Review Article

Hyperbaric oxygen therapy: Can it be a novel supportive therapy in COVID-19?

Address for correspondence:
Dr. Muralidhar Kanchi, Department of Anaesthesia and Intensive Care, Narayana Hrudayalaya, #258/A, Bommasandra Industrial Area, Anekal Taluk, Bangalore, Karnataka - 560 099, India.
E-mail: muralidhar.kanchi.dr@narayanahealth.org

Submitted: 21-May-2020
Revised: 23-Jun-2020
Accepted: 02-Sep-2020
Published: 01-Oct-2020

Access this article online
Website: www.ijaweb.org
DOI: 10.4103/ija.IJA_613_20
Quick response code

Kirubanand Senniappan, Salome Jeyabalan, Pradeep Rangappa[1], Muralidhar Kanchi[2]

Department of Anaesthesia, Narayana Institute of Cardiac Sciences, Narayana Health, [1]Department of Intensive Care, Columbia Asia Hospitals, [2]Department of Anaesthesia and Intensive Care, Narayana Institute of Cardiac Sciences, Narayana Health, Bangalore, Karnataka, India

ABSTRACT

The coronavirus disease 2019 (COVID-19) is a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Although 85% of infected patients remain asymptomatic, 5% show severe symptoms such as hypoxaemic respiratory failure and multiple end organ dysfunction (MODS) requiring intensive care unit (ICU) admission with a mortality rate of about 2.8%. Since a definitive treatment is yet to be identified, preventive and supportive strategies remain the mainstay of management. Supportive measures such as oxygen therapy with nasal cannula, face mask, noninvasive ventilation, mechanical ventilation and even extreme measures such as extracorporeal membrane oxygenation (ECMO) fail to improve oxygenation in some patients. Hence, hyperbaric oxygen therapy (HBOT) has been proposed as a supportive strategy to improve oxygenation in COVID-19 patients. HBOT is known to increase tissue oxygenation by increasing the amount of dissolved oxygen in plasma. HBOT also mitigates tissue inflammation thus reducing the ill effects of cytokine storm in COVID-19 patients. Though there is limited literature available on HBOT in COVID-19 patients, considering the present need for additional supportive therapy to improve oxygenation, HBOT has been proposed as a novel supportive treatment in COVID-19 patients.

Key words: Adult, coronavirus, COVID-19, hyperbaric oxygenation, respiratory distress syndrome

INTRODUCTION

The outbreak of coronavirus disease (COVID-19) started as a zoonotic disease and was possibly transmitted to humans from the wet market in Wuhan, China.[1] It has affected more than 200 countries, infecting 43,35,709 people, and leading to the death of 3 lakh people worldwide as of May 10, 2020.[2] In India it has affected 33 states and union territories with a mortality rate of around 2.8%.[3] The human race has survived the past pandemics by endurance, exploring and sharing knowledge and similarly will find a way to win this war against COVID-19.

The novel coronavirus was initially reported to cause lower respiratory tract symptoms such as fever, dry cough and dyspnoea. Later, atypical presentations which include gastrointestinal symptoms like diarrhoea, vomiting and cardiac symptoms like palpitation, chest pain and sudden cardiac death have also been reported. The mortality rate is higher in the elderly age group as compared to the younger population and in those with associated comorbidities like coronary artery disease, diabetes, and hyperlipidaemia. A plethora of management strategies have been adopted across the globe to reduce the morbidity and mortality due to this devastating disease. The treatment options include usage of antiviral drugs (remdesivir, favipiravir, lopinavir),

How to cite this article: Senniappan K, Jeyabalan S, Rangappa P, Kanchi M. Hyperbaric oxygen therapy: Can it be a novel supportive therapy in COVID-19? Indian J Anaesth 2020;64:835-41.

antibacterial drugs (azithromycin), antiprotozoal drugs (hydroxychloroquine), antihelminth (ivermectin), steroids and vitamin C. Supportive strategies include oxygen supplementation through face mask, non-invasive ventilation, mechanical ventilation and extracorporeal membrane oxygenation (ECMO).[1]

PATHOPHYSIOLOGY OF COVID-19

The life cycle of the virus starts with its attachment to the angiotensin converting enzyme-2 (ACE 2) receptor on the host cell. Lungs have higher expression of ACE 2 receptors. Virus then enters the cell through endocytosis and initiates the production of viral proteins and m-RNA. The release of mature virions leads to the death of the host cell which is phagocytosed by dendritic cells and macrophages. This complex acts as antigen presenting cells, resulting in the stimulation of T cell immunity. The severe symptoms of COVID-19 are associated with lymphopenia and the increased plasma concentration of protein inflammatory cytokines including interleukin (IL-6, IL-10), tumour necrosis factor alpha (TNF alpha), granulocyte cell stimulating factor (GCSF) and monocyte chemo attractant protein (MCP1). IL-8 released in the infected lung tissue acts as a chemo attractant for neutrophils and T cells which induce lung injury resembling adult respiratory distress syndrome (ARDS). Additionally, the endothelial injury promotes thrombosis at the capillary level as evidenced by elevated D dimer and fibrinogen levels resulting in ventilation perfusion mismatch in the lungs.[4]

Gattinoni *et al*. described 2 types of ARDS in patients suffering from respiratory failure in Covid-19. Type-1 patients had normal or near normal lung compliance. In such patients, oxygenation did not improve with lung recruitment manoeuvres and high positive end-expiratory pressure (PEEP) during mechanical ventilation. Prone positioning also failed to improve the oxygenation in that subset of patients. These patients typically showed increased right to left shunting and ventilation perfusion (Va/Q) mismatch. The Va/Q mismatch may be due to loss of hypoxic pulmonary vasoconstriction (altered vascular activity) and micro thrombi in the pulmonary vasculature. This author reported that type-2 ARDS patients classically responded to mechanical ventilation with high PEEP and low tidal volume strategy which was about 20 to 30% of patients with respiratory failure in Covid-19.[5]

Another theory for respiratory failure with preserved lung mechanics proposes a compliment mediated microvascular injury and thrombosis in that group of COVID-19 patients. Examination of lung and skin histological specimens from five patients with severe COVID-19 pneumonitis and normal lung compliance predominantly showed pauci-inflammatory septal capillary injury and fibrin deposition. The classic ARDS histopathologic findings such as hyaline membrane changes were absent in all the specimens in this case series.[6]

Initiation of ECMO in COVID-19 patients with respiratory failure not responding to conventional therapy, though it improved oxygenation, led to development of MODS in some patients. Moreover, mortality rate in ECMO patients was higher when compared to conventionally treated patients. The extra corporeal circulation induced systemic inflammatory response in addition to viral inflammation, probably offsets the minimal benefit obtained by improvement in oxygenation achieved with ECMO.[7]

Hyperbaric oxygen therapy – any benefit?

At sea level (1 atmosphere absolute (ATA) = 760 mmHg), the partial pressure of oxygen in the alveoli is around 95–110 mmHg which can be calculated using the following formula:

Alveolar oxygen partial pressure (PAO_2) = FiO_2 (Pb- PH_2O) – $PaCO_2$ × (FiO_2 + (1- FiO_2)/R)

FiO_2 - fraction of inspired oxygen concentration
Pb - atmospheric pressure (1ATA = 760 mmHg)
PH_2O - partial pressure of water (45 mmHg)
$PaCO_2$ - partial pressure of carbon dioxide in blood
R – Respiratory quotient (0.8)

As the atmospheric pressure and inspired concentration of oxygen increase, the alveolar partial pressure increases proportionately. For treating hypoxia due to any cause, the inspired oxygen concentration can be increased using various oxygen delivery devices, thus increasing alveolar partial pressure of oxygen. The supplemental oxygen can be delivered at normal atmospheric pressure or at increased pressure called hyperbaric oxygen therapy (HBOT). Nasal cannula, facemask and facemask with reservoir bag deliver a varying inspired oxygen concentration, and hence are classified as variable performance devices. Venturi devices can deliver fixed concentration of inspired oxygen over varying flow rates and hence are called as fixed performance devices. Achieving 100% inspired oxygen concentration is not possible with these devices and also, they do not provide respiratory

assistance. The application of continuous positive airway pressure through well-fitting mask or helmet can deliver 100% inspired oxygen concentration and can assist respiration. Noninvasive and invasive mechanical ventilation provide both oxygen delivery and respiratory support.[8] These systems of oxygen delivery work at normal atmospheric pressure and oxygen delivery is limited by the inspired oxygen concentration, partial pressure of oxygen, degree of lung pathology and haemoglobin concentration. The intrinsic limitation of these oxygen delivery systems is their inability to further increase the oxygen content of blood once haemoglobin is maximally saturated with oxygen. Inspiring 100% oxygen at sea level has very minimal effect on the dissolved oxygen content in plasma, whereas much higher values are achieved with HBOT. Mc Mohan *et al*. demonstrated that the dissolved oxygen content of arterial blood at 1ATA (760 mmHg) with a subject breathing room air, was 0.3 ml/dl. When 100% oxygen at 3ATA (2280 mmHg) was applied, at the same arterial haemoglobin concertation and diffusion ratio, the dissolved arterial oxygen content increased to 4.6 ml/dl. This increase is almost 15 times of that achieved at 1ATA.[9] Thus for an increase of every 1ATA, the oxygen dissolved in plasma increases to about 1.8 ml/dl.[10] Similarly Gill *et al*. stated that when breathing room air, tissue oxygen tension was around 55 mmHg, which increased to 500 mmHg (around tenfold increase) on breathing 100% oxygen at 3ATA.[11] Thus HBOT increases alveolar partial pressure of oxygen and thus the oxygen delivery when conventional methods of oxygen delivery failed. Compared to mechanical ventilation, HBOT is noninvasive in nature and causes minimal discomfort to the patient. HBOT also improved oxygenation in patients with pneumonia when conventional therapies failed. Additionally, HBOT reduces inflammatory response in aspiration pneumonitis.[12]

The hyperbaric hyperoxia induced vasoconstriction leads to increased systemic vascular resistance (SVR). Through the baroreceptor reflex, the increased SVR reduces the heart rate and decreases the cardiac output.[13] The vasoconstriction causes shifting of fluid from periphery to the centre, thus causing volume overload of the heart, precipitating congestive heart failure in patients with poor reserve.[14] Pulmonary vascular resistance (PVR) decreases due to pulmonary vasodilation during HBOT therapy.[9]

Hypoxaemia can further worsen the lung injury by releasing proinflammatory cytokines from the hypoxic cells. HBOT-related increase in tissue oxygenation ameliorates this effect of hypoxia. It also reduces the expression of adhesion molecules (ICAM-1, BETA 2 INTEGRIN) on cells, thus preventing the activation of inflammatory cells.[15] Multi-organ dysfunction (MODS) due to any cause is associated with overexpression of toll like receptors (TLR), TLR2 and TLR4. These receptors bind to lipopolysaccharides (LPS) and mediate further inflammatory response. Early initiation of HBOT can mitigate this inflammation by reducing the expression of TLR2 and TLR4.[16] The reduced inflammation results in reduced tissue oedema and improved tissue oxygenation.[17] HBOT induced oxidative stress causes production of reactive oxygen species (ROS). The ROS have antimicrobial property by directly acting on DNA, RNA or lipid molecules [Figure 1].[16]

Novel corona virus gains access to body cells through ACE receptors including B lymphocytes. Through the process of transcription and translation, the host cell is modified to produce structural and non-structural proteins ORF3 and ORF10 of the novel corona virus. The secreted viral non-structural proteins such as ORF3 and ORF10 attack the beta chain of haemoglobin and release porphyrin molecule. This makes haemoglobin inefficient in oxygen binding thereby reducing its oxygen carrying capacity [Figure 2].[18]

The oxygen is carried in the blood mostly as bound to haemoglobin while a small amount is dissolved in plasma at sea level. The oxygen content of arterial blood is calculated as follows-

CaO_2 = (Haemoglobin (g/dl) × 1.38 ml O_2× % oxygen concentration) + (0.003 × PaO_2)

CaO_2 = oxygen content in arterial blood

PaO_2 = partial pressure of oxygen in arterial blood

From the above formula it is evident that the dissolved oxygen content can be increased independent of haemoglobin level just by increasing the partial pressure of inspired oxygen. Henry's law states that the amount of oxygen dissolved in the blood is directly proportional to the partial pressure of oxygen above the blood. HBOT increases the partial pressure of oxygen in the lungs which in turn increases the dissolved portion of oxygen in plasma. Thus, the haemoglobin independent mechanism of oxygen transport may increase tissue oxygen delivery in Covid-19 patients. This phenomenon is also made use of in treating severely anaemic patients (Jehovah's witness) using HBOT therapy.[19]

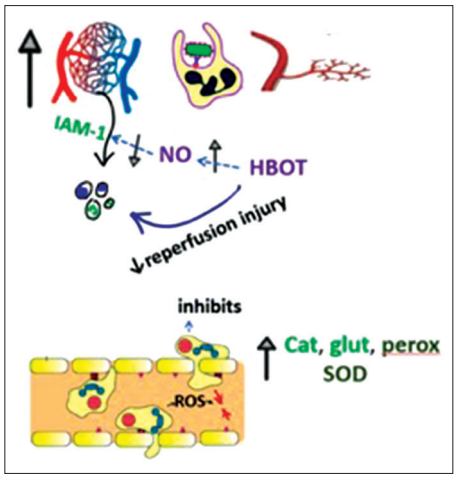

Figure 1: Mechanism of HBOT. Reduction of Nitric oxide (NO) due to inflammation causes vasoconstriction and expression of intercellular adhesion molecules (IAM-1) which aggravates the inflammation by attracting polymorphonuclear cells. HBOT increases NO level in injured tissue causing vasodilatation and suppression of inflammation. It also promotes phagocytosis by immune cells and also stimulates angiogenesis, thus helping in wound healing

Harch PG published the successful use of HBOT on COVID-19 patients with severe respiratory symptoms. The study was conducted in Wuhan Yangtze River shipping general hospital by Dr. Zhang Yangling. HBOT resulted in rapid relief of hypoxia related symptoms, correction of hypoxaemia, increased appetite, relief from headache and improvement in overall wellbeing. It also led to improved clinical objective parameters like arterial blood gas values, differential count, coagulation profile, liver function tests and clearance of lung pathology as evidenced by computed tomography (CT) scan imaging. By increasing the partial pressure of oxygen in alveoli, HBOT increases the amount of dissolved oxygen in the alveolar and inflammatory barrier, increases diffusion rate and the diffusion distance of oxygen. Thus, HBOT increases microcirculation and tissue oxygen delivery when compared to other oxygen delivery methods such as nasal cannula, face mask, non-invasive ventilation, invasive ventilation and ECMO [Figure 3].[20]

Thibodeaux K reported a case series of five COVID-19 patients with tachypnoea and desaturation who underwent HBOT therapy. This prevented endotracheal intubation and institution of mechanical ventilation in all the five patients with decrease in inflammation marker (D-dimer). An average of five cycles of HBOT at 2ATA, each cycle over a duration of 90 minutes was used. Among the five patients, three got discharged and two patients maintained adequate saturation with supplemental oxygen therapy via nasal cannula, at the time of this publication.[21]

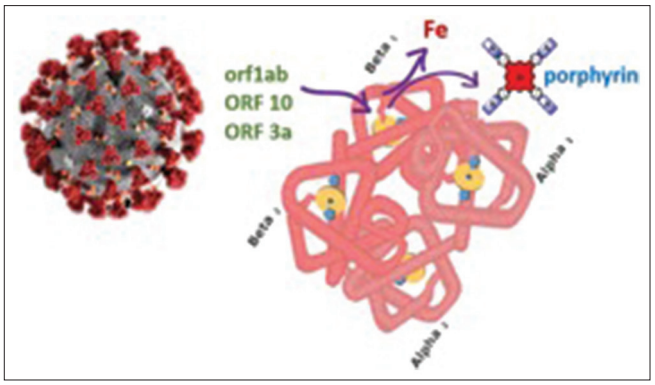

Figure 2: Proposed mechanism of hypoxia in COVID-19 due to dysfunctional haemoglobin

Guo D *et al*. reported a few cases of COVID-19 patients, with oxygen saturation of less than 93% with supplemental oxygen therapy who underwent HBOT. In these patients, arterial blood gas indices of oxygenation and leucocyte count improved with reduced D-dimer values and cholinesterase values after HBOT. Computed tomography of chest revealed that lung pathology was resolving in those patients. HBOT reduced the oxygen debt and the anti-inflammatory property reduced further tissue injury.[22]

Gorenstein *et al*. from Wintrope hospital, New York, reported initial outcome of an ongoing case control study of 20 cases treated with 2 ATA of hyperbaric oxygen therapy for 90 minutes daily and propensity matched controls. They found that subdistribution hazard ratio for time to death was 0.42 (p-value = 0.24, 95% CI of 0.10 to 1.79) when comparing cases treated with HBOT to propensity matched controls. Similarly, the in-hospital mortality rate and time to mechanical ventilation are higher in propensity matched control group comparing to cases treated with HBOT[23]

Though these studies had a limited sample size, it stimulated the HBOT enthusiasts across the world to explore the possibility of HBOT in treating COVID-19 patients. At present five clinical trials have been registered in the national clinical trial registry to evaluate HBOT usage in COVID-19 patients. The details of these trials can be seen in website www.clinicaltrials.gov and searched as hyperbaric oxygen and COVID-19.

The use of HBOT for a similar clinical situation dates back to 1918 when Dr. Orville Cunningham successfully used it to treat a dying patient during the Spanish flu pandemic. Another early use of hyperbaric chamber dates back to 1879 when Fontaine used it

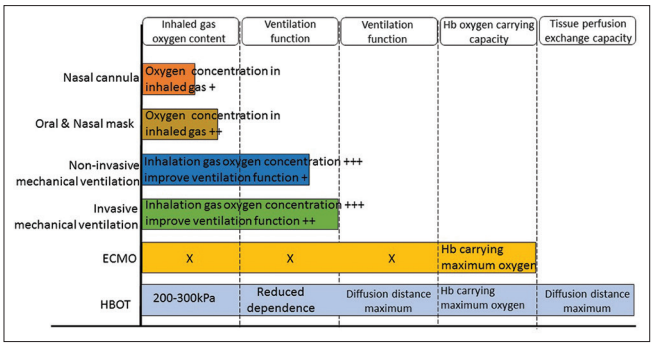

Figure 3: Effects of various oxygen therapies on inspired oxygen concentration, and on oxygen delivery to the tissues

to provide anaesthesia using nitrous oxide-oxygen mixture. Haldane demonstrated the use of pressurised oxygen chamber to improve oxygenation in carbon monoxide poisoning.[24]

Monoplace chambers are designed to accommodate only one person. The chamber is pressurised with oxygen. Oxygen flow across the chamber is laminar and the chamber is leakproof. Hence the risk of infection spread to the environment is negligible with this type of chamber. Oxygen delivery devices such as face masks and nasal cannula are not necessary as the chamber is pressurised with oxygen. Since HBOT is given in 90- to 120-minute sessions, multiple patients can be treated after appropriate disinfection of the chamber between each session. In the midst of COVID-19 pandemic with increased mortality among medical professionals, the monoplace HBOT chamber appears to be an attractive supportive treatment modality [Figure 4a].

Multiplace chambers are large enough to accommodate two or more patients and tenders at a time. Chamber is pressurised with air and the patients breathe oxygen through head tent, facemask, or endotracheal tube [Figure 4b]. Due to risk of infection spread to tenders and high cost of installation, multiplace chambers may not be the right choice to treat COVID-19 patients. Undersea and Hyperbaric Medical Society has published guidelines for safe use and disinfection of hyperbaric chambers-[25]

- Establishing hand wash station at the clinical entrance and ensuring regular hand washing
- After hand washing, all patients must wear a surgical mask till entering the hyperbaric chamber
- Limit the number of occupants in multiplace chambers so that one-meter distance can be maintained between the occupants

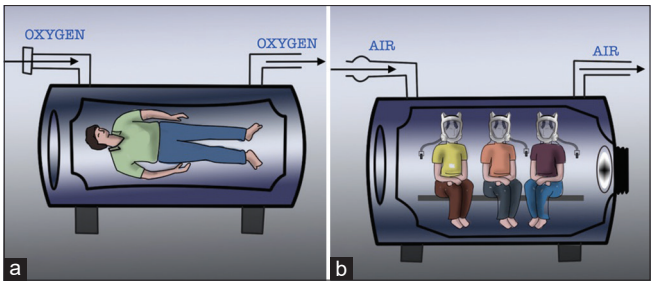

Figure 4: (a) Monoplace chamber pressurised with oxygen, patient is not required to use any hood/face, (b) Multiplace chamber pressurised with air and patient breathes oxygen through hood

- In multiplace chamber, ambient air isolation can be achieved by donning patient with hood or built-in-breathing system before closing the chamber door
- Staff/attendant inside the chamber should don appropriate personal protective equipment (PPE)
- To prevent breathing ambient air inside the chamber, air breaks can be avoided and chamber pressure can be maintained below 2ATA
- Regular disinfectant as per manufacturer recommendation can be used for chamber disinfection. All hoods and masks that have been used should be discarded.

How to monitor Covid-19 patients in hyperbaric chamber?

- Electrocardiogram, pulse-oximetry and temperature monitoring are routinely used in hyperbaric environment
- Automated external defibrillator (AED) paddles and external defibrillators pose a risk for fire accidents when activated in an environment with pressurised oxygen
- Non-invasive blood pressure monitoring (NIBP) can be used safely in multiplace chamber as the cuff and monitor are located inside the chamber. With NIBP cuff located inside the pressurised chamber and monitor outside, the motor should be strong enough to push air into the cuff against the pressure inside the chamber. Invasive blood pressure monitoring is safe to use in the hyperbaric environment
- Mainstream end tidal carbon-dioxide ($ETCO_2$) monitor is known to produce heat and so should not be used. When using side stream $ETCO_2$, gas flow through the sampling line should be monitored as the sample analyser is located outside the chamber and the pressure difference across the chamber can cause ventilator leak. Since ETCO2 displays the relative pressure, the

value should be multiplied by the ATA applied inside the chamber
- PO2 monitoring is a challenge as the super numeric values cannot be measured by ABG analysers. In multiplace chamber, blood gas analyser should be installed inside the chamber and for monoplace chamber, blood gas analysis should be done immediately after sampling since oxygen is readily lost from the sample with decompression
- If patient is endotracheally intubated, endotracheal tube cuff pressure should be continuously monitored since it is vulnerable to changes during compression and decompression
- Health care workers caring for suspected or proven COVID-19 patients should be educated in the appropriate handling of such patients and in the use of personal protective equipment.

With trained personnel and meticulous monitoring, hyperbaric therapy can be administered even to critically ill patients unless stringent precautions are taken. Moreover, HBOT does not interfere with other therapies used in treating COVID-19 patients.[26,27]

Complications of HBOT

Oxygen toxicity due to excess free radical generation, barotrauma to the middle ear, pneumothorax and inert gas uptake induced narcosis are the commonly reported complications of HBOT.[28]

SUMMARY

COVID-19 has become a serious threat to humanity despite the currently available advanced medical care. HBOT seems to be a promising supportive therapy with negligible side effects in treating COVID-19 patients. It has the additional advantage of less viral aerosolisation compared to other traditional ventilatory strategies used in improving oxygenation. More studies need to be done in this field before it can be recommended for the management of COVID-19 patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020;24:91-8.
2. Organization WH. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. World Health Organization. 2020. [cited on 2020 May 14]. Available from: https://covid19.who.int/?gclid=CjwKCAjwztL2BRATEiwAvnALcpJvfJoB2ZO9AW 4csc OjOPpuNNisqVVlTkpdslGJOuXSFkrhbLCafxo CjB0QAvD_BwE.
3. Mitra P, Misra S, Sharma P. COVID-19 pandemic in India: What lies ahead. Indian J Clin Biochem 2020;35:257-9.
4. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol 2020;215:108427.
5. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care 2020;24:154.
6. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, *et al*. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res 2020;220:1-13.
7. Zeng Y, Cai Z, Xianyu Y, Yang BX, Song T, Yan Q. Prognosis when using extracorporeal membrane oxygenation (ECMO) for critically ill COVID-19 patients in China: A retrospective case series. Crit Care 2020;24:148.
8. Standley TDA, Wheeler DW. Equipment for inhalation of oxygen and other gassess. In: Davey AJ, Diba A, editors. Ward's Anaesthetic Equipments. 6th edit. Elsevier; 2012. p. 207-23.
9. McMahon TJ, Moon RE, Luschinger BP, Carraway MS, Stone AE, Stolp BW, *et al*. Nitric oxide in the human respiratory cycle. Nat Med 2002;8:711-7.
10. Rao GSU. Current concepts in the intensive care management of neurosurgical patients. Indian J Anaesth 2008;5:494.
11. Gill AL, Bell CNA. Hyperbaric oxygen: Its uses, mechanisms of action and outcomes. QJM An Int J Med 2004;97:385-95.
12. Sahin SH, Kanter M, Ayvaz S, Colak A, Aksu B, Guzel A, *et al*. The effect of hyperbaric oxygen treatment on aspiration pneumonia. J Mol Histol 2011;42:301-10.
13. Demchenko IT, Zhilyaev SY, Moskvin AN, Krivchenko AI, Piantadosi CA, Allen BW. Baroreflex-mediated cardiovascular responses to hyperbaric oxygen. J Appl Physiol 2013;115:819-28.
14. Kirby JP, Snyder J, Schuerer DJE, Peters JS, Bochicchio GV. Essentials of hyperbaric oxygen therapy: 2019 review. Mo Med 2019;116:176-9.
15. Perng W-C, Wu C-P, Chu S-J, Kang B-H, Huang K-L. Effect of hyperbaric oxygen on endotoxin-induced lung injury in rats. Shock 2004;21:370-5.
16. Memar MY, Yekani M, Alizadeh N, Baghi HB. Hyperbaric oxygen therapy: Antimicrobial mechanisms and clinical application for infections. Biomed Pharmacother 2019;109:440-7.
17. Halbach JL, Prieto JM, Wang AW, Hawisher D, Cauvi DM, Reyes T, *et al*. Early hyperbaric oxygen therapy improves survival in a model of severe sepsis. Am J Physiol Integr Comp Physiol 2019;317:R160-8.
18. Wenzhong liu, Hualan L. COVID-19:Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism [Internet]. ChemRxiv; 2020 [cited 2020Sep13]. Available from: https://chemrxiv.org/articles/preprint/COVID-19_Disease_ORF8_and_Surface_Glycoprotein_Inhibit_Heme_Metabolism_by_Binding_to_Porphyrin/11938173/9.
19. Salmen M, Hendriksen S, Gorlin J, Leclaire M, Prekker ME. Oxygen delivery during severe anemia when blood transfusion is refused on religious grounds. Ann Am Thorac Soc 2017;14:1216-20.
20. Harch PG. Hyperbaric oxygen treatment of novel coronavirus (COVID-19) respiratory failure. Med Gas Res 2020;10:61-2.
21. Thibodeaux K, Speyrer M, Raza A, Yaakov R, Serena TE. Hyperbaric oxygen therapy in preventing mechanical ventilation in COVID-19 patients: A retrospective case series. J Wound Care 2020;29(Sup5a):S4-8.
22. Guo D, Pan S, Wang M, Guo Y. Hyperbaric oxygen therapy

may be effective to improve hypoxemia in patients with severe COVID-2019 pneumonia: Two case reports. Undersea Hyperb Med 2020;47:181-7.
23. Gorenstein SA, Castellano ML, Slone ES, Gillette B, Liu H, Alsamarraie C, *et al*. Hyperbaric oxygen therapy for COVID-19 patients with respiratory distress: Treated cases versus propensity-matched controls. Undersea Hyperb Med 2020 47:405-13 [Internet]. [cited 2020 Aug 16]. Online ahead of print. Available from: https://www.uhms.org/images/UHM-Journal/PRE-PROOF_-_HBO2_for_COVID_-_47-3_THIRD_QUARTER_2020_print_version_version_47-3.pdf.
24. Sekhar KC, Chakra Rao SSC. John Scott Haldane: The father of oxygen therapy. Indian J Anaesth 2014;58:350-2.
25. UHMS Guidelines for infection control, patient treatment, and staff safety considerations related to Hyperbaric Oxygen Therapy (HBO2) in monoplace and multiplace hyperbaric chambers during the novel coronavirus disease (COVID-19) outbreak-Undersea & Hyperbaric Medical Society [Internet]. [cited 2020 May 17]. Available from: https://www.uhms.org/covid-19-information/184-home-page-bulletins/899-uhms-guidelines-for-infection-control-patient-treatment-and-staff-safety-considerations-related-to-hyperbaric-oxygen-therapy-hbo2-in-monoplace-and-multiplace-hyperbaric-chambers-during-the-novel-coronavirus-disease-covid-19-outbreak.html.
26. Millar I. Hyperbaric intensive care technology and equipment. Diving Hyperb Med 2015;45:50-6.
27. Mathieu D, Ratzenhofer-Komenda B, Kot J. Hyperbaric oxygen therapy for intensive care patients: Position statement by the european committee for hyperbaric medicine. Diving Hyperb Med 2015;45:42-6.
28. Moon RE. Clinical care in extreme environments: At high and low pressure and in space. In: Miller RD, editor. Miller's Anesthesia. 8th ed. Philadelphia: Elsevier; 2015. p. 2685-7.