COVID-19: Hypoxia, inflammation and immune response

Coronaviruses are an extensive family of viruses that can cause disease in both animals and humans. In humans, different coronaviruses cause respiratory infections that can range from the common cold to more serious illnesses such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS).

COVID-19 is the most recently discovered infectious disease caused by the coronavirus and has been declared a pandemic and global emergency by the WHO.

The most recent reports, made in Wuhan, the epicenter of the outbreak, showed that the clinical manifestations of the infection are fever, cough, and dyspnea with radiological evidence of viral pneumonia (MacLaren, 2020). Approximately 15 to 30% of patients develop Acute Respiratory Distress Syndrome (ARDS). The WHO general recommendations for ARDS treatment include the management of patients with refractory respiratory hypoxemia, for whom it recommends extracorporeal oxygenation membranes as a therapeutic resource (MacLaren, 2020).

The virus can cause death through progressive hypoxemic respiratory failure, refractory multi-organ failure, or complications such as ischemic heart failure. The need for extracorporeal oxygenation membranes is a difficult decision when the resource is limited for the high demand in this highly transmissible pandemic. Many times, it is administered to unnecessary cases to the detriment of the most acute and serious cases. The benefit-risk assessment is constant and depends on many factors.

Computed tomography scans of the lungs in patients with COVID-19 diagnosed symptoms of the progressive disease of the airspace that radiologically represents the oxygen diffusion barrier. This is how hypoxia plays a significant role in the progress of the disease, which develops its course in up to 10 weeks, with the approximate peak on day 10 in patients who manage to recover from respiratory hypoxemic failure (Li, 2020; Pan, 2020).

When COVID 19 infects the upper and lower respiratory tract, it causes a mild or upper respiratory syndrome with consequent release of inflammatory cytokines, including interleukins (IL) – 1b and IL-6. Binding of COVID-19 to the Toll-like receptor (TLR) causes the release of pro-IL-1b, which is cleaved by caspase-1, followed by activation of the inflammasome with the production of IL-1b as the main mediator of pulmonary destruction, fever, and fibrosis (Conti, 2020; Li, 2020).

Recent studies have detected that the suppression of the pro-inflammatory interleukins IL-1 and IL-6 has had therapeutic effects in many inflammatory diseases including viral infections. Furthermore, suppression of IL-1b by IL-37 in the inflammatory state induced by COVID-19 may have a new therapeutic effect in a still unknown but very promising study. The same occurs with IL-38, which is also studied as a potential therapeutic strategy for this disease (Conti, 2020; Li 2020).

Knowing and controlling the generated immune response and the inflammatory cascade that triggers the coronavirus is essential for the control and elimination of the infection. Poor adjustment of this immune response at the time of infection can result in immunopathology, inflammation, and change in pulmonary gas exchange leading to hypoxia.

Systemic and pulmonary hypoxia feeds back the exacerbated inflammation in this infection since it occurs dysfunction of the effectors of the inflammation resolution (in the inflammasome complex), such as the mitochondria. It is the producer of reactive oxygen species necessary to regulate the inflammatory process and strengthen the clearance of noxas through the respiratory burst mediated by macrophages and monocytes in the first defense line (Weinber, 2015; Hurst, 2012).

Hyperbaric Oxygenation potential role

Hyperbaric oxygen produces an increase in lung oxygenation. In the oxygen cascade and the ventilatory phase of hyperbaric oxygen therapy (HBOT), the pulmonary alveolus is the direct contact organ and the main recipient of hyperoxia (Jain, 2017). In the alveolar exchange with HBOT, the partial pressure of oxygen is increased even when it is under the pulmonary shunt and it is very useful, except in patients with chronic severe obstruction where the exchange is interrupted and there is a risk of developing hypercapnia. HBOT does not alter lung function. Even in a prospective study in healthy individuals, there were no significant changes in forced expiratory volume (FEV) and forced respiratory flow (FEF). This shows that HBOT is safe for lung function, even if it is performed chronically (Haddany, 2019).

Dr. Paul Harch suggested that the disease caused by COVID 19 was similar to lung pathology in victims of the 1918 Spanish Flu (https://m.facebook.com/story.php?story_fbid=2822255517863411&id=100002369723763). At the time of this illness, Dr. Cunninghan treated patients with hypoxemia due to influenza. It should be noted that at that time there were no respirators, so additional oxygenation contributed significantly to resolving the hypoxemic respiratory failure in these patients.

Although the resolution of hypoxia is an important physio pathogenic factor in the development of the disease, what Dr. Cunningahn did not know at the time is that HBOT not only contributes to oxygenating tissues at the pulmonary and systemic level. Hyperoxia also has an important anti-inflammatory effect.

HBOT reduces the production and release of pro-inflammatory cytokines by neutrophils and monocytes (Gill A, 2004, Al Waili NS, 2006, Bosco G, 2018).

Studies reveal the effects of hyperbaric oxygenation on cytokine production (Al Waili NS, 2006). This therapy increases FGF production and collagen synthesis and decreases interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis alpha factor (TNF alpha). The effects of transforming beta 1 growth factor (TGFβ1) and platelet-derived growth factor (PDGFβ) are greater with HBOT (Al Waili NS, 2006, Yuan LJ, 2009).

Regarding the development of chronic inflammation, activation of the Toll-Like Receptors (TLR) system contributes to the maintenance of the inflammatory response. HBOT decreases TLR expression, NF-kB signaling pathways and the expression of these molecular platforms in different tissues (Meng XE, 2016, Wu ZS, 2018).

Furthermore, hyperbaric oxygen could increase the adaptive cellular immune response of peripheral blood mononuclear cells infected with HIV-1 virus (acquired immunodeficiency virus), through the increase of proteins that can inhibit viral replication (Budiarti R, 2018).

Given the emergency of patients with COVID-19 and the limited extracorporeal oxygenation resources, the hyperbaric chamber for infected patients suffering from respiratory hypoxemic failure could be used in cases without pulmonary contraindications for hyperbaric oxygenation therapy. In addition, it could decrease the inflammatory phase and perhaps speed up the times for recovery and release of beds required to assist these patients during the pandemic. Additional studies are needed and these hyperbaric chambers must be operated by qualified medical professionals who can carry out rigorous and reliable control of the need for other additional therapeutic requirements during the progression of the disease.

HBOT would contribute significantly to reducing morbidity, accelerating recovery times for patients suffering from the pandemic, optimizing health resources and reducing healthcare costs.

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