Hyperbaric Oxygen Therapy (HBOT) – Mechanisms of Action

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ABSTRACT

Hyperbaric Oxygen Therapy (HBOT) has been used for a range of diseases. The currently accepted mechanisms of action are discussed in this review article, ie restoration of normoxia, effects of hyperoxia and reduction of bubble size.

Keywords: Hyperbaric Oxygen Therapy (HBOT), Normoxia, Hyperoxia

INTRODUCTION

Hyperbaric Oxygen Therapy (HBOT) as defined by The Undersea and Hyperbaric Medical Society (UHMS) is "a treatment, in which a patient breathes 100% oxygen intermittently while inside a treatment chamber at a pressure higher than sea level pressure (ie >1 atmosphere absolute)". For a hyperbaric physician, oxygen is considered as a drug, and with any drug there is a dose and method of administration. The usual "prescription" is for the patient to breathe 100% oxygen at 2 to 2.8ATA (dosage) inside a hyperbaric chamber (method of administration) using a treatment table (Figure 1). Up to 1200mmHg arterial partial pressure can be achieved at a pressure of 2ATA. There is no other method to achieve such high levels of oxygen in the blood. This high level of oxygen is carried in plasma from the lungs via the circulation to the effect site (eg hypoxic tissues) to exert its therapeutic effects.

MECHANISMS OF ACTION

Restoration of Normoxia

A common indication for HBOT is chronic non healing wound such as a diabetic wound or radiation wound. In diabetic ulcers one of the underlying causes is small vessels disease producing a hypoxic wound environment. In radiation wounds, hypoxia is due to hypovascularity from radiation damage. Wound healing is a complex process with oxygen playing an important role. As an example, phagocytosis involves an oxidative burst and efficiency improves within physiologic range of tissue oxygen tension [1]. Another example is fibroblast migration which is inhibited at low oxygen tensions. Furthermore, production of collagen via hydroxylation of proline and lysine is very oxygen sensitive [2]. Similarly, angioneogenesis requires adequate oxygen levels [3].

Most hyperbaric centers use transcutaneous pulse oximetry to estimate periwound tissue oxygen tension to confirm hypoxia. A value of less than 40mmHg usually indicates the wound is unlikely to heal on its own. Subsequently, a 100% oxygen challenge at sea level and at 2.4ATA is administered. A rise above 100mmHg at sea level and >400mmHg at 2.4ATA indicates the potential of enhanced diffusion of oxygen via hyperbaric condition to restore normoxia and should assist in wound healing.

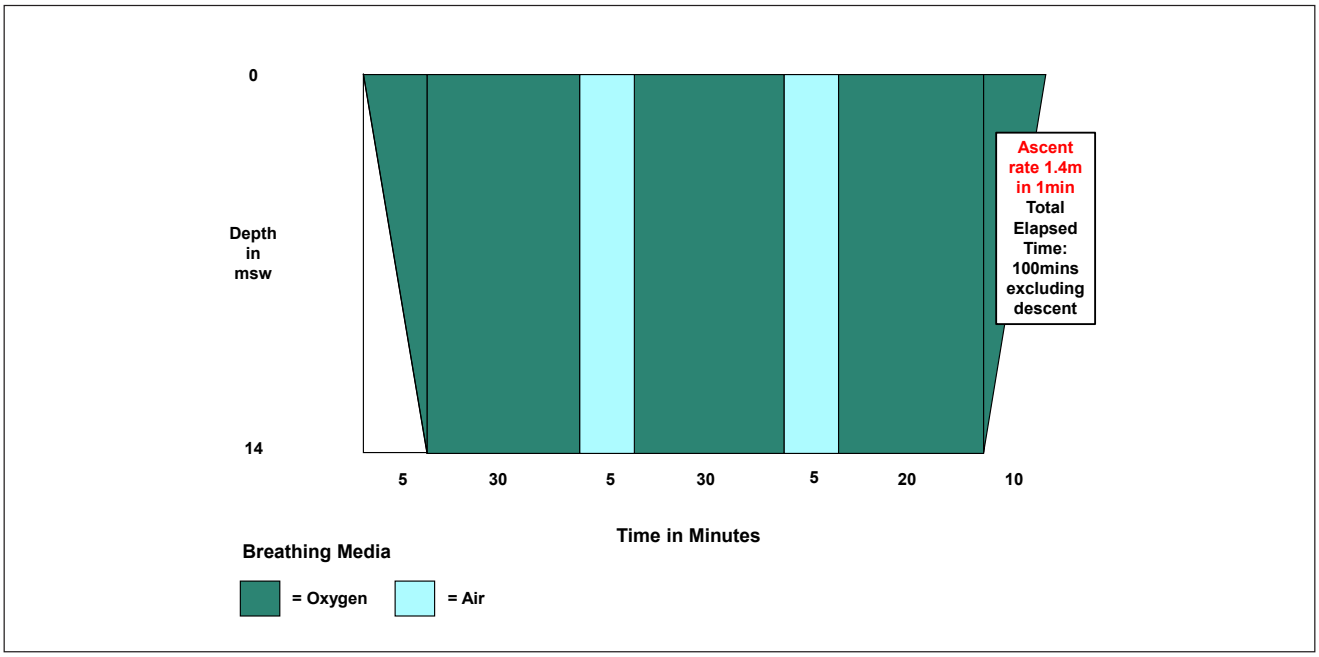

Figure 1: Typical Hyperbaric Oxygen Treatment Table used at Underwater and Hyperbaric Medicine (IPBAH, 96 Armed Forces Hospital)

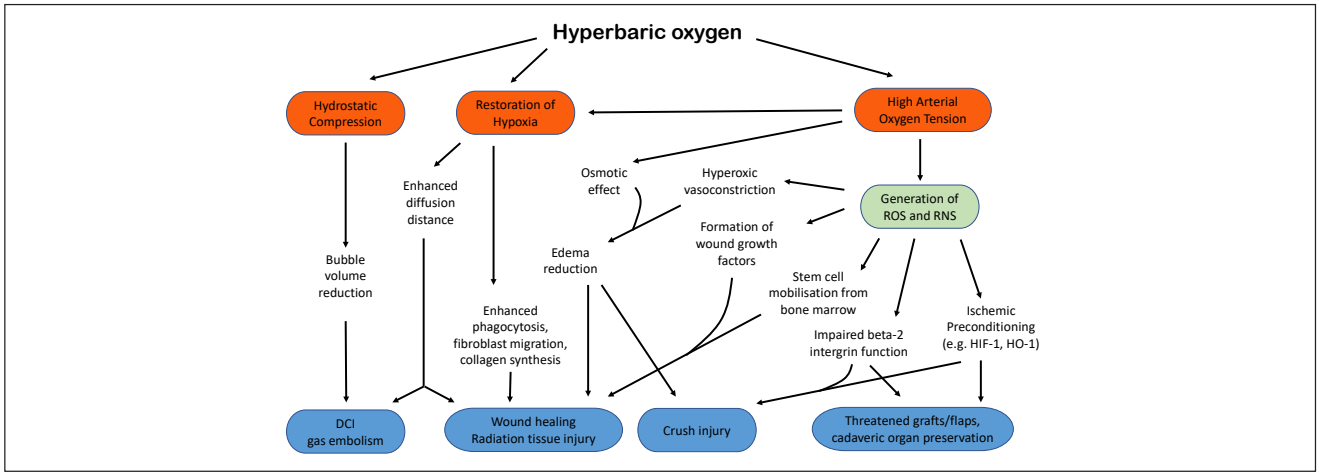

Figure 2: Summary of Mechanisms of Actions of Hyperbaric Oxygen

Achievement of Gross Hyperoxia

Recently there has been increasing interest in the physiology of high arterial oxygen tension achieved during HBOT and its possible consequences. It has always been known that in carbon monoxide (CO) poisoning, via the law of mass action, high oxygen tension will reduce the half life of carboxyhemoglobin (HbCO) [4]. Clinically, there is a poor correlation between the level of HbCO and neurological impairment. Though the use of hyperbaric oxygen in carbon monoxide poisoning is still controversial, it is postulated that some of the success seen with treatment with hyperbaric oxygen may be due to other effects of hyperoxia. Evidence suggest that CO adversely affects cell function via lipid peroxidation. Animal work suggests lipid peroxidation is inhibited by hyperbaric doses of oxygen partly mediated by hydroperoxyl (HO2) and hydrogen peroxide (H2O2) [5]. Current thinking places generation of HO2 and H2O2 as well as other reactive oxygen species (ROS) and reactive nitrogen species (RNS) central in the mechanism of hyperoxia and its therapeutic effects.

A complication of tissue ischaemia is interstitial oedema which worsens hypoxia. This is seen in conditions such as crush injuries and cerebral oedema. Hyperoxic mediated vasoconstriction is thought to help reduce oedema by reduction of capillary hydrostatic pressure. Zhilyaev et al in their study on rat brain suggested one of the mechanisms for hyperoxic vasoconstriction appears to be inactivation of nitric oxide by superoxide anions (a main ROS) [6]. Oedema reduction may also be due to the osmotic effect of high arterial oxygen tensions. An interesting paper by Hills calculated an approximate 8.5% increase in plasma oncotic pressure due to the high oxygen in arterial blood and a "pump" effect to maintain this gradient from consumption of oxygen at tissue level [7].

Another role of hyperoxia via generation of ROS and RNS is in ischaemia-reperfusion injury. Though the full picture is still unclear, the evidence is emerging that hyperoxia prevents binding and activation of leucocytes to damaged endothelium via inhibition of B2 integrin function and down regulation of ICAM-1, mediated by endothelial cell nitric oxide synthetase.

Clinically, this was illustrated by Yogaratnam et al in a paper using HBO preconditioning in patients undergoing cardiopulmonary bypass [8]. 100% oxygen at 2.4ATA 4 hours prior to coronary artery bypass graft surgery showed significant improvement in hemodynamics (increase in stroke volume, left ventricular stroke work and left ventricular stroke work index) post cardiopulmonary bypass. There were significant increases in markers of myocardial protection (increased eNOS/Hsp72) and they suggested HBO preconditioning offers endothelial protection and is effective in improving clinical outcome and in reducing cost.

Table 1. Likely Mechanisms of Action for a Range of Indications for HBOT

Mechanism of action	Indication
Restoration of normoxia	Problem Wounds Chronic Osteomyelitis Osteoradionecrosis Soft-tissue Radionecrosis Pyoderma Gangrenosum Decompression Illness
Achievement of hyperoxia	Decompression Illness (CAGE) Carbon Monoxide Poisoning Other toxic Gases Anaerobic Infections Cerebral Oedema Crush injuries Ischaemia/reperfusion injury
Reduction in bubble size	Decompression Illness Arterial Gas Embolism Gas Gangrene

Bubble Size Reduction

According to Boyle's Law, increase pressure will reduce bubble size. Compression from 1ATA to 2ATA will halve the volume of a spherical bubble. This physical effect is used in decompression sickness and arterial gas embolism in diving incidents, and for iatrogenic air embolism during various medical or surgical procedures. It is now understood that "crushing" the bubbles alone using pressure is usually inadequate due to endothelial damage by the passage of bubbles. Thus, the addition of oxygen under pressure was found to have better outcomes in treatment in these ischaemia-reperfusion injuries not dissimilar to the conditions mentioned in the paragraph above.

CONCLUSION

The mechanisms of action of HBOT can be summarized in **Figure 2**. From a greater understanding of the metabolic and chemical effects of hyperoxia and pressure, we are now able to better define the use of HBOT for the various indications in wound healing, chronic infections, toxic gas poisoning and in decompression illness (**Table 1**). Much still remains to be done in this area to guide appropriate use of HBOT to achieve further positive clinical outcomes.

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