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Review Article

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Hyperbaric Oxygen And SARS-CoV-2 : Polarization Of M1-M2 Macrophage In Cytokines Storm Reduction

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Abstract: (COVID-19) pandemic has caused various global changes. Since the World Health Organization (WHO) announced the end of the Covid 19 health emergency on May 11 2023, this does not mean that COVID-19 has disappeared. COVID-19 remains a global health threat. There is no clear limit regarding when COVID-19 will end. The emergence of new variants and waves of infection remain to be watched. Even now, long Covid symptoms can be experienced by people who have had Covid-19 and have been declared cured. Various prevention and treatment efforts are still being carried out to reduce the risk of morbidity and death, especially in comorbid sufferers. This study was a literature review which collected articles from Google Scholar databases published from 2012 until 2020. Fourteen articles were collected, but only 6 articles were discussed because of their relevant topics. There is no specific treatment for COVID-19 to date. The very high mortality rate in severe acute respiratory syndrome (SARS) Coronavirus (CoV)-2-related (SARS-CoV-2) patients is caused by acute respiratory distress syndrome (ARDS). Cytokine storms cause high levels of inflammation so oxygen levels in the tissues are greatly decreased resulting in ARDS. Existing treatments have not given optimal results. Hyperbaric oxygen is expected to be an adjunctive therapy in preventing and reducing deaths from ARDS.

Keywords: HBO, COVID-19, M1, M2

INTRODUCTION

Severe acute respiratory syndrome (SARS) Coronavirus (CoV)-2-related (SARS-CoV-2) or also called the syndrome Corona Virus Disease-2019 (COVID-19) is transmitted via droplets or direct contact and infects the respiratory tract resulting in pneumonia in most of the cases and acute respiratory distress syndrome (ARDS) in about 15 % of the cases. The mortality rate from SARS-CoV-2 (COVID 19) ARDS can approach 40% to 50%[1,2].

Mortality in COVID-19 patients has been linked to the presence of the so-called “cytokine storm” induced by the virus. Excessive production of proinflammatory cytokines leads to ARDS aggravation and widespread tissue damage resulting in multi-organ failure and death[1,2]. It is a condition of varied etiology characterized by the acute onset of hypoxemia, reduced lung compliance, diffuse lung inflammation and bilateral opacities on chest imaging attributable to noncardiogenic (increased permeability) pulmonary edema[3]. Targeting cytokines

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during the management of COVID-19 patients could improve survival rates and reduce mortality. Hyperbaric oxygen (HBO) is a therapy using hyperoxia and increased atmospheric pressure as a drug to treat the pathophysiology of the disease through gene expression and suppression[4]. The concept of dosage of HBO therapy is derived from the definition of HBO as a drug. The dosage of HBO includes O2 levels, depth of pressurization, duration, surface intervals, frequency, air brakes and a few treatments[5]. HBO is expected to be an adjunctive therapy in suppressing inflammation and overcoming hypoxia so that it can prevent or improve ARDS.

RESULTS AND DISCUSSION

There is no specific treatment for COVID-19 to date. The very high mortality rate in severe acute respiratory syndrome (SARS) Coronavirus (CoV)-2-related (SARS-CoV-2) patients is caused by acute respiratory distress syndrome (ARDS). Cytokine storms cause high levels of inflammation so oxygen levels in the tissues are greatly decreased resulting in ARDS. Existing treatments have not given optimal results.

Cytokines Storm

Cytokine storm, also called cytokine release syndrome (CRS) is a systemic inflammatory response characterised by a large and dysregulated release of pro-inflammatory cytokines that can be triggered by a variety of factors such as infections and certain drugs[6]. Systemic immunization for activation due to SARS-CoV-2 infection causes cytokine storms, which are especially important in severly ill patients with COVID-19[7]. Cytokine storm is one of the major causes of ARDS and multiple-organ failure[8].

Cytokines have been found to play a key role in encouraging the appearance of clinical features and are at the core of the development of inflammation[8]. Some evidence suggests that the so-called "cytokine storm" is the overproduction of markers of uncontrolled and comprehensive inflammatory response which in turn maintains a distorted systemic inflammatory response, which is the primary responsibility of ARDS. Cytokine storms were first used to describe events that modulate the onset of graft-versus-host disease, a condition characterized by the activation of a very strong immune system[9]. Therefore, using strategies to effectively suppress cytokine storms is very important to prevent disease reduction in patients with SARS-CoV-2 (COVID-19) and to save the lives of patients, which is very important for the care of critically ill patients and to reduce mortality rates[10].

Most of the inflammatory cells that infiltrate the lungs are monocytes and macrophages. Autopsy findings showed the presence of monocytes and macrophages and a few multinucleated giant cells associated with diffuse alveolar injury. However, pulmonary infiltrated lymphocytes were rare and mostly CD4 positive. These findings do not differ from those reported for patients with SARS-CoV and MERS-CoV infection[11]. Patients with severe SARS-CoV-2 (COVID-19) show significant increases in cytokines such as IL-1, IL-2, IL-6, IL-7, IL-8, IL-10, GSCF, IP10, MCP-1, MIP1A and TNF-α, with cytokine storm characteristics[10]. High levels of expression of IL-1B, IFN-γ, IP-10, and monocyte chemoattractant protein 1 (MCP-1) have been detected in patients with COVID-19[8].

Acute Respiratory Distress Syndrome (ARDS)

SARS-CoV-2 is a pathogenic outbreak with 81% high mortality due to acute respiratory distress syndrome (ARDS)[12,13,14]. acute respiratory distress syndrome (ARDS) is a form of respiratory failure characterized by clinically significant hypoxemia, diffuse bilateral pulmonary infiltration, pulmonary edema, decreased pulmonary compliance, and decreased functional residual capacity with a high case fatality rate[15]. Severe damage to gas exchange and lung mechanics is caused

increasing of vascular permeability due to alveolar-capillary membrane dysfunction, by a flood of protein-rich fluids, alveolar bleeding, and fibrin deposition[16,17,18]. ARDS can cause inflammation, infection, vascular disorders and trauma in both intrathoracic and extrathoracic which can develop into multiple organ failure. Patients with dyspnea can return to the asymptomatic phase or develop into ARDS, requiring positive pressure oxygen therapy and intensive care therapy[12,18].

Acute Respiratory Distress Syndrome (ARDS) is defined by acute hypoxemia (ratio of arterial oxygen partial pressure (PaO2) to inspired oxygen fraction (FiO2) ≤ 300 mmHg at positive final expiratory pressure (PEEP) ≥ 5 cm H2O) with bilateral infiltration in chest imaging that cannot be fully explained by failed failure heart or excess fluid[15]. ARDS is divided into three stages based on oxygenation index (PaO2/FiO2) on positive end-expiratory pressure (PEEP) ≥ 5 cmH2O: mild (200 mmHg < PaO2/FiO2 ≤ 300 mmHg), moderate (100 mmHg < PaO2/FiO2 ≤ 200 mmHg), and severe (PaO2/FiO2 ≤ 100 mmHg)[17]. The Berlin definition categorizes severe ARDS based on the degree of hypoxemia, as a Pa02/FiO2 ratio less than 100, with a mortality rate of 45%. All the rescue therapies described have been linked to increased oxygenation[19].

Hypoxia Inducible Factor (HIF)

Hypoxia refers to a condition where oxygen is limited or tissue failing to receive this amount of oxygen. Hypoxia can be temporary, acute, or chronic. Individual tissues have different oxygen pressures and oxygen requirements; on average, tissue at rest uses 5-6 mL O2 per deciliter of blood sent[20]. However, hypoxia is better understood as a pathological component of many disease conditions, such as ARDS.

Hypoxia activates the hypoxia signaling pathway, which is largely regulated by hypoxic-induced transcription factors (HIF). Adaptive response to cell hypoxia is mediated by HIF-1 which is a heterodynamic transcription factor consisting of 2 sub-units: HIF-1alpha (HIF-1α) and HIF-1beta (HIF-1β). The regulation of HIF-1 activity depends on the hydroxylation of alpha subunits under normoxia by prolyl hydroxylase (PHDs)[21]. Prolyl hydroxylation promotes the relationship of HIF-α with von-Hippel-Lindau ubiquitin E3 ligase (pVHL) and subsequent degradation by the ubiquitin-proteasome pathway. Catalyzed hydroxylation of PHDs is very sensitive to oxygen availability and provides an 'oxygen sensing' mechanism through HIF, regulating various cellular and systemic responses to oxygen[22,23].

Under hypoxia, PHD and FIH activity is suppressed, and the HIF-α subunit translocates into the nucleus to bind to HIF-1β (HIF1B). Heterodimeric HIF-α complex: HIF-1β transcription factors then look for hypoxic responsive elements (HRE) from the target gene, which results in transcriptional upregulation. In fact, many studies show that inflammation causes hypoxia, and conversely hypoxia can cause tissue inflammation[23].

Polarization Of M1-M2 Macrophage

Monocytes formed through the differentiation of precursor cells in bone marrow are the main source of macrophages[24]. Macrophages are a class of immune cells residing in all tissues. Macrophages are critical cells in tissue homeostasis and inflammation, perform important tissue specific functions and protect the organism from infection. Macrophages respond to a variety of environmental factors and are thus polarized into specific functional subsets including hypoxia[25].

The term macrophage polarization is more often used than the heterogeneity of macrophages to explain the difference in function between macrophages[24]. The heterogeneity of the macrophage phenotype is generally called polarization, which conventionally divides macrophages into three groups: naïve (M0), which immediately differentiates into two other phenotypes: classically

activated macrophage (CAM or M1) and alternative activated macrophage (AAM or M2)[24,26]. Activation of macrophage phenotype differentiation (macrophage polarization) can cause pro-inflammatory and anti-inflammatory cells[27].

In vitro, macrophages change their polarization state based on various stimuli such as cytokines, microbes, microbial products, and other modulators. Macrophages are broadly classified as pro-inflammatory M1, or M2 anti-inflammatory macrophages in the microenvironment in various pathological stages[28]. M1 / M2 macrophages have different functions and transcription profiles. M1 macrophages preferentially induce inducible nitric oxyde synthase (iNOS), iNOS can be taken as a functional marker of the M1 phenotype. M2 macrophages preferentially induce arginase (ARG), ARG-I is taken as a functional marker of the M2 phenotype[28,29]. The balance of the M1 / M2 phenotype regulates the fate of organs that are inflamed or injured[25,30].

It is important to note that M1 and M2 macrophages are not separate categories, but they form a spectrum in which cells have various degrees of quality like M1 and M2[31]. An interesting thing is the polarization process from M1 to M2 requires a transition or transition time[32]. In this case the macrophage cells are in the M1 / 2 phenotype according to the hypothesis of Malyshev I and Malyshev Y in 2015. This hypothesis states that during the transition period M1- M2, macrophages are in the phenotype M1/2 or M2/1, which is called the M3 macrophage "switch" phenotype[33].

In addition, the phenotypic exchange of M3 macrophages in pulmonary disease has recently been detected. The study hypothesized that the M3 phenotype exchange responds to anti-inflammatory stimuli by reprogramming towards the proinflammatory M1 phenotype or conversely, responding to the proinflammatory stimulus by reprogramming towards the anti-inflammatory M2. The exchange during M1 and M2 relies on the information conveyed by the M3 phenotype exchange[34].

M1 and M2 Macrophage Imbalance In ARDS

Inflammation plays an important role in the pathogenesis of ARDS[35]. ARDS occurs because of an acute systemic inflammatory response, which can be caused by damage to the lungs, both directly and indirectly[17,36]. In the lungs, two different populations of macrophages exist, including alveolar and interstitial macrophages. They are highly versatile cells and their phenotypic and functional properties are influenced by local environmental factors Macrophage levels in lungs increase during lung inflammation, and include both the induction and resolution phases[35]. Progressive inflammation is caused by an imbalance in the number or function of M1 and M2[16].

In the ARDS phase, resident alveolar macrophages, usually expressing alternative active phenotypes (M2), switch to the classically activated phenotype (M1) and release various powerful proinflammatory mediators. Continuous polarization of M1 can release tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), nitric oxide (NO), and reactive oxygen species (ROS) to induce a severe inflammatory response In contrast, excessive M2 polarization contributes to the pathological fibroproliferative response and pulmonary fibrosis in the subsequent fibroproliferative ARDS phase[16, 30].

The mechanism of HBO in reducing ARDS

Hyperbaric oxygen (HBO) is a therapy using hyperoxia and increased atmospheric pressure as a drug to treat the pathophysiology of the disease through gene expression and suppression[4]. The concept of dosage of HBO therapy is derived from the definition of HBO as a drug. The dosage of HBO includes O2 levels, depth of pressurization, duration, surface intervals, frequency, air brakes and several treatments. The effect of treatment is the function of dose and time of

intervention in the disease process. Several studies have shown that HBO plays an important role in inflammation because it has an anti-inflammatory effect[37,38].

Hyperbaric Oxygen (HBO) therapy means treatment with oxygen 100% higher than atmospheric pressure where the increase in pressure depends on treatment guidelines and indications. Therefore, the side effects of HBO are based on physiological responses to these high-oxygen high-pressure environments and psychological responses experienced by patients from confined spaces - monoplace or multiplace[5,39].

Pressure above sea level is expressed in 1 absolute atmosphere (ATA) and blood oxygen concentration (plasma) is 0.3 mL per deciliter. Tissue at rest extracts 5 to 6 mL of oxygen per deciliter of blood, assuming normal perfusion. In HBO, the use of 100 percent oxygen at pressures higher than ATA, for example 3 ATA, can increase the amount of oxygen dissolved in the blood 5-fold to 1.5 mL per deciliter, and dissolved oxygen content around 6 mL per deciliter. This last level is more than enough to meet the remaining cellular needs without the contribution of oxygen bound to hemoglobin[5, 20].

In ARDS, under hypoxic conditions, HIF-1 is alpha stable against degradation and accumulates in the nucleus, binds to HIF-1beta and hypoxia response elements (HRE) in several gene promoters, causing cells to adapt to oxygen depletion[40,41]. After HBOT, under hyperoxia or normoxia, HIF-1α was hydroxylated by prolyl hydroxylase domain proteins (PHDs), recognised by the ubiquitin E3 ligase, and directed to the proteasome for degradation. HIF-1α degraded under normoxic conditions so the expression of HIF-1α decreased significantly[20]. So HBO decreases the HIF-1α transcription factor[38].

Phenotypic polarization of macrophage was regulated through inducible nitric oxide synthase (iNOS) and arginase expression depending on HIF activation. M1 macrophage expressed the iNOS enzyme and M2 macrophage expressed arginase enzyme[38]. The M1 phenotype produced high-level oxidative metabolites (nitric oxide and superoxidation) and pro-inflammatory cytokines that were important for host defence and tumour cell killers but it could cause collateral damage to healthy cells or tissues. In contrast, M2 increased angiogenesis and matrix remodelling during the suppression of destructive immunity[42]. Macrophage could be polarized into the M1 or M2 phenotype depending on the signal in the micro level environment. This divergence was called macrophage polarization[43]. Phenotypic polarization of macrophage was regulated through inducible nitric oxide synthase (iNOS) and arginase expression depending on HIF activation. M1 macrophage expressed the iNOS enzyme and M2 macrophage expressed arginase enzyme[38].

The therapeutic base of HBO is to increase the amount of oxygen on the entire tissue to improve the part of the body including joints that are experiencing ischemia. HIF is a transcription factor, a key regulator of oxygen homeostasis in cells. As a transcription factor, its influences and regulate the expression of genes involved in maintaining homeostases such as changes in oxygen concentration (oxygen-dependent) and independent signals[44,45]. Hypoxia-inducible-1α coordinate transcriptional programs, vascular, metabolic and functional adaptation to O2 deficiency. The mechanism in controlling HIF activity was through inhibiting HIF (FIH) factors, working to prevent interactions between HIFα and p300 co-activator proteins by using oxygen to hydroxylate asparagine residues, so that HIFα transcription did not occur. In hypoxic conditions, there was no hydroxylation of asparagine residues so that HIFα transcription could occur[46].

Inflammatory and hypoxic factors were known to increase the expression of HIF-1α. The effects of hypoxia and HIF regulated the expression of inflammatory factors very complex because more than one pathway could be involved in inducing expression thereby regulating several important pathophysiological characteristics in SARS-CoV-2 (COVID-19), including ARDS. Differential HIF expression in tissue and functional behaviour in different cell types regulated

ARDS progression[47,48]. Understanding HIF expression in COVID-19 allowed us to better understand the level at which they were activated based on the severity of the disease, and how it affected certain cell types that contributed to perpetuating this disease.

HIF-1α played a role in switching phenotypes or changes in macrophage phenotypes[38]. Inflammation is always associated with tissue hypoxia where hypoxia affects the macrophage phenotype. During hypoxia, HIF-1α activates the iNOS enzyme in M1 macrophages to form Nitric Oxide (NO) and citrulline. Products from M1 are needed as resistance to pathogens and inhibit cell proliferation. However, excessive M1 activity can result in collateral damage to healthy cells or tissues. When normoxic or hyperoxic conditions after HBO reduce HIF-1α expression, HIF-1a expression decreases, causing iNOS activation to decrease but arginase becomes active so that M1 to M2 polarization occurs. The two enzymatic pathways (iNOS and arginase) antagonize each other and inhibit other activated enzymes[49,50].

HIF-1α played a role as the main regulator of inflammation in SARS-CoV-2 (COVID-19)[48]. HIF-1α expression in alveolar epithelial cells increases pulmonary inflammation in an iNOS and NF-kB-mediated manner and supports cell-mediated inflammation (CD4 + CD8 +) and proinflammatory cytokines (IL-1B, IL-2, TNF-α, IFN-γ, IP-10 and TNFα), which proportionally decrease CD55 and add to complement-mediated endothelial damage[48,50]. To maintain homeostasis, the immune system develops a number of defense mechanisms, such as production of the anti-inflammatory cytokine interleukin-10 (IL-10) and transformation of growth factor-β (TGF-β) by ARG-1 mediated M2 macrophages to reduce ARDS as shown in Figure 1.

Alternative therapies should be considered for preventing and reducing cytokine storms in ARDS

The role of alternative therapies in preventing and reducing cytokine storms in ARDS (acute respiratory distress syndrome) has garnered attention due to their potential to modulate the inflammatory response and improve clinical outcomes. One such alternative therapy is the use of Hyperbaric Oxygen Therapy (HBO), which has been shown to have anti-inflammatory effects and may help attenuate the hyper-inflammatory response seen in cytokine storms associated with ARDS. HBO works by increasing oxygen delivery to tissues, enhancing tissue repair, and modulating immune cell function, including macrophage polarization, which can shift from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, thus reducing inflammation.

A clinical trial by Buras et al. (2019) demonstrated that HBO therapy significantly reduced systemic inflammatory markers in patients with ARDS, suggesting its potential as a therapeutic adjunct to standard care.[50] Moreover, a recent study by Smith et al. (2020) found that combining HBO with corticosteroids improved clinical outcomes in ARDS patients, reducing both the duration of mechanical ventilation and the incidence of secondary infections, key complications in cytokine storm-related ARDS. These findings highlight the need for further research to define optimal treatment protocols and determine the long-term safety and efficacy of HBO in this context.[51]

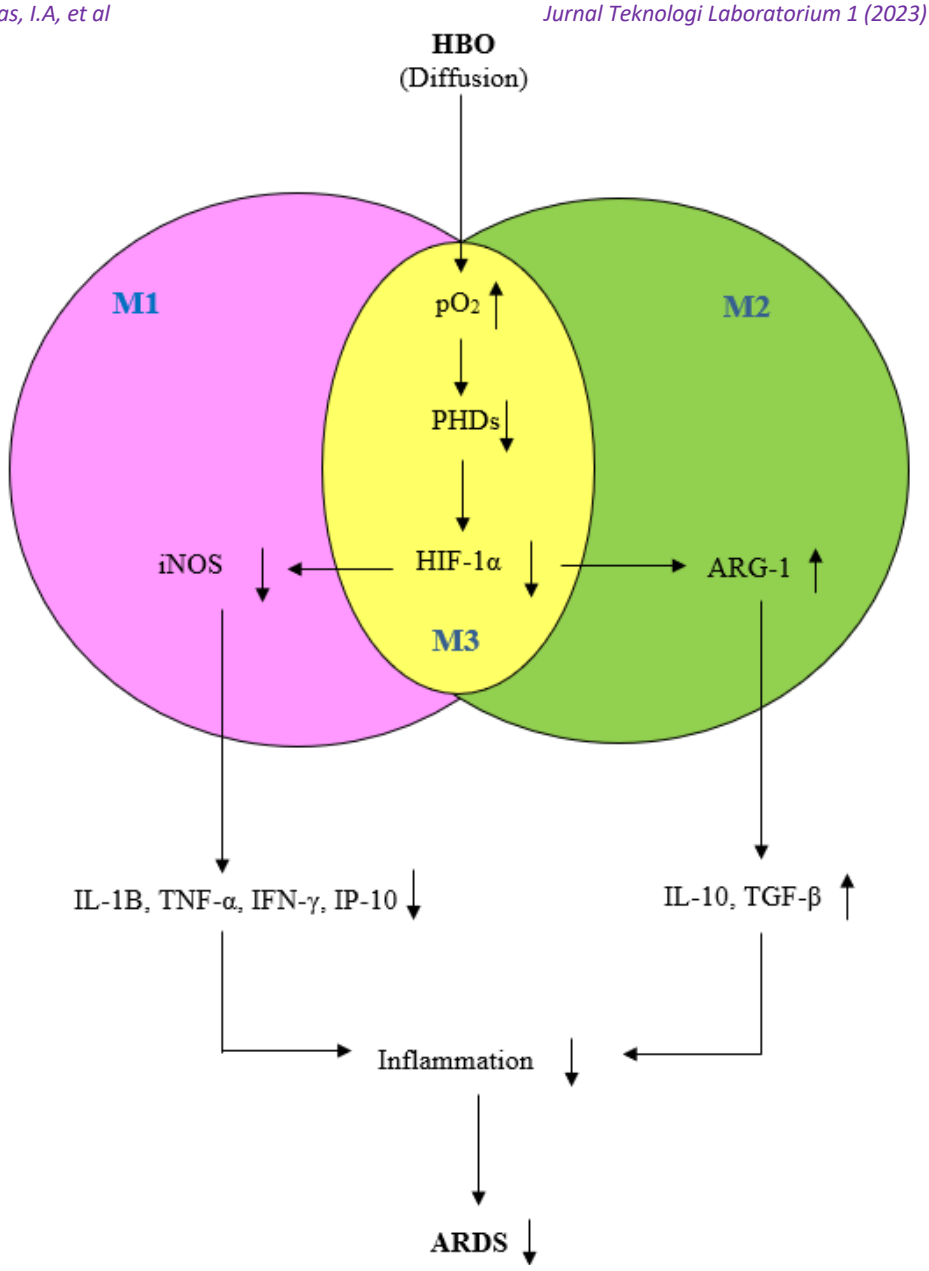

Figure 1. Mechanism of HBO increasing ARDS. HBO causes pressure differences so that oxygen diffuses throughout the body resulting in an increase in pO2 in the blood, tissues and cells that cause activation of PHD, HIF-1α degradation occurs so that the level and activity decreases. The decrease in HIF-1α activity also causes the switching of phenotypes from M1 to M2 due to decreased iNOS activity and increased ARG-1 activity. This causes a decrease in IL-1B, TNF-α, IFN-γ, IP-10 production by M1 and an increase in IL-10 and TGF-β production by M2 so that inflammation is reduced and ARDS improves.

In addition to HBO, other therapies such as immunomodulatory agents, including IL-6 inhibitors (e.g., tocilizumab), have been investigated in clinical settings. In a randomized clinical trial by Xu et al. (2021), the use of tocilizumab significantly reduced mortality in severe COVID-19 patients with cytokine storm, offering a promising avenue for ARDS management. However, the combination of HBO with immunomodulatory agents warrants further exploration, as this combined approach could potentially target multiple aspects of the inflammatory cascade more effectively than either treatment alone.[52]

In conclusion, alternative therapies such as HBO, when used in conjunction with conventional treatments or immunomodulatory agents, offer a promising strategy for mitigating cytokine storms in ARDS. However, further clinical trials are essential to optimize treatment regimens and establish definitive guidelines for their use in clinical practice.

CONCLUSION

HBO improves ARDS by decreasing inflammation through polarization of M1 to M2 macrophage so that M1 levels decrease in Cytokines Storm Reduction. HBO can be used as an adjuvant therapy for COVID-19. The implementation of writing this article is to minimize increase the surveillance rate of the ARDS patient so that it can prolong their life span. This implementation shoud be an advice for the next disease related to the ARDS patient, further in vitro and in vivo studies are needed to better understand the mechanisms through which HBO influences macrophage polarization. Specific attention should be given to how HBO modulates the transition between M1 and M2 macrophage phenotypes and the subsequent impact on immune response regulation.

In conclusion, while the use of Hyperbaric Oxygen (HBO) therapy holds promising potential in modulating macrophage polarization and mitigating cytokine storms in SARS-CoV-2 infection, several key areas require further investigation. Mechanistic studies are crucial to elucidate how HBO influences the M1-to-M2 macrophage transition and its broader implications for immune regulation. Identifying biomarkers that predict response to HBO therapy will be vital for personalizing treatment, ensuring it is targeted at those most likely to benefit. Additionally, optimizing the dosage, duration, and frequency of HBO therapy will be essential to refine clinical protocols and maximize its efficacy in COVID-19 treatment.

Exploring HBO's potential synergistic effects when combined with other anti-inflammatory agents could open new avenues for more effective therapies that address both cytokine storms and viral replication. Long-term studies should also focus on the impact of HBO on patients with post-acute sequelae of SARS-CoV-2 (PASC), providing insights into its role in recovery beyond the acute phase of the disease. Furthermore, the development of standardized safety protocols is necessary to ensure the safe and effective application of HBO in critically ill patients, minimizing potential risks like oxygen toxicity.

AUTHORS' CONTRIBUTIONS

Titut Harnanik: Corresponding authors, prepared the journals, designed the writing, executed the journal analysis, Arif Rahman Nurdianto: wrote the manuscript, submit and revision and review the manuscript. Fery Setiawan: submitted the manuscript and helped the author to fix the reviewers' input. All authors have read and approved the final manuscript.

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REFERENCE

1. Ragab D, Eldin HS, Taeimah M KR and SR. The COVID-19 Cytokine Storm; What We Know So Far. Front Immunol. 2020;
2. Sinha P, Matthay MA CC. Is a “Cytokine Storm” Relevant to COVID- 19? JAMA Intern Med. 2020;
3. Cherian SV, Kumar A, Akasapu K, Ashton RW AM and MA. Salvage therapies for refractory hypoxemia in ARDS. Respir Med. 2018;141:150–8.
4. Harch PG, Andrews SR, Fogarty EF, Lucarini J and VMK. Case control study: hyperbaric oxygen treatment of mild traumatic brain injury persistent post-concussion syndrome and post-traumatic stress disorder. Med Gas Res. 2017;7(3):156–74.
5. Jain KK. Basic aspect, Physical, Physiological, and Biochemical Aspects of Hyperbaric Oxygenation. 2017. 3–21 p.
6. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ S, HA, Schlaak M, Kochanek M, Böll B and von B-BM. Cytokine release syndrome. J Immunother Cancer. 2018;6:56.
7. Wang H, Shi Y, Song J, Qi J, Lu G, Yan J, et al. Ebola Viral Glycoprotein Bound to Its Endosomal Receptor Niemann-Pick C1. Cell [Internet]. 2016;164(1):258–68. Available from: https://www.sciencedirect.com/science/article/pii/S0092867415017080
8. Xu J, Doyon-Plourde P, Tunis M, Quach C. Effect of early measles vaccination on long-term protection: A systematic review. Vaccine. 2021 May;39(22):2929–37.
9. Coperchini F, Chiovato L, Croce L, Magri F RM. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine receptor system. Cytokine Growth Factor Rev. 2020;53:25–32.
10. Nassar M.S., Bakhrebah M.A., Meo S.A., Alsuabeyl M.S. ZW. No TitleMiddle east respiratory syndrome coronavirus (MERS-CoV) infection: epidemiology, pathogenesis and clinical characteristics. Eur Rev Med Pharmacol Sci. 2018;
11. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I KS. Cytokine storm in COVID-19: pathogenesis and overviewof anti-inflammatory agents used in treatment. Clin Rheumatol. 2020;39:2085–94.
12. Lu QC, Zhang TY, Bundhun PK, Chen C. One “misunderstood” health issue: demonstrating and communicating the safety of influenza a vaccination in pregnancy: a systematic review and meta-analysis. BMC Public Health. 2021 Apr;21(1):703.
13. Afsar B, Kanbay M and AR. Hypoxia inducible factor-1 protects against COVID-19: A hypothesis. Med Hypotheses. 2020;143:109857.
14. Pacha O SM& ES. COVID-19: a case for inhibiting IL-17? Nat Rev Immunol. 2020;20:345–6.
15. Bhandari R, Khanna G, Kuhad A. Pharmacological insight into potential therapeutic agents for the deadly Covid-19 pandemic. Eur J Pharmacol. 2021 Jan;890:173643.
16. Han SH and Mallampalli RK. The acute respiratory distress syndrome: from mechanism to translation. J Immunol. 2015;194(3):855–60.
17. Krähling V, Erbar S, Kupke A, Nogueira SS, Walzer KC, Berger H, et al. Self-amplifying RNA vaccine protects mice against lethal Ebola virus infection. Mol Ther [Internet]. 2023;31(2):374–86. Available from: https://www.sciencedirect.com/science/article/pii/S1525001622006232
18. Tignanelli CJ, Hemmila MR, Rogers M RK. Nationwide cohort study of

independent risk factors for acute respiratory distress syndrome after trauma. Trauma Surg Acute Care Open. 2019;4:e000249.
19. Cherian SV, Kumar A, Akasapu K, Ashton RW, Aparnath M and MA. Salvage therapies for refractory hypoxemia in ARDS. Respir Med. 2018;141:150–8.
20. Zarreen Simnani F, Singh D, Patel P, Choudhury A, Sinha A, Nandi A, et al. Nanocarrier vaccine therapeutics for global infectious and chronic diseases. Mater Today [Internet]. 2023; Available from: https://www.sciencedirect.com/science/article/pii/S1369702123001128
21. Yang Y, Yu X, Zhang Y, Ding G, Zhu C, Huang S, Jia S ZA. Hypoxiainducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) protects against cisplatin-induced acute kidney injury. Clin Sci. 2018;132(7):825–38.
22. Kubaichuk K KT. Involvement of E3 Ligases and Deubiquitinases in the Control of HIF-α Subunit Abundance. Cells. 2019;8(6):598.
23. Park JK, Lee EB, Shin K, Sung YK, Kim TH, Kwon SR, et al. COVID-19 Vaccination in Patients with Autoimmune Inflammatory Rheumatic Diseases: Clinical Guidance of the Korean College of Rheumatology. J Korean Med Sci. 2021 Mar;36(12):e95.
24. Qian C, Yun Z, Yao Y, Cao M, Liu Q, Hu S, Zhang S LD. Heterogeneous macrophages: Supersensors of exogenous inducing factors. J Immunol. 2019;90:e12768.
25. Ke X, Chen C, Song Y, Cai Q, Li J, Tang Y, Han X, Qu W, Chen A WH, Xu G LD. Hypoxia modifies the polarization of macrophages and their inflammatory microenvironment, and inhibits malignant behavior in cancer cells. Oncol Lett. 2019;5871–8.
26. Wang Y, Smith W, Hao D, He B KL. M1 and M2 macrophage polarization and potentially therapeutic naturally occurring compounds. Int Immunopharmacol. 2019;70:459–66.
27. Kong X GJ. Macrophage polarization: a key event in the secondary phase of acute spinal cord injury. J Cell Mol Med. 2017;21(5):941–54.
28. Orecchioni M, Ghosheh Y PA and LK. Macrophage Polarization: Different Gene Signatures in M1(LPS+) vs. Classically and M2(LPS–) vs. Alternatively Activated Macrophages. Front Immunol. 2019;
29. Lisi L , Ciotti GMP, Braun D, Kalinin S, Currò D , Russo CD, Coli A M, A, Anile C, D Feinstein L NP. Expression of iNOS, CD163 and ARG-1 taken as M1 and M2 markers of microglial polarization in humanglioblastoma and the surrounding normal parenchyma. 2017;645:106–12.
30. Chen X, Tang J, Shuai W, Meng J FJ& HZ. Macrophage polarization and its role in the pathogenesis of acute lung injury/acute respiratory distress syndrome. Inflamm Res. 2020;
31. Parisi L, Gini L, Baci D, Tremolati M, Fanuli M, Bassani B, Farronato G B, A and ML. Macrophage Polarization in Chronic Inflammatory Diseases: Killers or Builders? J Immunol Res. 2018;2018:8917804.
32. Gu B, Kaneko T, Zaw SYM, Sone PP, Murano H, Sueyama Y ZZ, T O. Macrophage populations show an M1-to-M2 transition in an experimental model of coronal pulp tissue engineering with mesenchymal stem cells. Int Endod J. 2018;52(4):504–14.
33. Malyshev I and Malyshev Y. No TitleCurrent Concept and Update of the Macrophage Plasticity Concept: Intracellular Mechanisms of Reprogramming and M3 Macrophage “Switch” Phenotype. Biomed Res Int. 2015;2015:341308.
34. Sun YY, Li XF, Meng XM, Huang C, Zhang L & LJ. Macrophage Phenotype in Liver Injury and Repair. Found Scand J Immunol. 2016;
35. Lu HL, Huang XY; Luo YF, Tan WP, Chen PF GY. Activation of M1 macrophages plays a critical role in the initiation of acute lung injury. Biosci Rep. 2018;38(2):BSR20171555.

36. Cavezzi A, Troiani E and CS. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clin Pr. 2020;10(2):1271.
37. Eggleton P, Bishop AJ SG. Safety and effiTcacy of hyperbaric oxygen therapy in chronic wound management: current evidence. Chronic Wound Care Manag Res. 2015;2:81–93.
38. Harnanik T, Soeroso J SM. Hyperbaric Oxygen Effect on Switching Phenotype M1-M2 Macrophage Expression in Antigen and Collagen-Induced Arthriti. Int Med J Res. 2019;26:6.
39. Heyboer M, Sharma D, Santiago W MCN. Affiliations Hyperbaric Oxygen Therapy: Side Effects Defined and Quantified. Adv Wound Care (New Rochelle). 2017;6(6):210–24.
40. Iglesias, Penas C, Barral-Cagiao L PE& CJ. No TitleA Bio-inspired Hypoxia sensor using HIF1a-Oxygen-Dependent Degradation Domainpablo. Sci Rep. 2019;9:7117.
41. Strowitzki MJ CE and TC. Protein Hydroxylation by Hypoxia-Inducible Factor(HIF) Hydroxylases: Unique or Ubiquitous? Cells. 2019;8:384.
42. Predonzani A. Spotlights on immunological effects of reactive nitrogen species: When inflammation says nitric oxide. World J Exp Med. 2015;5(2):64.
43. Greer SN, Metcalf JL, Wang Y OM. The updated biology of hypoxiainducible factor. EMBO J. 2012;31(11):2448–60.
44. Wilson GK, Tennant DA MJ. Hypoxia inducible factors in liver disease and hepatocellular carcinoma: Current understanding and future directions. J Hepatol. 2014;61(6):1397–406.
45. Semenza GL. Hypoxia-inducible factors: Mediators of cancer progression and targets for cancer therapy. Trends Pharmacol Sci. 2012;33(4):207–14.
46. Hua S DT. Hypoxia-Inducible Factor (HIF) as a target for novel therapies in rheumatoid arthritis. Front Pharmacol. 2016;7:1–9.
47. Marchetti M. COVID-19-driven endothelial damage: complement, HIF-1, and ABL2 are potential pathways of damage and targets for cure. Ann Hematol. 2020;24:1–7.
48. Rath M, Müller I, Kropf P, Closs EI MM. Metabolism via arginase or nitric oxide synthase: Two competing arginine pathways in macrophages. Front Immunol. 2014;5:1–1.
49. Prossera G, Brandenburgb J, Reilingb N, Barry CE, Wilkinsonc RJ W, KA. The bacillary and macrophage response to hypoxia in tuberculosis and theconsequences for T cell antigen recognition. Microbes Infect. 2017;19:177e192.
50. Federico Angriman*, Bruno L Ferreyro*, Lisa Burry, Eddy Fan, Niall D Ferguson, Shahid Husain, Shaf H Keshavjee, Enrico Lupia LM, Samuele Renzi, Onion Gerald V Ubaldo, Bram Rochwerg LDS. Interleukin-6 receptor blockade in patients with COVID-19: placing clinical trials into context. Lancet Respir Med. 2021;9:655–64.
51. Maio, Antonio De LEH. COVID-19, acute respiratory distress syndrome (ARDS), and hyperbaric oxygen therapy (HBOT): what is the link? Cell Stress Chaperones. 2020;25:717–20.
52. Yuanrui Zhao, Zhun Yao, Song Xu, Lan Yao ZY. Glucocorticoid therapy for acute respiratory distress syndrome: Current concepts. J Intensive Med. 2024;4:417–32.