

# Hyperbaric Oxygen Therapy: The Future of Medicine

R.K. Muniandy\*

*Department of Anaesthesia and Intensive Care, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah (UMS)*

Hyperbaric Oxygen Therapy (HBOT) has always been a controversial medical therapy for the current modern medical treatment. Throughout the years, multiple studies have been done to explore the use of HBOT. Now, the US Food and Drug Administration (FDA) has approved several indications for the use of HBOT. However, there are many more uses for HBOT which are yet to be explored, or with insufficient evidence due to lack of controlled study for the indication of HBOT. This article explores the current proven evidence for the use of HBOT, and the possible future application of HBOT.

**Keywords:** Hyperbaric Oxygen Therapy; HBOT; FDA

## I. INTRODUCTION

Hyperbaric Oxygen Therapy (HBOT) is defined as a procedure that involves the exposure of the body to 100% oxygen at a pressure of more than 1 atmosphere absolute (ATA) (Leach *et al.*, 1998). This can be provided in a monoplace Figure 1) or a multiplace chamber (Figure 2). The monoplace chamber is a small airtight chamber which is usually pressurised with pure oxygen. The multiplace chamber on the other hand can accommodate several patients at the same time, and patients will breathe hyperbaric oxygen through tightfitting hoods or masks.



Figure 1. Monoplace chamber



Figure 2. Multiplace chamber

## II. MECHANISM OF HBOT

There are two main mechanisms of HBOT, pressure and oxygen (Kocaman Ürütük, 2020).

### A. The Effects of Pressure

Boyle's Law states that the volume of a quantity of gas is inversely proportional to the pressure surrounding it (Zumdahl, 2002). Based on this, gases will contract when pressure is applied externally. When the chamber is pressurised, which is called the compression phase of HBOT, a contraction occurs in gas-containing cavities in the body. Due to this effect, it is possible to reduce the size of air bubbles present in the tissue and intravascular area.

\*Corresponding author's email: [rajeshkumar@ums.edu.my](mailto:rajeshkumar@ums.edu.my)

### B. The Effects of Oxygen

Based on Henry's law, the solubility of gases will increase under pressure. At room air, the haemoglobin will be 95% saturated, with 19ml of oxygen being carried in every 100ml of blood, specifically by haemoglobin. Another 0.32ml of oxygen is dissolved in plasma. If inspired oxygen is increased to 100%, the oxygen carried by haemoglobin may increase to 20ml in every 100ml of blood, and 2.09ml will be dissolved in plasma. During HBOT, the amount of dissolved oxygen in plasma will increase to 4.44mls per 100mls at 2 ATA, and 6.80mls at 3 ATA (Leach *et al.*, 1998). The dissolved oxygen which is carried by the plasma will provide the amount needed for tissues to survive, despite no oxygen carried by the haemoglobin.

## III. HISTORY OF HBOT

The first hyperbaric chamber was made by Nathaniel Henshaw, a British clergyman and physician, in 1662 (Henshaw & Simpson, 1857). He called it the chamber domicilium (Figure 3), which was pressurised using bellows. At that time, the chamber was used to facilitate digestion and breathing, while preventing respiratory infections. Henshaw believed that patients who had acute conditions would benefit from an increased air pressure.



Figure 3. Chamber domicilium, the first hyperbaric chamber in the world.

In the 1830's, France started exploring the use of HBOT. The first true compressed hyperbaric tank arrived in 1834 under the direction of Dr Junod. This device was able to generate 4 atmospheres pressure. He referred to his treatment as "Le Bain d'air Comprime" (the compressed air bath). Dr Junod claimed that the use of HBOT may increase the circulation to the internal organs and the brain. This will then result in feelings of better general health (Krishnamurti, 2020).

In 1879, a French surgeon, Fontaine, built a pressurised mobile operating room (Kindwall & Hunt, 1995). Somewhere during this time, HBOT was available in many major European countries. These chambers were used to treat asthma, emphysema, chronic bronchitis, and anaemia.

Back in the United States, Orwill Cunningham in 1928, built the largest hyperbaric chamber in the world, in Lawrence, Kansas. This pressurised hospital was six stories high and could achieve a pressure of 3 ATA (Kindwall & Hunt, 1995). Each floor had 12 rooms, with amenities like a hotel. At that time, he used it to treat Spanish influenza during the First World War.

In Malaysia, HBOT started in 1996, at the Institute of Underwater and Hyperbaric Medicine (IUHM), Armed Forces Hospital Lumut (Rozali *et al.*, 2006). This was made to support the medical needs of military, commercial and recreational diving. Over the last several years, a few private hyperbaric chambers have been established around the country, serving patients with different problems and backgrounds. In Sabah, there is a multi-place chamber located at the Royal Malaysian Navy, Sepanggar. This chamber serves the military and emergency cases from the local Ministry of Health hospitals.

#### IV. INDICATION OF HBOT

There are currently 14 conditions that are approved by the US Food and Drug Administration (FDA), with sufficient evidence for HBOT. The list is listed in Table 1 (Moon, 2019).

Table 1. FDA-approved indications for HBOT.

No.	Indications
1	Air or gas embolism
2	Anaemia (severe anaemia when blood transfusion cannot be used)
3	Burns (severe and large burns treated at a specialised burn centre)
4	Carbon monoxide poisoning
5	Crush injury
6	Decompression sickness (diving risk)
7	Gas gangrene
8	Hearing loss (complete hearing loss that occurs suddenly and without any known cause)
9	Infection of the skin and bone (severe)
10	Radiation injury
11	Skin graft flap at risk of tissue death
12	Vision loss (when sudden and painless in one eye due to blockage of blood flow)
13	Wounds (non-healing, diabetic foot ulcers)

##### A. Air or Gas Embolism

Gas embolism can happen due to direct gas entry via veins or arteries, or due to in-situ formation due to gas supersaturation in divers, compressed air workers, or aviators. Arterial gas embolism (AGE) may occur during ascent after breathing compressed gas at depth (Moon, 2019). It can also happen during accidental injection of air bubbles into the artery during procedures or surgeries. Venous gas embolism (VGE) occurs after compressed gas diving. It can also occur when air enters the venous system and causes an obstruction in the pulmonary circulation. (McCarthy *et al.*, 2016). During HBOT, air bubbles can be reduced in size, and eventually eliminated through the lungs (Ratzenhofer-Komenda *et al.*, 2006).

##### B. Carbon Monoxide Poisoning

Carbon monoxide (CO) is an odourless, tasteless, colourless, non-irritating gas formed by burning fuel (Hopkins & Woon,

2006). CO will enter the bloodstream through inhalation and will then bind to haemoglobin molecules with a greater affinity compared to oxygen. This will create carboxyhaemoglobin. Carboxyhaemoglobin will impair oxygen transport and utilisation (Rose *et al.*, 2017). The indications for HBOT are when COHb level is above 25%, evidence of ongoing end-organ ischaemia, metabolic acidosis (pH<7.1) and loss of consciousness. In pregnant women, a COHb level > 15% or evidence of fetal distress is an indication for HBOT (Ho *et al.*, 2012). In HBOT, the partial pressure of oxygen in arterial blood will be raised, thus facilitating its dissociation from haemoglobin (Cabb & Robin, 1987).

##### C. Clostridial Myositis and Myonecrosis

Clostridial myositis and myonecrosis is an acute, rapidly progressive, non-pyogenic, invasive clostridial infection of the muscles. It is characterised by profound toxemia, extensive oedema, massive death, and a variable degree of gas production. If not identified early, it can be fatal (JS *et al.*, 2022). It is caused by the anaerobic bacteria *Clostridium perfringens* (Boinpally *et al.*, 2018). These organisms are found almost everywhere. During trauma, clostridial organisms enter the tissues and produce toxins. This toxin causes the formation of occlusive intravascular aggregates, which causes a rapid, irreversible decline in muscle blood flow and ischaemic necrosis of tissue. *Clostridium perfringens* growth and toxin production is restricted at high O<sub>2</sub> tensions. High O<sub>2</sub> tension will also achieve bacteriostasis, which will encourage free radical formation and facilitate neutrophilic oxidative function. Early HBOT is essential for reducing morbidity and mortality (Sison-Martinez *et al.*, 2022).

##### D. Crush Injury and Compartment Syndromes

Crush injury is caused by direct physical crushing of the muscles. Compartment syndrome is defined as a localised rapid rise of tension within a muscle compartment, which may lead to metabolic disturbances (Rajagopalan, 2010). With the rising pressure, there will be a decrease in blood perfusion, which will lead to ischaemia. Ischaemia may also result from direct traumatic injury to blood vessels (Buettner & Wolkenhauer, 2007). HBOT has shown to increase blood

diffusion, helps in tissue oxygenation (Strauss & Garcia-Covarrubias, 2008).

### *E. Decompression Sickness*

The cause of decompression syndrome (DCS) is saturation of inert gas in the bloodstream and tissues, which may lead to the formation of gas bubbles (Moon *et al.*, 1995). These bubbles may have mechanical, embolic, or biochemical effects. This dissolved gas will be driven out of solution when leaving a higher-pressure environment to a lower-pressure environment, such as ascending from depth during self-contained underwater breathing apparatus (SCUBA) diving, leaving a caisson worksite, or ascending to altitude in an unpressured aircraft. Patients will present with pain, or stroke-like signs and symptoms. Delayed effects may cause capillary leak, extravasation of plasma and haemoconcentration (Boussuges *et al.*, 1996). These bubbles, which have lost its spheric form, may disappear or be eliminated from the lungs (Hardy, 2008; Welslau, 2006; Kindwall & Hunt, 1995).

Recompression is usually done with US Navy Treatment Table 6, where patients are compressed to 2.8 bar while breathing 100% oxygen. If one treatment produces a complete resolution, no additional treatment will be needed (Anon, 2008).

### *F. Diabetic Foot*

Diabetic foot disease is said to affect 15 to 25% of diabetics (AWC *et al.*, 2014). Diabetes may lead to amputations of the lower limbs, which may affect the patient, their families and our country. Wound healing occurs through various phases of regeneration, and oxygen remains an important part of treatment. In chronic wound, affected tissues become hypoxic, which hinders ulcer healing. With HBOT, the oxygen concentration in the patient's blood will be increased, leading to an increase of oxygen delivery to the wound (Thackham *et al.*, 2008). With higher oxygen levels, wound tissues have shown better wound healing and less bacterial colonisation (Guo *et al.*, 2010).

### *G. Exceptional Blood Loss (Anaemia)*

Anaemia is defined as a haemoglobin level of 13g/dl or lower for men and 12g/dl or lower for women (Price & Schrier, 2008). Patients who have anaemia run the risk of lacking adequate oxygen-carrying capacity by blood. The presentation of patients with anaemia ranges from pallor, fatigability, malaise, and headache to more severe signs and symptoms like hypotension and shortness of breath. HBOT will flood the body with oxygen, and the oxygen levels in the body's tissue can return to normal (McLoughlin *et al.*, 1999). In severe anaemia cases, HBOT can bring the body back to normality, allowing treatment of the underlying causes. This is important for patients who are un-transfusible. These patients who cannot accept blood transfusions for medical or religious purposes are at risk of morbidity and death after acute and unexpected blood loss from conditions including postpartum bleeding, trauma, and intraoperative haemorrhage.

### *H. Intracranial Abscess*

Intracranial abscess is a focal, intracerebral infection that usually begins as a localised area of cerebritis, which may develop into a collection of pus surrounded by a well-vascularised capsule (Gortvai *et al.*, 1987). Clinical presentation of brain abscess includes headache (70%), nausea and vomiting (50%), seizures (25-35%), nuchal rigidity and papilloedema (25%), focal neurologic deficit (50%) and fever (45-50%) (Mustafa *et al.*, 2014). Intracranial abscess can be a life-threatening infection if left untreated. The standard treatment of intracranial abscess would be administration of intravenous antibiotics, followed by surgical craniotomy to remove the abscess (Lee *et al.*, 2006). However, surgical intervention is not without risk. The use of HBOT will increase the oxygen tension in the infected tissues resulting in improvement in phagocytic killing of bacteria (Kutlay *et al.*, 2005). This may reduce the risk for surgery.

### *I. Necrotising Fasciitis*

Necrotising fasciitis (NF) is an infection of any layers within the soft tissue compartment (dermis, subcutaneous tissue, superficial fascia, deep fascia, or muscle). NF is managed

with supportive therapy and antimicrobial therapy. A broad-spectrum antimicrobial therapy is used early to cover for gram-positive, gram-negative, and anaerobic organisms (Vijayakumar *et al.*, 2014). A surgical wound debridement will be done if indicated. Since the necrotising infections are associated with reduced tissue oxygen tension, which leads to ischaemia, increasing the oxygen partial pressure with HBOT will help in reversing the ischaemia process (Hedetoft *et al.*, 2021).

### *J. Osteomyelitis*

Osteomyelitis is an inflammatory process of the bone and bone marrow. It is caused by an infection, which may lead to local bone destruction, necrosis, and eventually an apposition of new bone (Lew & Waldvogel, 1997). Chronic osteomyelitis is considered one of the most difficult orthopaedic conditions to treat (Geurts *et al.*, 2017). The management of osteomyelitis usually involves antibiotics and surgical removal of infected and necrotic tissues. However, antibiotic treatment regime is still unclear. With HBOT, studies have shown that in spinal, tibial or femoral osteomyelitis, HBOT resulted in the eradication of the infection (Savidou *et al.*, 2018). These benefits may be the effect of either neo-vascularisation of the ischaemic tissues or the hyperoxygenation that results in the suppression of anaerobic bacteria and stimulation of leukocytes (Kaide & Khandelwal, 2008).

### *K. Delayed Radiation Injury*

Radiation therapy is a treatment of invasive cancer. However, delayed radiation complications are seen after a latent period of 6 months or more and may develop many years after the radiation therapy (Feldmeier, 2004). When late radiation tissue injury (LRTI) occurs, tissues will undergo a progressive deterioration characterised by a reduction in the density of small blood vessels (reduced vascularity) and the replacement of normal tissue cells with dense fibrous tissue (fibrosis). This will cause an insufficient oxygen supply to sustain normal function (Rubin, 1984). These problems may be very difficult to resolve. HBOT can increase the number of blood vessels in irradiated tissues (Bennett *et al.*, 2016). This neovascularisation in hypoxic tissues can improve the healing of the damaged tissue.

### *L. Skin Grafts and Flaps*

The current management of compromised grafts and flaps include local wound care, vacuum-assisted closure, surgical debridement, and additional reconstructive procedure (Francis & Baynosa, 2017). However, this will increase patient morbidity and cost of health care. It is known that hypoxia is the underlying factor in non-healing tissue and compromised grafts and flaps (Sheffield, 1998). Oxygen will help fibroblast function and collagen synthesis, needed in wound healing. HBOT will assist in these processes.

### *M. Thermal Burns*

Thermal burns may cause profound activation of white cells and platelets, destruction of the microvasculature, and accumulation of oedema (Hart *et al.*, 1974). Thermal burns may cause high morbidity, disability, prolonged hospitalisation, and limitations in performing daily activities (Legrand *et al.*, 2020). HBOT is indicated for patients with burns that extend into the dermis and beyond. HBOT should be initiated early after the injury (Cianci & Sato, 1994).

### *N. Sudden Sensorineural Hearing Loss*

Idiopathic sudden sensorineural hearing loss is defined as a sensorineural hearing loss greater than 30 dB occurring in at least three continuous audiometric frequencies over 72 hours or less (Hughes *et al.*, 1996). Despite the use of corticosteroid, vasodilator, immunosuppressant, and antiviral medication for the management of this problem, there is still no standard treatment (Rauch, 2008). HBOT has shown a significant effect when used in combination with steroids (Fujimura *et al.*, 2007). There are also case reports to show the effectiveness of the treatment.

Although all 14 indications have been proven to provide a positive response, they can be classified based on their urgency (Table 1). This is just a guide for treating multiple patients with different diagnoses.

Table 1. List of applications of HBOT based on urgency  
(Modified from Goldman, 2009).

Type of therapy		Application
Urgent	Primary Therapy	• Decompression sickness
		• Carbon monoxide poisoning
	Adjunctive	• Crush injury/Compartment syndrome
		• Gas gangrene
		• Air or gas embolism
		• Necrotising fasciitis
		• Delayed effects of radiation
		• Osteomyelitis
		• Thermal burn
		• Compromised skin graft of flap
Non-urgent	Adjunctive	• Diabetic foot
		• Exceptional blood loss (anaemia)
		• Intracranial abscess
		• Sudden sensorineural hearing loss

## V. POTENTIAL USE OF HBOT

In recent years, there have been many studies done with HBOT. Despite not listed by the FDA, some have been showing promising results, which may help in treating patients. HBOT is being considered as an adjunctive or alternative therapy. Although existing medical result does not support the consensus due to the lack of empirical evidence, several case studies have been encouraging and warrants more rigorous research to be carried out.

### A. Cognitive Improvement

Studies have shown a favourable outcome that may potentially influence cognitive improvement following HBOT for severe brain injuries (Marcinkowska *et al.*, 2021). Post-stroke patients suffer from reduced cognitive performance and memory difficulties. HBOT for stroke patients has shown significant improvements in all memory measures. These changes are seen in improvements of brain metabolism, especially in the temporal areas (Kim *et al.*, 2015). HBOT may be able to reduce oxidative stress, inflammation, and neural apoptosis, thereby improving functional recovery from stroke (Cozene *et al.*, 2020). Besides stroke patients, studies have shown that HBOT may improve cognitive performance in both normal young and elderly patients (Jacobs *et al.*, 1969). Cognitive function among patients with cognitive deficits may also benefit from HBOT, especially with spatial working memory and memory quotient (Yu *et al.*, 2015).

### B. Post-Surgery Healing

Surgeries will disrupt the integrity of the body. In normal wound healing after surgeries, Day 1 will be haemostasis. Between day one to day 3, the inflammatory phase will occur. Until the 15<sup>th</sup> Day, the remodelling phase will occur. However, infection and ischaemia may cause wound healing delay (Urutuk, 2020). Infection will cause a response in the inflammatory phase of wound healing, which will result in rapid depletion of oxygen in the tissue. This will then result in insufficient blood flow because of tissue oedema. Therefore, the wound will be hypoxic, hypoglycaemic, acidotic, hyperkalemic, hyperlactic, and hypercarbia. Studies done for using HBOT during perioperative period has showed positive results (Boet *et al.*, 2020; Friedman *et al.*, 2019). Therefore, it is very important to identify patients who might have delayed healing and refer them early for HBOT. HBOT can also be helpful in prevention and relieve in complications of aesthetic applications (Zamboni & Baynosa, 2008; Nemiroff, 1988; Mesimeris, 2006). This includes risky grafts and flaps in plastic surgery. In orthopaedic surgeries, HBOT can also help in post-operative wound healing and avascular necrosis (Kemmer *et al.*, 2006; Ditri *et al.*, 2006).

### C. Adjuvant to Radiation Oncology

Radiotherapy targets the cancerous tissue. However, neighbouring normal tissues may also be damaged. These damaged tissues will lose its blood supply, and fibrosis will develop, accompanied by hypoxia. HBOT removes hypoxia in these tissues, which will then speed up the new cell construction, collagen production and angiogenesis/neovascularisation (Feldmeier DO, 2008; Hampson *et al.*, 2011; Marx *et al.*, 1985).

### D. Pain Management

HBOT has been postulated to be effective as an adjunctive treatment of chronic pain (Sutherland *et al.*, 2016). Increased oxygen delivery to the tissues with HBOT may prevent tissue damage in ischemic tissues (Yildiz *et al.*, 2004). Evidence have shown that HBOT has a positive clinical effect on pain experienced by patients with Fibromyalgia Syndrome (FMS) (Efrati *et al.*, 2015). After 2 months of HBOT treatment, patients had a significant increase in pain thresholds, and fewer tender points. They also had an increased physical functionality, decreased psychological distress, and an increase in their health-related quality of life. Patients with myofascial pain syndrome (MPS) also benefited from HBOT. Their pain threshold was increased at three months post-treatment (Kiralp *et al.*, 2009). These patients also had a decrease in their disability, and an increase in their health-related quality of life. There are other pain conditions that may be helped with HBOT. These includes headaches and migraines (Yildiz *et al.*, 2006; Shafee *et al.*, 2021), complex regional pain syndrome (Sutherland *et al.*, 2015) and trigeminal neuralgia (Barilaro *et al.*, 2017).

### E. Cancer

Solid tumours often contain areas subjected to acute or chronic hypoxia (Michieli, 2009). This hypoxic environment will allow cancer cells to survive and proliferate (Harris, 2002). Tumour hypoxia develops because of the structural and functional abnormalities of the tumour vasculature. Cancer growth often overrides the ability of the cancer vasculature to adapt to the increasing oxygen demand.

Studies have shown that HBOT can be inhibitory and reduce cancer growth in some cancer types, like breast cancer. On the other hand, cervical and bladder cancers appear to be no responders to HBOT (Moen & Stuhr, 2012).

### F. Children with Autism

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by persistent impairments in reciprocal social communication and social interaction (American Psychiatric Association, 2013). It is postulated that children with autism might benefit from HBOT. This is because there might be a potential increase in cerebral perfusion occurring during the HBOT treatment. HBOT might result in an elevation of arterial partial pressure of oxygen, leading to an increase in oxygen delivery to the brain (Calvert *et al.*, 2007). Several studies have shown that HBOT in children with ASD has shown statistically significant improvement in clinical symptoms (Rossignol *et al.*, 2012; Chungpaibulpatana *et al.*, 2008).

### F. Erectile Dysfunction

Penile blood flow disruption is caused by inadequate vascular perfusion is present in at least 60% of Erectile Dysfunction (ED) (Virag *et al.*, 1985). The first-line treatment used for ED relies on the vasodilation effect of phosphodiesterase-5 inhibitors (PDE5Is) (Bella *et al.*, 2015). However, this vasodilation is usually transient and dependent on the presence of adequate blood vessels within the corpora cavernosa (CC). HBOT has been shown to induce generation of new blood vessels (angiogenesis) in the brain and non-healing wounds. Therefore, studies are currently being carried out to be used in ED patients. One study has shown penile angiogenesis and improved erectile function (Hadanny *et al.*, 2018). Penile angiogenesis was also demonstrated by MRI analysis.

## VI. ADVERSE EFFECTS OF HBOT

Despite being a safe treatment method, HBOT does carry some risks, mainly due to an increased pressure and hyperoxia (Jacobs *et al.*, 1969).

Table 2. Provides a summarised contraindications for HBOT and should be known to providers of HBOT (Gawdi & Cooper, 2021).

Absolute contraindications	Untreated pneumothorax
Relative contraindications	<ul style="list-style-type: none"> <li>Chronic obstructive pulmonary disease.</li> <li>Asthma.</li> <li>Internal cardiac defibrillator.</li> <li>Patients on epidural infusion. <ul style="list-style-type: none"> <li>These devices may malfunction under pressure.</li> </ul> </li> <li>High fever or epilepsy. <ul style="list-style-type: none"> <li>This may decrease the seizure threshold, therefore making oxygen toxicity more likely.</li> </ul> </li> <li>The inability to equalise ears/sinuses. <ul style="list-style-type: none"> <li>This can be caused by previous surgery, radiation, or acute upper respiratory tract infection.</li> </ul> </li> <li>Claustrophobia.</li> <li>Previous Eye surgeries.</li> <li>History of spontaneous pneumothorax.</li> <li>Diabetes mellitus dependent on insulin therapy. <ul style="list-style-type: none"> <li>HBOT may induce hypoglycaemia.</li> </ul> </li> <li>Nicotine and caffeine addiction.</li> </ul>

## VII. CONCLUSION

HBOT has been proven to benefit many medical problems around the globe. It may also improve the quality of life of

patients. However, more research is still needed to expand the indications for HBOT.

## VIII. REFERENCES

- American Psychiatric Association, 2013, 'Diagnostic and statistical manual of mental disorders', Med Hypotheses, vol. 67, no. 2, pp. 216-228.
- Anon, US Navy diving manual revision 6, Scribd, viewed 25 February 2022 <<https://www.scribd.com/doc/8162578/US-Navy-Diving-Manual-Revision-6-PDF>>.
- AWC, L, Zaim, MR, Helmy, HH & Ramdhan, IMA 2014, 'Economic impact of managing acute diabetic foot infection in a tertiary hospital in Malaysia', Malaysian Orthopaedic Journal, vol. 8, no. 1, pp. 46-49.
- Barilaro, G, Masala, Parracchini, R, Lesu, C, Caddia, G, Sarzi-Puttini, P & Atzeni, F 2017, 'The Role of Hyperbaric Oxygen Therapy in Orthopedics and Rheumatological Diseases', Israel Medical Association Journal, vol. 19, no. 7, pp. 429-434.
- Bella, AJ, Lee, JC, Carrier, S, Benard, F & Brock, GB 2015, 'CUA practice guidelines for erectile dysfunction', Canadian Urological Association Journal, vol. 9, no. 1-2, p. 23.
- Bennett, MH, Feldmeier, J, Hampson, NB, Smee, R & Milross, C 2016, 'Hyperbaric oxygen therapy for late radiation tissue injury', Cochrane Database of Systematic Reviews.
- Boet, S, Leonardo, M, Olivia, CB, Cole, E, Pierre, L, Rodrigue, P, Michel, P, Marie-Anne, M & Michael, B 2020, 'Can



- preventive hyperbaric oxygen therapy optimise surgical outcome?' *European Journal of Anaesthesiology*, Publish Ahead of Print.
- Boinpally, H, Howell, RS, Mazzie, J, Slone, E, Woods, JS, Gillette, BM, Castellano & M, Gorenstein, S 2018, 'A Wolf in sheep's clothing: An unusual presentation of Diabetic Myonecrosis', *Advances in Skin & Wound Care*, vol. 31, no. 9, pp. 394–398.
- Boussuges, A, Blanc, P, Molenat, F & Sainty, JM 1996, 'Haemoconcentration in neurological decompression illness', *International Journal of Sports Medicine*, vol. 17, no. 05, pp. 351–355.
- Buettner, MF & Wolkenhauer, D 2007, 'Hyperbaric oxygen therapy in the treatment of open fractures and crush injuries', *Emergency Medicine Clinics of North America*, vol. 25, no. 1, pp. 177–188.
- Calvert, JW, Cahill, J & Zhang JH 2007, 'Hyperbaric oxygen and Cerebral Physiology', *Neurological Research*, vol. 29, no. 2, pp. 132–141.
- Chungpaibulpatana, J, Sumpatanarax, T, Thadakul, H, Chantharatreeerat, C, Konkaew, M & Aroonlimsawas, M 2008, 'Hyperbaric oxygen therapy in Thai autistic children', *J Med Assoc Thai*, vol. 91, no. 8, pp. 1232–1238.
- Cianci, P & Sato, R 1994, 'Adjunctive hyperbaric oxygen therapy in the treatment of Thermal burns: A review', *Burns*, vol. 20, no. 1, pp. 5–14.
- Cozene, B, Sadanandan, N, Gonzales-Portillo, B, Saft, M, Cho, J, Park, JP & Borlongan, CV 2020, 'An extra breath of fresh air: Hyperbaric oxygenation as a stroke therapeutic', *Biomolecules*, vol. 10, no. 9, p. 1279.
- Ditri, L, Yehuda, M, Reis, ND & Montanari, M 2006, 'Femoral head necrosis. Handbook on Hyperbaric Medicine', pp. 547–552.
- Efrati, S, Golan, H, Bechor, Y, & Faran, Y 2015, 'Hyperbaric oxygen therapy can diminish fibromyalgia syndrome – prospective clinical trial', *PLOS ONE*, vol. 10, no. 5.
- Feldmeier, JJ 2004 'Principles of wound management, Problem wounds: the irradiated wound. Wound Care Practice', Arizona: Best Publishing Company, pp. 369–88.
- Feldmeier, JJ 2008, 'Hyperbaric oxygen therapy for delayed radiation injuries', *Physiology and Medicine of Hyperbaric Oxygen Therapy*, pp. 231–256.
- Francis, A & Baynosa, RC 2017, 'Hyperbaric oxygen therapy for the compromised graft or flap', *Advances in Wound Care*, vol. 6, no. 1, pp. 23–32.
- Friedman, T, Menashe, S, Landau, G, Sherf, M, Wiser, I, Seligman, Y, Friedman, M, Hadanny, A, Efrati, S & Heller, L 2019, 'Hyperbaric oxygen preconditioning can reduce post abdominoplasty complications: A retrospective cohort study', *Plastic and Reconstructive Surgery - Global Open*, vol. 7, no. 10.
- Fujimura, T, Suzuki, H, Shiomori, T, Udaka & T, Mori 2007, 'Hyperbaric oxygen and steroid therapy for idiopathic sudden sensorineural hearing loss', *European Archives of Oto-Rhino-Laryngology*, vol. 264, no. 8, pp. 861–866.
- Gabb, G & Robin, ED 1987, 'Hyperbaric oxygen: A therapy in search of diseases', *Chest*, vol. 92, pp. 1074–1082.
- Gawdi, R & Cooper, JS 2021, 'Hyperbaric Contraindications. In: StatPearls', Treasure Island (FL): StatPearls Publishing, viewed 27 February 2022 <<https://www.ncbi.nlm.nih.gov/books/NBK557661/>>.
- Geurts, J, Hohnen, A, Vranken, T & Moh, P 2017, 'Treatment strategies for chronic osteomyelitis in low- and middle-income countries: Systematic Review', *Tropical Medicine & International Health*, vol. 22, no. 9, pp. 1054–1062.
- Goldman, RJ 2009, 'Hyperbaric oxygen therapy for wound healing and limb salvage: A systematic review', *PM & R*, vol. 1, no. 5, pp. 471–489.
- Gortvai, P, Louvois, JD & Hurley, R 1987, 'The bacteriology and chemotherapy of acute pyogenic brain abscess', *British Journal of Neurosurgery*, vol. 1, no. 2, pp. 189–203.
- Guo, S & DiPietro, LA 2010 'Critical review in oral biology & medicine: Factors affecting wound healing', *J. Dent Res*, vol. 89, no. 3, pp. 219–229.
- Hadanny, A, Lang, E, Copel, L, Meir, O, Bechor, Y, Fishlev, G, Bergan, J, Friedman, M, Zisman, A & Efrati, S 2018, 'Hyperbaric oxygen can induce angiogenesis and recover erectile function', *International Journal of Impotence Research*, vol. 30, no. 6, pp. 292–299.
- Hampson, NB, Holm, JR, Wereford-Brown, CE & Feldmeier, J 2011, 'Prospective assessment of outcomes in 411 patients treated with hyperbaric oxygen for chronic radiation tissue injury', *Cancer*, vol. 118, no. 15, pp. 3860–3868.
- Hardy, K 2008, 'The physics of Hyperbaric Oxygen therapy', *Physiology and Medicine of Hyperbaric Oxygen Therapy*, pp. 57–64.
- Harris, AL 2002, 'Hypoxia — a key regulatory factor in tumour growth', *Nature Reviews Cancer*, vol. 2, no. 1, pp. 38–47.
- Hart, GB, O'Reilly, RR, Broussard, ND, Cave, RH, Goodman, DB & Yanda, RL 1974, 'Treatment of burns with hyperbaric oxygen', *Surg Gynecol Obstet*, vol. 139, no. 5, pp. 693–696.
- Hedetoft, M, Bennett, MH & Hyldegagaard, O 2021, 'Adjunctive hyperbaric oxygen treatment for necrotising

- soft-tissue infections: A systematic review and meta-analysis', *Diving and Hyperbaric Medicine Journal*, vol. 51, no. 1, pp. 34–43.
- Henshaw, IN & Simpson, A 1857, 'Compressed air as a therapeutic agent in the treatment of consumption, asthma, chronic bronchitis and other diseases', Edinburgh: Sutherland and Knox.
- Ho, RCM, Cheng, W, Chua, ANC & Mak A 2012, 'Neuropsychiatric aspects of carbon monoxide poisoning: Diagnosis and management', *Advances in Psychiatric Treatment*, vol. 18, no. 2, pp. 94–101.
- Hopkins, RO & Woon, FL 2006, 'Neuroimaging, cognitive, and neurobehavioral outcomes following carbon monoxide poisoning', *Behavioral and Cognitive Neuroscience Reviews*, vol. 5, no. 3, pp. 141–155.
- Hughes, GB, Freedman, MA, Haberkamp, TJ & Guay ME 1996, 'Sudden sensorineural hearing loss', *Otolaryngologic Clinics of North America*, vol. 29, no. 3, pp. 393–405.
- Jacobs, EA, Winter, PM, Alvis HJ & Small SM 1969, 'Hyperoxygenation effect on cognitive functioning in the aged', *New England Journal of Medicine*, vol. 281, no. 14, pp. 753–757.
- JS, S-MJHSC, 'Hyperbaric treatment of Clostridial myositis and Myonecrosis', National Center for Biotechnology Information, viewed 25 February 2022 <<https://pubmed.ncbi.nlm.nih.gov/29763178/>>.
- Kaide, CG & Khandelwal, S 2008, 'Hyperbaric oxygen: Applications in infectious disease', *Emergency Medicine Clinics of North America*, vol. 26, no. 2, pp. 571–595.
- Kemmer, A, Stein, T & Hierholzer, C 2006, 'Persistent osteomyelitis', *Handbook on Hyperbaric Medicine*, pp. 429–449.
- Kim, HS, Choi, MH, Baek JH, Park, SJ, Lee, JC, Jeong, UH, Kim, SP, Kim HJ, Choi, YC, Lim, DW & Chung, SC 2015, 'Effects of 92% oxygen administration on cognitive performance and physiological changes of intellectually and developmentally disabled people', *Journal of Physiological Anthropology*, vol. 34, no. 1.
- Kindwall, EP & Hunt, TK 1995, 'Hyperbaric Medicine Practice', *Plastic and Reconstructive Surgery*, vol. 96, no. 4, p. 985.
- Kiralp, MZ, Uzun, G, Dincer, O, Sen, A, Yildoz, S, Tekin, L & Dursun, H 2009, 'A novel treatment modality for myofascial pain syndrome: Hyperbaric oxygen therapy', *Journal of the National Medical Association*, vol. 101, no. 1, pp. 77–80.
- Kocaman Ürütük, F 2020, 'Current approach to hyperbaric oxygen therapy', *Istanbul Medical Journal*, vol. 21, no. 4, pp. 234–241.
- Krishnamurti, C 2020, 'Historical aspects of hyperbaric physiology and medicine', *Respiratory Physiology*.
- Kutlay, M, Colak, M, Yildiz, S, Demircan, N & Akin, ON 2008, 'Stereotactic aspiration and antibiotic treatment combined with hyperbaric oxygen therapy in the management of bacterial brain abscesses', *Neurosurgery, Suppl.*, pp. 540–546.
- Leach, RM, Rees, PJ & Wilmshurst, P 1998, 'ABC of oxygen: Hyperbaric Oxygen therapy', *BMJ*, vol. 317, no. 7166, pp. 1140–1143.
- Lee, TH, Chang, WN, Su, T, Chang, HW, Lui, CC, Ho, JT, Wang, HC & Lu, CH 2007, 'Clinical features and predictive factors of intraventricular rupture in patients who have bacterial brain abscesses', *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 78, no. 3, pp. 303–309.
- Legrand, M, Barraud, D, Constant, I, Devauchelle, P, Donat, N, Fontaine, M, Goffinet, L, Hoffmann, C, Jeanne, M, Jonquieres, J, Leclerc, T, Lefort, H, Louvet, N, Losser, MR, Lucas, C, Pantet, O, Roquilly, A, Rousseau, AF, Soussi, S, Wiramus, S, Gayat, E & Blet, A 2020, 'Management of severe thermal burns in the acute phase in adults and children', *Anaesthesia Critical Care & Pain Medicine*, vol. 39, no. 2, pp. 253–267.
- Lew, DP & Waldvogel, FA 1997, 'Osteomyelitis', *New England Journal of Medicine*, vol. 336, no. 14, pp. 999–1007.
- Marcinkowska, AB, Mankowska, ND, Kot, J & Winkowski, PJ 2022, 'Impact of hyperbaric oxygen therapy on cognitive functions: A systematic review', *Neuropsychology Review*.
- Marx, RE, Johnson, RP & Kline, SN 1985, 'Prevention of osteoradionecrosis: A randomized prospective clinical trial of hyperbaric oxygen versus penicillin', *The Journal of the American Dental Association*, vol. 111, no. 1, pp. 49–54.
- McCarthy, CJ, Behraves, S, Naidu, SG & Oklu, R 2016, 'Air embolism: Practical tips for prevention and treatment', *Journal of Clinical Medicine*, vol. 5, no. 11, p. 93.
- McLoughlin, PL, Cope, TM & Harrison, JC 1999, 'Hyperbaric oxygen therapy in the management of severe acute anaemia in a Jehovah's witness', *Anaesthesia*, vol. 54, no. 9, pp. 891–895.
- Mesimeris, TA 2006, 'Compromised skin graft and Flap', *Handbook on Hyperbaric Medicine*, pp. 329–361.

- Michieli, P 2009, 'Hypoxia, angiogenesis and cancer therapy: To breathe or not to breathe?', *Cell Cycle*, vol. 8, no. 20, pp. 3291–3296.
- Moen, I & Stuhr, LE 2012, 'Hyperbaric oxygen therapy and cancer—A Review', *Targeted Oncology*, vol. 7, no. 4, pp. 233–242.
- Moon, RE 2019, 'Undersea and hyperbaric Medical Society: Hyperbaric Oxygen Therapy Indications:14<sup>th</sup> Edition'
- Moon, RE, Vann, RD & Bennett PB 1995, 'The physiology of decompression illness', *Scientific American*, vol. 273, no. 2, pp. 70–77.
- Mustafa, M, Iftikhar, M, Ibrahim, MY & Muniandy, RK 2014, 'Healthcare associated vancomycin-resistant enterococci', *IOSR Journal of Pharmacy (IOSRPHR)*, vol. 4, no. 7, pp. 18–24.
- Nemiroff, PM 1988, 'Differing opinions on hyperbaric oxygen therapy', *Chest*, vol. 94, no. 3, pp. 670–671.
- Price, EA & Schrier, SL 2008, 'Anemia in the elderly: Introduction', *Seminars in Hematology*, vol. 45, no. 4, pp. 207–209.
- Rajagopalan, S 2010, 'Crush injuries and the crush syndrome', *Medical Journal Armed Forces India*, vol. 66, no. 4, pp. 317–320.
- Ratzenhofer-Komenda, B, Favory, R, Welslau, W & Smolle-Juttner, FM 2006, 'Physiologic effects of hyperbaric oxygen on Oxygen Transport and tissue oxygen pressure', *Handbook on Hyperbaric Medicine*, pp. 49–73.
- Rauch, SD 2008, 'Idiopathic sudden sensorineural hearing loss', *New England Journal of Medicine*, vol. 359, no. 8, pp. 833–840.
- Rose, JJ, Wang L, Xu, Q, McTiernan, CF, Shiva, S, Tejero, J & Gladwin, MT 2017, 'Carbon Monoxide Poisoning: Pathogenesis, Management, and Future Directions of Therapy', *Am J Respir Crit Care Med*, vol. 195, no. 5, pp. 596–606.
- Rossignol, DA, Bradstreet, JJ, Dyke, KV, Schneider, C, Freedendfeld, SH, O'Hara, N, Cave, S, Buckley, JA, Mumper, EA & Frye, RE 2012, 'Hyperbaric oxygen treatment in autism spectrum disorders', *Medical Gas Research*, vol. 2, no. 1, p. 16.
- Rozali, A, Rampal, KG, Zin, BM, Sherina, MS, Khairuddin, H, Halim, MA & Sulaiman, A 2006, 'Development of Underwater and Hyperbaric Medicine in Malaysia', *Med J Malaysia*, vol. 61, no. 5, pp. 647–650.
- Rubin, P 1984, 'The franz buschke lecture: Late effects of chemotherapy and radiation therapy: A new hypothesis.', *International Journal of Radiation Oncology\*Biophysics*, vol. 10, no. 1, pp. 5–34.
- Savvidou, OD, Kaspilis, A, Bolia, LK, Chloros, GD, Goumenos, SD, Papagelopoulos, PJ & Tsiodras, S 2018, 'Effectiveness of hyperbaric oxygen therapy for the management of chronic osteomyelitis: A systematic review of the literature', *Orthopedics*, vol. 41, no. 4, pp. 193–199.
- Sheffield, PJ 1998, 'Measuring tissue oxygen tension: a review', *Undersea Hyper Med*, vol. 25, pp. 179–188.
- Sison-Martinez, J, Hendriksen, S & Cooper, JS 2022, 'Hyperbaric Treatment of Clostridial Mositis and Myonecrosis [Updated 2021]', *Treasure Island (FL): StatPearls Publishing*.
- Shafee, R 2021, 'A successful treatment of chronic migraine with hyperbaric oxygen therapy', *EMJ Neurology*.
- Strauss, MB & Garcia-Covarrubias, L 2008, 'Crush injuries', *Physiology and Medicine of Hyperbaric Oxygen Therapy*, pp. 427–449.
- Sutherland, AM, Clarke, HA, Katz, J & Katznelson, R 2016, 'Hyperbaric oxygen therapy: A new treatment for chronic pain? ', *Pain Practice*, vol. 16, no. 5, pp. 620–628.
- Thackham, JA, McElwain, DLS & Long, RJ 2008, 'The use of hyperbaric oxygen therapy to treat chronic wounds: A Review', *Wound Repair and Regeneration*, vol. 16, no. 3, pp. 321–330.
- Urutuk, FK 2020, 'Current Approach to Hyperbaric Oxygen Therapy', *Istanbul Med J*, vol. 21, no. 4, pp. 234–241.
- Vijayakumar, A, Pullagura, R & Thimmappa, D 2014, 'Necrotizing fasciitis: Diagnostic challenges and current practices', *ISRN Infectious Diseases*, pp. 1–8.
- Virag, R, Bouilly, P & Frydman, D 1985, 'Is impotence an arterial disorder?', *The Lancet*, vol. 325, no. 8422, pp. 181–184.
- Welslau, W 2006, 'Physics of hyperbaric pressure', *Handbook on Hyperbaric Medicine*, pp. 15–23.
- Yildiz, S, Uzun, G & Kiralp, MZ 2006, 'Hyperbaric oxygen therapy in chronic pain management', *Current Pain and Headache Reports*, vol. 10, no. 2, pp. 95–100.
- Yildiz, S, Kirapl, MZ, Akin, A, Keskin, I, Ay, H, Dursun, H & Cimsit, M 2004, 'A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy', *J. Int. Med. Res.*, vol. 32, pp. 258–262.
- Yu, R, Wang, B, Li, S, Wang, J, Zhou, F, Chu, S, He, X, Wen, X, Ni, X, Liu, L, Xie, Q & Huang, 2015, 'Cognitive enhancement of healthy young adults with hyperbaric oxygen: A preliminary resting-state fmri study', *Clinical Neurophysiology*, vol. 126, no. 11, pp. 2058–2067.

Zamboni, WA & Baynosa, RC 2008, 'Compromised grafts and flaps', *Physiology and Medicine of Hyperbaric Oxygen Therapy*, pp. 373–395.

Zumdahl, D 2002, 'In World of Chemistry (2<sup>nd</sup> ed.)', pp. 398-439.