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Review

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Hyperbaric oxygen: its uses, mechanisms of action and outcomes

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Introduction

Hyperbaric oxygen therapy (HBO) is increasingly used in a number of areas of medical practice. It is a unique intervention whose method of action is not well understood. Clinicians may request its use for their patients, but often will not fully understand its mechanisms. It is hoped that this review and discussion of HBO and the literature surrounding its use may be useful to clinicians who are unsure whether their patients will benefit from this exciting intervention.

Hyperbaric oxygen therapy is defined by the Undersea and Hyperbaric Medical Society (UHMS) as a treatment in which a patient intermittently breathes 100% oxygen while the treatment chamber is pressurized to a pressure greater than sea level (1 atmosphere absolute, ATA).[1] The pressure increase must be systemic, and may be applied in monoplace (single person) or multiplace chambers. Multiplace chambers are pressurized with air, with oxygen given via face-mask, hood tent or endotracheal tube; while monoplace chambers are pressurized with oxygen.

We began by obtaining the most recent UHMS committee report,[1] and performed Medline searches (1966 to present), with the search terms 'hyperbaric' and 'oxygen', combining this basic search with searches for each of the thirteen indications recommended by the UHMS. Using information from these papers, and the resulting references, this paper outlines the history, physiology, current indications for and effects of hyperbaric oxygen therapy.

History of hyperbaric medicine

Hyperbaric therapy was first documented in 1662, when Henshaw built the first hyperbaric chamber, or 'domicilium'.[2] Since this time, reports of beneficial effects from increased pressure have increased, and by 1877, chambers were used widely for many conditions, though there was little scientific rationale or evidence. In 1879, the surgical application of hyperbaric therapy in prolonging safe anaesthesia was realized and explored.[3]

In 1927, Cunningham[4] reported improvement in circulatory disorders at sea level and deterioration at altitude, and a patient who was grateful to Cunningham for his recovery after HBO treatment, built the huge 'steel ball hospital' chamber, but this was closed when Cunningham failed to produce evidence for its use.

Early chambers used compressed air rather than oxygen, due to early reports of oxygen toxicity.[5] Drager was the first to explore the use of pressurized oxygen in decompression sickness, and his protocols were put into practice by Behnke and Shaw in the late 1930s.[6]

Research conducted by the US military after the Second World War brought greater knowledge

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about survivable pressures. As a result, the use of HBO increased, and throughout the late 1950s and early 1960s, HBO was used to potentiate radiotherapy effects,[7] prolong circulatory arrest during surgery,[8] and to treat anaerobic infections[9] and carbon monoxide poisoning.[10] Unfortunately, HBO has also been used without a solid evidence base in conditions such as dementia, emphysema and arthritis. Concerns about lack of scientific progress and regulation led the UHMS to form a *Committee on Hyperbaric Oxygen Therapy* in the late 1970s, which is now the international authority on HBO.

Physiological basis of hyperbaric oxygen therapy

The effects of HBO are based on the gas laws, and the physiological and biochemical effects of hyperoxia.

Boyle's law states that at a constant temperature, the pressure and volume of a gas are inversely proportional. This is the basis for many aspects of hyperbaric therapy, including a slight increase in chamber temperature during treatment; and the phenomenon known as 'squeeze', occurring when blocked eustachian tubes prevent equalization of gas pressure, resulting in painful compression of gas in the middle ear. In patients who cannot independently achieve pressure equalization, the placement of tympanostomy tubes should be considered to provide a channel between the inner and outer ear air spaces.[11] Similarly, trapped gas can enlarge dangerously during decompression, such as in the rare example of a pneumothorax occurring at pressure.

Dalton's law states that in a mixed gas each element exerts a pressure proportional to its fraction of the total volume (partial pressure).

Henry's law states that the amount of gas dissolved in a liquid or tissue is proportional to the partial pressure of that gas in contact with the liquid or tissue. This is the basis for increased tissue oxygen tensions with HBO treatment. However, it also has implications for decompression needs in the air-breathing attendants in multiplace chambers, as their tissue concentrations of inert gases (particularly nitrogen) will also be increased. This nitrogen will dissolve in the blood and may come out of solution and form arterial gas emboli during depressurization.

Most oxygen carried in the blood is bound to haemoglobin, which is 97% saturated at atmospheric pressure. Some oxygen is however carried in solution, and this portion is increased at pressure due to Henry's Law, maximizing tissue oxygenation. When breathing normobaric air, arterial oxygen tension is approximately 100 mmHg, and tissue oxygen tension approximately 55 mmHg. However, 100% oxygen at 3 ATA can increase arterial oxygen tensions to 2000 mmHg, and tissue oxygen tensions to around 500 mmHg,[12] allowing delivery of 60 ml oxygen per litre of blood (compared to 3 ml/l at atmospheric pressure), which is sufficient to support resting tissues without a contribution from haemoglobin.[13,14] As the oxygen is in solution, it can reach physically obstructed areas where red blood cells cannot pass, and can also enable tissue oxygenation even with impaired haemoglobin oxygen carriage, such as in carbon monoxide poisoning and severe anaemia.

HBO increases generation of oxygen free radicals, which oxidize proteins and membrane lipids, damage DNA and inhibit bacterial metabolic functions. HBO is particularly effective against anaerobes, and facilitates the oxygen-dependent peroxidase system by which leukocytes kill bacteria.[15] HBO also improves the oxygen-dependent transport of certain antibiotics across bacterial cell walls.[16]

HBO improves wound healing by amplifying oxygen gradients along the periphery of ischaemic wounds, and promoting oxygen-dependent collagen matrix formation needed for angiogenesis.[17,18]

During reperfusion, leukocytes adhere to ischaemic tissues, releasing proteases and free radicals, which leads to pathological vasoconstriction and tissue destruction.[19] This worsens crush injuries and compartment syndromes, and causes failure of skin flaps, grafts and reattachment procedures.[20] This free radical damage has been implicated in neuronal injury following ischaemia and exposure to drugs and poisons. Zamboni[21] demonstrated reduced leukocyte adherence and post-ischaemic vasoconstriction with HBO in ischaemic rat tissue, and more recently Thom[22] demonstrated reduced lipid peroxidation with HBO in rats with carbon monoxide poisoning.

Hyperoxia in normal tissues due to HBO causes rapid and significant vasoconstriction,[23] but this is compensated for by increased plasma oxygen carriage, and microvascular blood flow in ischaemic tissue is actually improved with HBO.[21] Such vasoconstriction does however reduce post-traumatic tissue oedema, which contributes to the treatment of crush injuries, compartment syndromes and burns.[24]

Finally, HBO limits post-ischaemic reductions in ATP production, and decreases lactate accumulation in ischaemic tissue.[25]

In summary, HBO has complex effects on immunity, oxygen transport and haemodynamics. The positive therapeutic effects come from a reduction in hypoxia and oedema, enabling normal host responses to infection and ischaemia.

Indications and uses for hyperbaric oxygen therapy

In hypoxic conditions, whether due to ischaemia or other factors, HBO reduces infection and cell death and maintains tissue viability while healing occurs. HBO is widely accepted as the only treatment for decompression sickness (DCS) and arterial gas embolism, and the UHMS lists thirteen conditions (Table 1) for which '...research data and extensive positive clinical experience have become convincing'.[1] Treatment recommendations mentioned in this paper are taken from the UHMS report,[1] and are evidence-based where possible, but the nature of the treatment means that much of the knowledge comes from clinical experience rather than trials.

Arterial gas embolism

Arterial gas embolism, first described by Brauer,[26] occurs when air bubbles enter or form in the circulation. There are many causes, including mechanical ventilation; central line placement and haemodialysis.[27,28] However, the commonest cause in patients referred for HBO therapy is acute severe diving injury and pulmonary barotrauma, which may require very aggressive pressure therapy.

The bubbles cause tissue deformation and vessel occlusion, impairing tissue perfusion and oxygenation. Biochemical effects at the blood-gas interface also cause endothelial damage, changes in haemostasis and activation of leukocytes.[29]

Clinical effects depend on the location of the embolus, with symptoms ranging from muscle and joint pain to much more serious cardiac and CNS disease, which may result in arrhythmias, ischaemia, confusion, focal neurological deficits and loss of consciousness. An important risk factor in the development of arterial gas embolus is the existence of a patent foramen ovale. This can allow the usual venous nitrogen bubbles developed during decompression to cross into the arterial circulation and become the more dangerous arterial gas emboli. Similarly, small venous bubbles formed during ascent may be adequately removed at the pulmonary capillaries, but this filtration capacity is overwhelmed in the case of larger emboli, and bubbles may pass into the arterial circulation.[30]

HBO reduces bubble size in accordance with Boyle's law—at 3 ATA, bubble volume is reduced by about two-thirds.[31] Dexter[32] concluded that HBO is worth consideration for any embolus large enough to be seen on CT. Hyperoxia increases the diffusion gradient with the embolized gas, moving gas into solution where it can be metabolized.[32]

There have been no clinical trials into the use of HBO in air embolism, but a 2003 case series of 19 patients in the USA with iatrogenic cerebral arterial gas embolism, showed significant improvement in symptoms with HBO treatment, although there was no control group and end-points were not clearly defined.[33] HBO is most effective when initiated early, but can be successful after hours or even days.[34] There are few clinical trials with HBO in air embolism, as it is widely accepted as the only life-saving treatment, but extensive clinical experience and UHMS advice suggests maximal benefit with 100% oxygen at 2.8 ATA, and repeated treatments until no further improvement is seen, typically after no more than 5–10 treatments.[1,35]

Table 1 UHMS approved indications for hyperbaric oxygen therapy[1]

Air or gas embolism
Carbon monoxide poisoning; cyanide poisoning; smoke inhalation
Clostridial myostitis and myonecrosis (gas gangrene)
Crush injuries, compartment syndromes and other acute traumatic peripheral ischaemias
Decompression sickness
Enhancement of healing in selected problem wounds
Exceptional blood loss anaemia
Intracranial abscess
Necrotizing soft tissue infections
Refractory osteomyelitis
Skin flaps and grafts (compromised)
Delayed radiation injury (soft tissue and bony necrosis)
Thermal burns

Carbon monoxide poisoning

Carbon monoxide poisoning is a common form of poisoning, with common mechanisms including faulty heating appliances or deliberate self harm and attempted suicide. On inhalation, it has an anaesthetic effect, and the high affinity of carbon monoxide (CO) for haemoglobin results in reduced arterial oxygenation, causing the acute hypoxic symptoms listed in Table 2. It also causes delayed neurological symptoms (Table 3) by binding to cytochrome-c oxidase and disrupting mitochondrial function, and by causing free-radical release and lipid peroxidation.

Table 2 Acute clinical manifestations of carbon monoxide poisoning

Dizziness	Confusion	Ataxia	Myocardial ischaemia
Headache	Blurred vision	Tachycardia	Myonecrosis
Nausea	Muscle cramps	Tachypnoea	Seizures
Vomiting	Abdominal pain	Coma	Dysrhythmias

From reference 98.

Table 3 Delayed neurological sequelae of carbon monoxide poisoning

Chronic headaches	Neurological deficits
Cognitive deficits	Movement disorders
Personality disorders	Parkinson's disease
Aphasia	Psychosis
Apraxia	Gait disturbances
Cortical blindness	

From reference 98.

The standard treatment for CO poisoning is oxygen, to reverse hypoxia, compete with CO for haemoglobin binding, and promote carboxyhaemoglobin dissociation. Effects are increased at high pressure, shortening carboxyhaemoglobin half-life from 4–6 h to <30 min.[36] HBO has been shown in animals to promote CO dissociation from cytochrome-c oxidase, reduce brain lipid peroxidation, and inhibit leukocyte adhesion[22,36–38]. However, in 2001, Gilmer[39] found no benefit in preventing neurological sequelae at one month in mice. HBO may also reduce cyanide toxicity, which commonly occurs with combustion-related CO poisoning, though there is insufficient evidence to recommend its routine use for this indication.[1]

A clinical trial by Raphael found no benefit with HBO, but treatments were at low pressures and many were delayed.[40] More recently, Thom[41] found significantly reduced neurological sequelae with HBO, but Scheinkestel[42] found no significant differences in mortality and neurological symptoms at one month. More recently, a high quality study in 2002 found that three HBO treatments within 24 h of acute CO poisoning appeared to reduce the risk of cognitive sequelae at 6 weeks and 12 months.[43] However, another recent study[44] found no benefit, illustrating the lack of a clear consensus.

While the scientific rationale and physiological evidence for HBO is clear, this does not translate into clear clinical benefit. Clinical trial results are not entirely convincing, and conflict continues regarding benefits and disadvantages. A Cochrane Review in 2000 found no clear benefit in its unselected use in carbon monoxide poisoning.[45] However, the trials examined looked at patients with varying severity of poisoning and different treatment regimes, making conclusions and clinical guidelines difficult. The UHMS recommend HBO for serious intoxication (coma, unconsciousness, seizures, focal neurological deficits or cardiac effects)[1]. As in air embolism, treatments as recommended by the UHMS (at 2.4–3.0 ATA for up to 120 min) are repeated within 6–8 h if there is persistent neurological dysfunction, until there is no further improvement.[1]

Clostridial myostitis and myonecrosis (gas gangrene)

Clostridial myonecrosis is an acute anaerobic infection caused by clostridial spores germinating within hypoxic, devitalized tissue. Patients present acutely with severe pain, toxaemia and oedema. Haemolytic and liquefactive toxins, particularly alpha-toxin, cause extensive tissue destruction, jaundice, anaemia, renal failure and cardiotoxicity, and are so rapid-acting that often no immune response is mounted. It is commonest in contaminated traumatic wounds, but may also occur following surgery. Treatment is debridement and antibiotic therapy,[9] and adjunctive HBO is known to have antibacterial and anti-toxin effects (particularly blocking alpha-toxin production).[46] There are many case reports and clinical series supporting combined therapy with HBO, antibiotics and surgery in these conditions, reducing need for drastic surgery and amputation.[47] The UHMS recommends that three 90-min treatments should be given at 3.0 ATA in the first 24 h, followed by twice-daily treatments for 4–5 days, until clinical improvement is seen.[1]

Crush injuries, compartment syndromes and other acute traumatic peripheral ischaemias

In acute traumatic peripheral ischaemias (ATPIs), extravasation of intravascular fluid increases diffusion distance from capillary to cell, resulting in progressive, self-perpetuating ischaemia, oedema and inadequate healing. There is severe damage centrally, with progressive improvement in adjacent

tissues. Ischaemia and oedema may continue even when the primary injury is controlled.[24]

Management involves maintenance of perfusion by surgical repair, blood replacement and anticoagulation.[24] HBO improves tissue oxygen tensions by increasing plasma-based oxygenation and increasing erythrocyte deformability.[21] Intermittent hyperoxia stimulates fibroblast and collagen synthesis, enabling angiogenesis, tissue repair and optimal healing.[48] Hyperoxic vasoconstriction resolves oedema without impairing oxygen delivery, and reverses the ischaemia-oedema cycle.[49] HBO also antagonizes free-radical-associated lipid peroxidation, reducing reperfusion injury.[22]

Published research is limited, but a high quality randomized controlled trial in 1996 demonstrated significant improvement in healing with HBO.[50] Cost benefits are substantial, by minimizing the many costly complications of ATPIs.[20] Adjunctive HBO increases tissue oxygenation and decreases oedema, facilitating surgical repair and other treatments. The UHMS recommends treatment within 4–6 h of injury, given at 2.0–2.5 ATA at least once daily for several days, although guidelines vary depending on the type of injury.[1]

Decompression sickness

Decompression sickness (DCS) occurs mainly in scuba divers, when inert gas (mainly nitrogen) comes out of solution during ascent and decompression, forming bubbles in the capillaries and tissues.[33] Doppler studies have shown that most divers have venous bubbles even on decompression, even when conservative dive tables are followed, but these smaller bubbles are not necessarily pathological.[51] Symptoms depend on the location of the bubbles, and include fatigue, joint pains, rash, neurological and cardio-respiratory symptoms, coma and death, and occur due to physical distortion, vessel occlusion, clotting and immune changes. Predisposing factors include dehydration, injury, exertion at depth and cold exposure.[52]

Since the 1930s,[6] HBO has been the definitive treatment for DCS, although no randomized controlled trials have compared it to normobaric oxygenation. HBO recompresses bubbles and forces gas back into solution for a more controlled ascent. Inert nitrogen is replaced by rapidly-metabolized oxygen, and bubbles move either to the lungs where they are excreted, or to smaller vessels where obstruction is less important, and surface tension forces eventually collapse the bubbles. HBO also counteracts platelet and leukocyte activation and endothelial interactions.[21]

HBO is the only established lifesaving treatment for DCS, and the UHMS recommend rapid treatment at 2.8 ATA, repeated up to ten times if symptoms persist.[1,35]

Enhancement of healing in selected problem wounds

Problem wounds, mainly diabetic foot ulcers and arterial insufficiency ulcers, are among the commonest conditions treated with HBO in the UK. Hypoperfusion, ischaemia and infection impair healing by decreasing fibroblast proliferation, collagen production and angiogenesis.[15,18] *In vitro* research, animal studies and clinical experience have demonstrated that HBO can 'restore a favourable cellular milieu in which the wound healing process and the host antibacterial mechanisms are enhanced'.[1] Since 1967, HBO has been reported to enhance oxygenation, fibroblast proliferation, collagen synthesis, epithelialization and neovascularization, increase bactericidal activity, and be toxic to anaerobes.[17,18,53]

Diabetic wounds are associated with peripheral neuropathy, vascular disease and impaired local immunity. Chemotaxis, phagocytosis, bacterial killing and lymphocytic function are reduced, impairing inflammation and healing. Morbidity and mortality are high, and improved healing and limb salvage have been shown with HBO.[54,55] Zamboni found significantly greater reduction in wound size with HBO in a small, non-randomized study,[56] though the control group consisted of only five patients who refused HBO therapy. Bakker recognized the potential of adjunctive HBO in diabetic wounds,[57] but emphasized the need for a multidisciplinary prospective randomized controlled trial. A double-blind randomized controlled trial in 2003 demonstrated improved healing and cost-benefits with adjunctive HBO in diabetic ulcers, compared to a placebo group receiving hyperbaric air, although the sample was small.[58] Another recent study found a doubling of the mean healing rate of non-ischaemic chronic foot ulcers in selected diabetic patients with HBO treatment.[59]

Other non-diabetic problem wounds include venous stasis ulcers, for which Hammarlund[60] found improved healing with HBO.

In summary, some wounds fail to heal even with appropriate cleansing, debridement, closure and antibiotics. HBO is a relatively safe, non-invasive means of improving healing by enhancing oxygenation, decreasing oedema, and modifying healing and immune responses. Limb preservation and speedier healing make this a cost-effective method of wound care, and recent reviews have concluded

that HBO is very useful in the management of problem wounds.[61,62] Protocols vary greatly, but the UHMS recommend treatment at 2.0–2.5 ATA for 90–120 min once or twice daily, combined with grafts and infection control.[1] Review should be after 30 treatments, or 10 treatments post-grafting.[1]

Exceptional blood loss anaemia

Without replacement of red blood cells in major blood loss or haemolysis, tissue hypoxia and ischaemia will soon occur. Where whole blood transfusion is not possible, for religious or practical reasons, HBO may compensate for such a haemoglobin deficiency by increasing levels of plasma-dissolved oxygen to enable oxygenation while erythrocyte regeneration occurs. This is useful as a short-term measure, but is inconvenient and expensive, and the risk of oxygen toxicity limits treatment duration. It has been successfully used in severe haemorrhagic shock and blood loss anaemia, and Hart[63] described 70% survival in 26 patients who received HBO after losing >50% of their circulating volume. The UHMS recommend treatments at up to 3 ATA for 2–4 h periods, three or four times a day, until hypoxic symptoms have resolved and red blood cells have been regenerated.[1]

Intracranial abscess

Mortality has decreased in conditions such as cerebral abscess, subdural empyema and epidural empyema, due to improved diagnosis, minimally invasive CT-guided aspiration, and improved antibiotic therapy, enabling more conservative and less radical management. In patients with severe infection or immune compromise, who may be unresponsive to standard aspiration and antibiotic treatment, adjunctive HBO inhibits the predominantly anaerobic micro-organisms, reduces cerebral oedema, and modifies the immune response. Clinical evidence is limited, but the UHMS recommends HBO for multiple, deep or dominantly-located abscesses, or in patients with immune compromise, poor surgical risk, or resistance to conventional treatment.[1] Treatments are once or twice daily, at 2.0–2.5 ATA for 60–90 min, and success is determined by clinical and radiological findings.[1] The average number of treatments is thirteen, and a utilization review is recommended after twenty treatments.[1]

Necrotising soft tissue infections

Necrotising fasciitis is a rapidly-progressive and usually traumatic bacterial infection of the deep fascia with secondary subcutaneous and cutaneous involvement. Haemolytic streptococci are typical pathogens, but polymicrobial infection, host diabetes and vascular disease are all common. Local hypoxia occurs, with up-regulation of endothelial adherence molecules, resulting in leukocyte adhesion and endothelial cytotoxicity.[1] An obliterative endarteritis occurs, causing tissues to become hypoxic, hypovascular and hypocellular. Leukocytes may become sequestered in vessels, impairing local immunity, and incomplete substrate oxidation results in hydrogen and methane accumulation in the tissues. Tissue necrosis occurs, with purulent discharge and gas production, and reports of mortality range from 30% to 75%.[1] Conventional treatments are surgical debridement and systemic antibiotics.

In animal studies, HBO has a direct antibiotic effect, improving tissue oxygen tension, leukocyte function and bacterial clearance.[64] Integrin inhibition decreases leukocyte adherence, reducing systemic toxicity.[65] HBO has been reported to reduce mortality by up to two-thirds.[66] HBO is particularly indicated in bacterial gangrene and non-clostridial myonecrosis (which have high mortality and morbidity), and in compromised or unresponsive hosts.[67] The UHMS recommends twice-daily treatments for 90–120 min at 2.0–2.5 ATA, reduced to once daily when the patient's condition is stabilized.[1] Further treatments may be given to reduce relapse, and a utilization review is recommended after 30 treatments.[1]

Refractory osteomyelitis

These chronic, unresponsive bone infections are caused by bacteria that may remain dormant for years. Combined with antibiotics, debridement, and removal of foreign material, HBO is recommended in localized and diffuse osteomyelitis, particularly with vascular or immune compromise.[1] HBO maximizes plasma-based oxygenation and provides the intermittent hyperoxia needed for collagen synthesis and angiogenesis,[18] increasing vascularity and oxygenation.[68] Leukocyte-mediated bacterial killing is increased, as is the efficacy of certain antibiotics, by optimizing oxygen-dependent aminoglycoside transport across bacterial cell walls.[69] HBO directly and indirectly kills anaerobes, and promotes oxygen-dependent osteoclastic resorption of necrotic bone.[1] Reduction of oedema, inflammation and compartment pressure is also important.

HBO was first used in refractory osteomyelitis by Slack in 1965,[70] and its efficacy has been confirmed in controlled animal studies.[59] In 1992,

Davis[71] reported its successful use in advanced malignant otitis externa, a progressive and potentially fatal form of refractory pseudomonal osteomyelitis of the ear canal and base of skull, usually affecting elderly diabetic patients.

Treatment depends on disease severity, but UHMS recommendations are generally for 90–120 min daily at 2.0–2.5 ATA, in conjunction with debridement, antibiotics and nutritional support, and review is recommended after 40 treatments.[1]

Delayed radiation injury (soft tissue and bony necrosis)

Radiation therapy impairs cellular proliferation, causing a progressive, obliterative endarteritis, which results in hypocellular, hypovascular and hypoxic tissue. This is seen clinically as oedema, ulceration, bony necrosis and poor wound healing that can persist for years after the initial insult. High radiation doses may result in spontaneous radionecrosis.

HBO increases vascular density and oxygenation in radiation-damaged tissue.[72] It improves tissue oxygen gradients and angiogenesis and enhances leukocyte bactericidal activity. Oxygen tension is increased to normal levels, enabling fibroblast proliferation, collagen formation and angiogenesis at the wound edges, further improving oxygenation and re-epithelialization.[73] This facilitates healing and may enable grafts to be placed.

In 1973, Mainous[74] reported improved mandibular healing with HBO after radiotherapy for head and neck tumours. Marx reported in 1985 that prophylactic HBO before tooth extractions in heavily irradiated mandibles prevented mandibular osteoradionecrosis more effectively than penicillin.[75] HBO treatment of mandibular osteoradionecrosis is recommended by the UHMS to consist of 30 daily 90-min sessions at 2.4 ATA, with surgical debridement in more advanced disease.[1]

HBO may reduce the incidence and progression of soft tissue radionecrosis, such as laryngeal radionecrosis,[68] although there is less support for this in the literature than for osteoradionecrosis. In 1997, Neovius reported complete healing with HBO in 12/15 patients with problem wounds following surgery and radiotherapy.[76] Pre-operative HBO for such patients was reported by Marx in 1995 to reduce wound dehiscence and infections, and improve healing in soft tissue flap surgery.[77]

Successful treatment with HBO is also documented in other post-radiation damage, including chest wall necrosis, radiation-induced haemorrhagic cystitis, and central nervous system radiation damage.[78] A recent trial, however, found little evidence for HBO in radiation-induced brachial plexopathy, though there were some improvements in warm sensory threshold and long-standing arm lymphoedema.[79]

In summary, there is extensive, but not conclusive, evidence for HBO in radiation injury, particularly in mandibular osteoradionecrosis, though randomized controlled trials are lacking. One particularly detailed economic analysis in osteoradionecrosis found that it was six times more expensive not to use HBO![80] UHMS recommendations for HBO in radiation injury usually consist of daily 90–120 min sessions at 2.0–2.5 ATA for about 40 days.[1]

Skin flaps and grafts (compromised)

A number of animal studies have established improved survival of skin flaps and grafts with HBO. In 1982, Marx reported enhanced angiogenesis, healing and flap survival,[81] and in 1987, Nemiroff reported significantly increased microvasculature in animals treated with HBO.[82] A 2002 trial found improved auricular composite graft survival in rabbits treated with HBO.[83] In skeletal microcirculation models, HBO significantly reduced endothelial leukocyte adherence and prevented the progressive vasoconstriction of reperfusion injury.[21] Other mechanisms include fibroblast stimulation and collagen synthesis.

Clinically, significant improvements with HBO in skin grafts and flaps have been reported since 1967.[53] HBO maximizes compromised tissue viability, and facilitates graft placement in an irradiated field or with impaired microcirculation. The UHMS recommends twice-daily treatment at 2.0–2.5 ATA for 90–120 min, reducing to once-daily when the graft or flap has stabilized.[1] A utilization review is recommended after 20 treatments, whether preparing a site for grafting, or maximizing survival of a new graft.[1]

Thermal burns

Severe burns have a central area of coagulation that is subject to rapid deterioration, due to insufficient oxygen and nutrient supply from the surrounding tissues. Burn therapy comprises respiratory care, antibiotics, debridement, and parenteral nutrition, with the aims of reducing oedema, preserving borderline tissue and enhancing host defences.

There is evidence that HBO reduces haemoconcentration, coagulability and vascular damage in thermal burns.[84] As previously discussed, hyperoxic vasoconstriction decreases oedema, and increases collagen formation and angiogenesis. Phagocytic

bacterial killing is also improved, and white cell endothelial adherence is inhibited, preventing capillary damage.[21] HBO maintains ATP levels and microvascular integrity, and reduces infection.[1] HBO decreases healing time[58], hospitalization and mortality compared to controls[79], and reduces need for grafting.[1] However, others have found no benefit from HBO in thermal burns.[85] Concerns that HBO may worsen pulmonary damage in thermal burns are unproven.

The UHMS recommends three sessions within 24 h of injury, and 90-min treatments twice-daily thereafter, at 2.0–2.4 ATA.[1]

Complications and contraindications

HBO is a relatively safe treatment, but does carry some risks, due to the increased pressure and hyperoxia. The commonest effect of oxygen toxicity is a progressive, reversible myopia, thought to be due to physical lens deformation.[86] There is no evidence for other optical side-effects such as cataracts.[86] CNS toxicity may occur, and has been known since Paul Bert documented the seizure-potentiating effect of HBO in 1878,[87] but the UHMS feel this is not justified within well-defined oxygen tolerance limits.[1] Interestingly, a 2003 paper reported an apparent increase in oxygen-induced convulsions over recent years, though the reasons for this were unknown.[88]

Middle ear and sinus barotraumas are preventable by equalization techniques or tympanostomy tubes,[11] and otitis media can be prevented with pseudoephidrine.[89] Inner ear barotrauma is extremely rare, but tympanic rupture can result in permanent hearing loss, tinnitus and vertigo. Pulmonary barotrauma and pneumothorax are extremely rare, particularly without pre-existing lung disease. Dental barotrauma may rarely cause pain under a dental filling.

There have been some concerns that HBO could stimulate malignant growth by increasing tumour oxygenation. This was not supported by Feldmeier in his report of 1994,[90] or his review in 2003,[91] and he concluded that a history of malignancy should not be a contra-indication for HBO therapy.

Clinical and experimental evidence does not support claims that HBO during pregnancy can cause a range of foetal complications, including spina bifida and limb defects.[92] Psychological side-effects such as claustrophobia are common. Accidents are a risk due to the enriched oxygen and inaccessibility, with over 50 reported deaths due to fire in the last 20 years.[93]

The only absolute contraindication to HBO is an untreated tension pneumothorax, and this must be excluded before treatment.[1] Relative contra-indications include impaired pressure equalization, and cardiac disease.

Conclusions

HBO has been recommended and used for a wide range of medical conditions, with a varying evidence base. Evidence for its widespread use in decompression sickness and air embolism is strong, and the UHMS recommends the use of HBO in these and eleven other conditions. There is extensive anecdotal literature suggesting its use in a range of other conditions (Table 4), including ischaemic stroke, multiple sclerosis and sports injuries.[94–96] However, evidence for these is flawed, and a recent pilot study found that HBO may actually be harmful in patients with ischaemic stroke.[97] HBO is expensive, not universally available, and not without risks, and further research is needed to establish its efficacy and safety in other conditions. It has been described as 'a therapy in search of diseases',[13] but in conditions such as decompression sickness, its use as a life-saving measure is well established, and the ethics of withholding treatment from a control group would be questionable.

Table 4 Other suggested indications for hyperbaric oxygen therapy

Acute cerebrovascular incidents	Spinal cord injury
Cerebral oedema	Intra-abdominal abscess
Head injury	Acute central retinal artery insufficiency
Meningitis	Brown recluse spider bite
Ischaemia-reperfusion injury	Sickle cell crisis
Lepromatous leprosy	Fracture healing and bone grafting
Pseudomonas colitis	Hydrogen sulphate or carbon tetrachloride poisoning

From reference 98.

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