

Hyperbaric oxygenation and COVID-19

An Overview

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Summary

As the SARS-CoV-2 (“COVID-19”) pandemic progressed evidence emerged that some patients are experiencing prolonged multiorgan symptoms and complications beyond the initial period of acute infection and illness.¹ Patients are presenting with physical, neurological and mental issues after COVID-19. Current treatment recommendations for Post-COVID-19 Syndrome/Long-COVID-19 (“Long-COVID”) is to provide supportive care and to manage symptoms as appropriate.

Hyperbaric oxygenation may be able to provide relief to some of these symptoms and form part of a care plan for Long-COVID patients. The following is merely an overview of the currently published information on Long-COVID and hyperbaric oxygenation and not intended as a therapeutic guide.

What is hyperbaric oxygenation?

Hyperbaric oxygenation/Hyperbaric Oxygen Therapy/HB02 Therapy/HBOT (“Hyperbaric oxygenation”) is breathing oxygen while under pressures exceeding 1 atmosphere absolute (“ATA”), thus enhancing the amount of oxygen dissolved in the body tissues. Hyperbaric oxygenation is standard treatment in a number of countries for a wide range of indications including air gas embolism, severe soft tissue infection (eg MRSA, necrotising fasciitis), chronic wounds and ulcers, late radiation injury, thermal burns, crush injuries and reperfusion injuries, cerebral oedema and certain neurological conditions, central retinal artery occlusion, compromised grafts/skin flaps, carbon monoxide poisoning and decompression illness.²

When a patient is given oxygen under pressure, haemoglobin is saturated, but the blood can be hyperoxygenated by dissolving oxygen within the plasma. Normally most oxygen carried in the blood is bound to haemoglobin, which is 97% saturated at standard pressure. Some oxygen, however, is carried in solution, and this portion is increased under hyperbaric conditions due to Henry's law. Because the oxygen is in solution, it can reach areas where red blood cells may not be able to reach and can also provide tissue oxygenation in the setting of impaired haemoglobin concentration or function.

Hyperbaric oxygenation also encourages vasoconstriction, angiogenesis, fibroblast proliferation/ collagen synthesis, and stem cell production. Hyperoxia in normal tissues causes vasoconstriction, but this is compensated by increased plasma oxygen content and microvascular blood flow. This vasoconstrictive effect does, however, reduce post-traumatic tissue oedema, which contributes to the treatment of crush injuries, compartment syndromes, and burns. Hyperbaric oxygenation is particularly effective against anaerobes and facilitates the oxygen-dependent peroxidase system by which leukocytes kill bacteria. Hyperbaric oxygenation is also used in clinical practice to treat inflammatory conditions and can reduce the inflammatory response.

Hyperbaric oxygenation utilises well established technology and it has been used to successfully treat a number of indications for many years. Most recently researchers in the field of hyperbaric medicine have produced a number of compelling manuscripts to address appropriate clinical indications for this technology.³ Nevertheless wholehearted acceptance of the science has been slow to follow for some indications.^{4 5} Furthermore, there is a great deal of divergence from country to country in usage and familiarity. For example in the Netherlands, Germany, France, Israel, Japan, South Korea, Russian and China it is very well established where as in the UK and Ireland it is less utilised.

What are the contraindications for hyperbaric oxygenation?

The safety of low-pressure hyperbaric oxygenation is relatively high. Side effects of hyperbaric oxygenation are mostly barotraumatic and rarely oxygen related. There is currently only one absolute contraindication to hyperbaric oxygen therapy, which is untreated pneumothorax. Placing a patient in a chamber and changing the pressure around them can

result in a tension pneumothorax occurring on ascent, which could quickly become life-threatening.

Relative contraindications include unhealed tympanic perforation, claustrophobia, congenital spherocytosis, chemotherapy with certain medications (bleomycin, cisplatin, doxorubicin, disulfiram) if chemotherapy is performed on the same day as session, and certain implanted devices (eg pacemakers - certain devices may not have been pressure tested). Other relative contraindications such as uncontrolled asthma⁶, chronic obstructive pulmonary disease, or bullous lung disease may increase a patient's risk of rare complications as a result of hyperbaric oxygenation. Individuals with such conditions may be better facilitated in hospital-based chambers where they can be appropriately monitored and supported. For a full list of contraindications, please refer to the appropriate literature.⁷

Background: Hyperbaric oxygenation and COVID-19

Hyperbaric oxygenation is currently being used off-label to treat COVID-19 pneumonia patients and Long-COVID in the USA and in other countries.⁸ This application has its origins in the demonstrated success in treatment with hyperbaric oxygenation of severe anaemia and carbon monoxide poisoning.⁹ The use of hyperbaric oxygenation for COVID-19 is a novel application of an existing and understood technology and there is a strong physiological and biological basic science case to support its use. Furthermore, hyperbaric oxygenation is already used in clinical practice to treat inflammatory conditions; the initial experimental and empirical data suggest that hyperbaric oxygenation may reduce inflammatory response in COVID-19.¹⁰

Many of the beneficial effects of hyperbaric oxygenation can be explained by improvement of tissue oxygenation, it is now understood that the combined action of hyperoxia and hyperbaric pressure triggers both oxygen and pressure sensitive genes, resulting in inducing regenerative processes including stem cells proliferation and mobilization with anti-apoptotic and anti-inflammatory factors.¹¹ For patients with COVID-19, hyperbaric oxygenation has been shown to mitigate the inflammatory reactions and to effectively deliver oxygen to patients.¹²

The Undersea and Hyperbaric Medicine Society ("UHMS") has adopted an evidence-based approach to the use of hyperbaric oxygenation for COVID-19 and in light of the current pandemic situation have made their COVID-19 resources publicly available. A more extensive discussion of mechanisms whereby hyperbaric oxygenation is likely to favourably impact the pathological features of COVID-19 is available on the UHMS website.¹³ A number of trials, case reports and reviews have also been published.¹⁴

A consistent finding from these reports is that hyperbaric oxygenation has been safe for acute COVID-19 despite concerns that this group of patients, who are maintained continuously on high FiO₂s (fractions of inspired oxygen), would be especially sensitive to pulmonary oxygen toxicity when a course of hyperbaric oxygenation was added to their oxygen load.¹⁵ Additionally, investigators report an almost instantaneous relief in fatigued patients labouring to breathe when placed in the hyperbaric chamber under pressure.¹⁶ They are observed to relax and even achieve some much-needed sleep due to the success of

hyperbaric oxygenation in delivering adequate oxygenation.¹⁷ Chest CTs taken before and after the hyperbaric oxygenation showed significant improvement and resolution of some of the lung lesions in each patient. The evidence and mechanism of hyperbaric oxygenation would suggest that it would have a similar impact on non-acute eg Long-COVID patients. There are a number of clinical trials registered investigating the use of hyperbaric oxygenation for COVID-19 and for Long-COVID.¹⁸

What is Long-COVID?

Long-COVID is a term to describe the effects of COVID-19 that persist for weeks or months beyond the initial illness and infectious period. More details of how many people are affected by Long-COVID are still emerging, but research from the UK (Office for National Statistics) suggests around 1/5 people who test positive for COVID-19 have symptoms for five weeks or longer. For around 1/10 people, they last twelve weeks or longer. There is growing awareness of the long-term impacts. As per the HSE literature, the physical problems include fatigue, reduced mobility, muscle and joint pain/weakness/stiffness, cough, breathlessness, gastrointestinal issues, and lack of sense of smell or taste. Neurological and mental issues after COVID-19 include insomnia, cognitive dysfunction (memory/concentration/speech issues - commonly referred to as “brain fog”), mood changes, anxiety, or depression.

Hyperbaric oxygenation and Long-COVID

Hyperbaric oxygenation has been studied and used to help people with similar symptoms to Long-COVID. Please see below the symptoms that hyperbaric oxygenation may be able to address.

- **Fatigue**

Fatigue is one of the most common symptoms reported by Long-COVID patients. Studies have shown that hyperbaric oxygenation decreases chronic fatigue syndrome and increases quality of life.¹⁹ While this study was on a small sample and did not have a control arm, it did demonstrate some promising results. Anecdotally, many users report better quality sleep after a session and better energy levels.

- **Muscle and Joint pain/Weakness/Stiffness**

Many Long-COVID patients report muscle and joint pain/weakness/stiffness. Hyperbaric oxygenation has been utilized and has recently shown promising results in the management of fibromyalgia and other chronic pain disorders. Hyperbaric oxygenation exhibits a significant anti-inflammatory effect through reducing production of glial cells and inflammatory mediators which results in pain alleviation in different chronic pain conditions.²⁰

To date, several randomised controlled trials have demonstrated the efficacy of hyperbaric oxygenation in decreasing the severity of symptoms and increasing the quality of life of fibromyalgia patients.²¹ Participants have reported improved pressure pain threshold,

endurance and functional capacity, as well as physical performance. Hyperbaric oxygenation may be able to relieve Long-COVID patients with similar pain symptoms.

- **Cough and Breathlessness**

Evidence suggests COVID-19 causes lung damage and long-term respiratory complications.²² The extent and severity of such complications of COVID-19 infection remain to be seen, but emerging data indicate that many patients experience persistent respiratory symptoms months after their initial illness. With COVID-19, there have been reported instances of CT imaging abnormalities even in recovered asymptomatic COVID-19 patients. It is as yet unknown what these changes mean long term, whether they will persist and form scar tissue or simply heal. However, it is theorised that this lung damage is a contributing factor to the shortness of breath/chest tightness and other pulmonary symptoms associated with Long-COVID.

Since inflammation can lead to fibrosis in several forms of interstitial lung disease, treatment that targets inflammation is key.²³ Hyperbaric oxygenation has an anti-inflammatory effect that may be able to help ease the lung inflammation caused by COVID-19.²⁴ In one of the early studies on hyperbaric oxygenation for COVID-19, the appearance of COVID-19 pneumonia on CT scans cleared in three to five days after the patients started hyperbaric oxygenation. According to the report, the density of the lung lesions appeared to reduce after hyperbaric oxygenation.²⁵

- **Gastrointestinal Issues**

Some Long-COVID patients are presenting with gastrointestinal complaints – lack of appetite, diarrhoea, vomiting and nausea. The physiology of these complaints in the context of Long-COVID is not yet fully understood and patients are currently being offered symptomatic treatment. Investigators have used hyperbaric oxygenation to treat Inflammatory Bowel Disease (“IBD”) including Crohn’s disease and Ulcerative Colitis. A 2012 systematic review concluded that hyperbaric oxygenation lowered markers of inflammation and oxidative stress and ameliorated IBD in both human and animal studies.²⁶ It is hypothesised that hyperbaric oxygenation may similarly be able to relieve some of the gastrointestinal symptoms of Long-COVID due to these physiological effects.

- **Lack of Sense of Smell or Taste**

COVID-19 causes a reduction in sense of smell and taste in many patients. The chemosensory deficits are one of the earliest symptoms of COVID-19, and sometimes the only symptom of COVID-19 in otherwise asymptomatic carriers.²⁷ The majority appear to recover their sense of smell and taste within 3 - 4 weeks, however for some it takes several weeks or months to recover. The mechanisms as to why people lose their sense of smell or taste are not yet fully understood. There is no treatment as yet. If the mechanism is neurological, hyperbaric oxygenation may speed up the healing process (see Cognitive Issues). However, there is only anecdotal evidence and limited case reports on hyperbaric oxygenation efficacy for this symptom.²⁸

- **Cognitive Issues**

Long-COVID patients frequently present with concentration impairment, memory decline and deterioration of cognitive function (brain fog). Hyperbaric oxygenation is used for concussion, brain injury and post-stroke.²⁹

There is currently a study underway in Israel investigating hyperbaric oxygenation for Post-COVID Syndrome focusing on the neurological symptoms.³⁰ COVID-19 can cause neuroinflammation, that might be prolonged and lead to signs of post-COVID-19 syndrome. One of the options to reverse hypoxia, reduce neuroinflammation and induce neuroplasticity is hyperbaric oxygenation. Hyperbaric oxygenation relieves hypoxia as the physiological effects of the therapy alters the concentration of oxygen in the plasma and assists haemoglobin to achieve full oxygen-carrying capacity. This helps the recovery of brain tissue.³¹ This experimental application of hyperbaric oxygenation could have promising results.

Some carbon monoxide poisoning patients will go on to develop delayed neuropsychiatric syndrome (“DNS”). This syndrome manifests as cognitive deficits, personality changes, movement disorders, and focal neurologic deficits. The deficits usually resolve after one year but may become permanent. Studies seem to indicate that hyperbaric oxygenation helps at reducing the risk of DNS by helping with the ischemia-reperfusion injury in the central nervous system (“CNS”).³² While the mechanism of injury and the cause of DNS after carbon monoxide poisoning is different from Long-COVID, it is of interest that hyperbaric oxygenation appears to relieve the symptoms caused by an ischemic insult to the brain and the CNS.

- **Mood Changes, Anxiety and Depression**

Many Long-COVID patients are presenting with mental health issues - mood changes, anxiety and depression. There are a limited number of small-scale studies looking at hyperbaric oxygenation and mental health (eg anxiety, depression and mood swings) in the context of recovery from other conditions.³³ The general trend is positive, however, these are mostly case studies on small samples and there is limited data available. In a case control study on the safety, feasibility, and effectiveness of hyperbaric oxygenation for mild traumatic brain injury and persistent Post-Concussion Syndrome, 75% of the subjects who had indicated significant anxiety before the study commenced, self-reported as no longer anxious afterwards and similar percentages reported cessation of panic attacks after treatment.³⁴ Notably, many participants in that study also reported improvement in their physical symptoms which may contribute to the improvement of their mental health symptoms. This may or may not be applicable to Long-COVID.

Conclusion

COVID-19 and its sequelae are an evolving situation and we are still learning about its impacts. Hyperbaric oxygenation is an established therapy with relatively few risks and contraindications. There is currently one active trial on hyperbaric oxygenation for Long-COVID and several positive anecdotal reports from hyperbaric centres around the world. Given its established success in treating hypoxia-induced tissue damage many of its exponents have extrapolated that hyperbaric oxygenation may also be of benefit in managing Long-COVID.

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