poisoning are loss of consciousness, neurological abnormalities, myocardial ischemia, pulmonary edema, metabolic acidosis, headache and delayed neurological features that may become permanent if not treated at an early stage. At 2–3 ATA for 60–90 minutes breathing 100% oxygen helps to treat this condition.<sup>26</sup>

### Decompression sickness and arterial gas embolism

Decompression sickness caused due to sudden alteration in atmospheric pressure is commonly noted in scuba divers, aviators and deep tunnel workers as there is a change in atmospheric pressure when they leave that environment. Delay in treating decompression sickness with hydration and HBOT can result in permanent symptoms and even death.<sup>27</sup> After deep water diving when the divers surface rapidly at sea level attitude the partial pressure of nitrogen dissolved in the tissues exceed the ambient atmospheric pressure to form air bubbles in the blood and tissues.<sup>28</sup> Even at an altitude of over 5500 m decompression sickness can occur. In air embolism the air can enter the blood circulation during the placement of catheters in arteries and veins, cardiothoracic surgery, hemodialysis. Decompression sickness can cause skin rashes, joint pain, paralysis, confusion, convulsions, difficulty in speech, visual disturbances, and balance disturbance; sensory loss bladder dysfunction, sphincter dysfunction; loss of coordination in the limbs; shortness of breath, which may lead to death secondary to blockage of vital blood vessels by air emboli. Hyperbaric oxygen recompression given at a pressure of 250–300 kPa for 2–5 hours relieves the symptoms.

### Osteoradionecrosis

Osteoradionecrosis (ORN) is noted when the bone exposed to radiation undergoes necrosis and becomes exposed under soft-tissue. ORN occur commonly after radiotherapy in head and neck carcinoma.<sup>29</sup> It commonly affects the mandible in orofacial region. ORN results in irreversible tissue death, which is seen as exposed bone for more than 3 months duration.<sup>30</sup> ORN can occur between an interval of 4 months to 2 years after radiotherapy.<sup>31</sup> In ORN through ulcerated mucosa exposed bone seen that causes severe pain, dysesthesia, halitosis, dysgeusia and food lodgment. In ORN initially there is suppression of osteoclast related bone turnover.<sup>32,33</sup> Radiotherapy causes hypoxia in tissues and hypocellularity resulting in tissue breakdown and chronic non-healing wounds. HBOT increases the oxygen concentration by correcting the hypoxia and cell regeneration. Around 30 preoperative and 10 post-

**Table 4: Complications associated with hyperbaric oxygen therapy**

No.	Complications and side effects
1	It can cause severe damage to lungs by altering lung capacity leading to subcutaneous emphysema, intrapulmonary hemorrhage
2	Barotrauma of the ear due to increased air pressure in the middle-ear cannot be equalized with the external pressure, the eardrum will bow inward, leading to pain and possibly rupture, leading to hearing loss
3	Excessive fluid buildup can rupture the middle ear
4	Can cause sinus pathology as barosinusitis can lead to epistaxis
5	Changes in vision, causing myopia
6	Barodontalgia/odontocrexia (pain in a tooth caused by a change in atmospheric pressure)
7	Accumulation of fluids inside lungs
8	Change in brain electrical activity may cause seizures

operative HBO sessions for 90 minutes are recommended to prevent mandibular osteonecrosis after surgery on irradiated facial and neck tissue.<sup>6</sup>

### Skin grafts, flaps, and wound healing

HBOT is beneficial and useful in wound healing process. It can also have therapeutic importance in wounds from burns and diabetic ulcers.<sup>34–36</sup> It has a positive role in compromised flaps and can increase the effective size of composite graft survival, and improve prognosis of flap survival. Generally the skin grafts contain different tissue types with varying sizes that lack proper blood supply and are depended on the host for nutrient. HBOT acts by increasing oxygenation in the blood vessels and tissues by improving fibroblast function, collagen synthesis and neovascularization that helps in wound healing. HBO, given at a pressures of 2.0–2.5 ATA for duration of 90–120 minutes twice daily, helps in complete saturation of hemoglobin with oxygen in the circulation, along with a 10-fold increase in the dissolved oxygen plasma level.<sup>37</sup>

### Brain stroke

HBOT also helps in treatment of brain trauma and acute cerebral edema mostly associated with chronic stages of strokes causing memory and speech loss.<sup>38</sup> HBOT induces angiogenesis and the recruitment of progenitor cells to the damaged regions.<sup>39</sup> Cell death is the focus of HBOT treatment, as it reduces the inflammatory cytokine level that is associated with limiting peri-infarct tissue loss.<sup>40</sup> Hyperbaric oxygen suppresses the increased circulating macrophages in the acute phase and accelerated macrophage invasion into the contused muscle. This helps to increase the number of proliferating and differentiating satellite cells and the amount of regenerated muscle fibers.

## HYPERBARIC OXYGEN PRE-CONDITIONING

Hyperbaric oxygen exposure before few procedures that create a preventive therapeutic situation is called as “preconditioning.” Hyperbaric oxygen pre-conditioning has a beneficial effect in diving, ischemic and inflammatory conditions. Oxygen





pre-breathing causes reduced post-diving bubble leading to reduced decompression requirements and more rapid return to normal platelet function after a decompression. During the reperfusion of ischemic tissue, oxygenated blood increases numbers and activities of oxidants generated in tissues. Hyperbaric oxygen pre-conditioning causes the activation of antioxidative enzymes in the central nervous system, including catalase, superoxide dismutase and heme oxygenase-1.<sup>41</sup> Hyperbaric oxygen pre-conditioning also protects against focal cerebral ischemia and traumatic brain injury. Hyperbaric oxygen preconditioning has cerebral-protective and cardiac-protective effects.<sup>42</sup> Hyperbaric oxygen pre-conditioning attenuates brain edema, microglia activation, and inflammation after intracerebral hemorrhage.

## CONCLUSION

Hyperbaric therapy utilizes high pressure oxygen response. It elevates the concentration of oxygen in hemoglobin and plasma. Based on its solubility under pressure increases the diffusion gradient for its delivery deeper into tissues, which is the main mechanism of HBOT. Ultimately the increases in dissolved oxygen generated by hyperbaric therapy have several physiologic effects that can change tissue responses to numerous physiological changes. Long term studies should be conducted to see its outcome in different therapeutic treatment regimens along with its complications and side effects that required obtaining the clinical and cost effective results.

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Both authors contributed in selecting the topic, extensive searching, reviewing the current management and writing the article.

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