Oxygen Dynamics in COVID-19: A Review of the Interplay Between Hypoxia, Hyperoxia, and Their Implications on Pathological Mechanisms

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Abstract

This article review explores the intricate interplay between oxygen dynamics and COVID-19, investigating the relationships between hypoxia, hypoxemia, hyperoxia, and hyperoxemia. The primary aim is to provide a nuanced understanding of how deviations from optimal oxygen levels influence the course of COVID-19, with implications for diagnosis and therapeutic interventions. A thorough literature review was conducted to gather and analyze existing research on the relationships between oxygen dynamics and COVID-19. The exploration focused on studies investigating hypoxia, hypoxemia, hyperoxia, and hyperoxemia in the context of the disease. Relevant data and findings were extracted to construct a comprehensive overview of the complex interplay between oxygen levels and the pathological mechanisms associated with COVID-19. The review reveals the intricate relationship between hypoxia and hypoxemia, elucidating how oxygen deprivation and systemic oxygen deficiency contribute to the progression and severity of COVID-19. Simultaneously, an exploration of the relationship between hyperoxia and hyperoxemia unveils the impact of oxygen levels beyond the norm on the pathological landscape of the virus. The etiology and pathophysiology of COVID-19 are examined in detail, with a focus on the role of hypoxia and hyperoxia in shaping the disease's progression. Pneumonia and Acute Respiratory Distress Syndrome (ARDS) are discussed as critical manifestations of COVID-19, emphasizing their intricate relationship with oxygen dynamics. In conclusion, this comprehensive review provides valuable insights into the complex interplay between oxygen levels and the pathological mechanisms associated with COVID-19. The findings underscore the significance of considering oxygen dynamics in the diagnosis and treatment of the disease. By unraveling the relationships between hypoxia, hypoxemia, hyperoxia, and hyperoxemia, this study aims to inform clinicians, researchers, and healthcare practitioners, offering a holistic understanding of the dynamic nature of oxygen regulation in the context of COVID-19.

Keywords: COVID-19; hypoxia; hypoxemia; hyperoxia; hyperoxemia

1. Introduction

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has ushered in an unprecedented era of medical challenges, prompting intensive research to decipher the intricacies of its pathogenesis. Central to the understanding of COVID-19's impact is the dynamic regulation of oxygen within the human body (Rauf et al., 2020). Oxygen, a vital element for cellular metabolism and survival, plays a pivotal role in the progression and severity of respiratory infections. In the context of COVID-19, the relationships between hypoxia, hypoxemia, hyperoxia, and hyperoxemia are emerging as critical factors that shape the course of the disease (Chen et al., 2020). This review embarks on an exploration of the multifaceted interplay between

oxygen dynamics and COVID-19, aiming to unravel the complexities that underlie the pathological mechanisms associated with variations in oxygen levels.

As the virus infiltrates the respiratory system, a profound understanding of hypoxia and hypoxemia becomes imperative. Hypoxia, characterized by insufficient oxygen at the cellular level, is intricately linked to the severity of COVID-19. Understanding the nuanced relationship between hypoxia and hypoxemia is crucial for deciphering the disease's progression (Bhutta et al., 2022). This review dissects the molecular and physiological underpinnings of hypoxia, shedding light on how oxygen deprivation at the cellular level contributes to the systemic manifestation of hypoxemia in COVID-19 patients. By unraveling this intricate relationship, we aim to provide insights into potential diagnostic markers and therapeutic targets, addressing a critical aspect of COVID-19 management.

In parallel, the exploration of hyperoxia and hyperoxemia adds another layer of complexity to the oxygen dynamics in COVID-19 (Singer et al., 2021). While oxygen therapy is a cornerstone in the treatment of respiratory distress, the potential for hyperoxia-induced complications cannot be overlooked (de Graaff et al., 2011). This review delves into the delicate balance between providing sufficient oxygen to meet cellular demands and the potential harm associated with elevated oxygen levels. The implications of hyperoxemia on the pathological mechanisms of COVID-19 are examined, emphasizing the need for a nuanced approach to oxygen therapy. By elucidating the dual role of hyperoxia in both aiding recovery and potentially exacerbating complications, we aim to guide clinicians in optimizing therapeutic interventions tailored to individual patient needs.

The intricate interplay between oxygen dynamics and the etiology and pathophysiology of COVID-19 forms another focal point of this review. The virus's ability to manipulate cellular oxygen regulation mechanisms and the resulting impact on host physiology are critical aspects that demand thorough investigation. By examining the molecular pathways and physiological responses triggered by the virus, we aim to provide a comprehensive understanding of how COVID-19 orchestrates pathological changes in the host, with oxygen dynamics serving as a central player in this complex narrative.

2. Review Content

2.1 Etiology and Patophysiology of COVID-19

COVID-19, first identified in Wuhan, Hubei Province, People's Republic of China, is caused by the SARS-CoV-2 virus (Rauf et al., 2020). SARS-CoV-2 itself is a positive-strand RNA virus with a crown-like structure formed by glycoprotein projections when observed under an electron microscope (Cascella et al., 2022). The SARS-CoV-2 virus itself is related to the MERS-CoV virus which causes Middle East Respiratory Syndrome (MERS) and the SARS-CoV-1 virus which causes Severe Acute Respiratory Syndrome (SARS) (Peeri et al., 2020). However, COVID-19, which is caused by the SARS-CoV-2 virus, is very contagious and has infected more than 500 million people worldwide (ECDC, 2022). Based on Rauf's research in 2020, it was found that this virus has more than 88% genetic similarity to the SARS-like virus that infects bats, so the latest hypothesis highlights the possibility that this virus infects humans zoonotically (Rauf et al., 2020). The SARS-CoV-2 virus that causes COVID-19 continues to mutate during its development, resulting in various variants that have different severity of symptoms. WHO determines the existence of Variants of Concern (VOC), Variants of Concerns Lineage under Monitoring (VOC-LUM), and Variants of Interest (VOI) (WHO, 2022). Based on the latest consensus, it is believed that the SARS-CoV-2 virus spreads through respiratory droplets (WHO, 2021). However, there is evidence suggests that the virus may not be limited to droplet

transmission alone (Galbadage et al., 2020). The spread of the SARS-CoV-2 virus is suspected to occur through aerosols (Wang and Du, 2020). Aerosols are collections of solid and liquid particles dispersed and suspended in the air. If SARS-CoV-2 spreads through aerosols, research by Evans in 2020 suggests that transmission through this method could result in a smaller virus dose compared to other methods (Evans, 2020). SARS-CoV-2 is also suspected to spread through contact with surfaces (fomites), based on the characteristics observed in SARS-CoV-1. Research indicates similarities in fomite transmission between SARS-CoV-1 and SARS-CoV-2. The virus can remain active for 2-3 days on plastic and stainless steel surfaces, 24 hours on cardboard surfaces, and around 4 hours on copper surfaces (van Doremalen et al., 2020).

In broad terms, the epidemiological spread of COVID-19 can be divided into three phases (Sun et al., 2020). First, is local transmission. In this phase, local transmission likely occurred in the Hainan seafood market. Starting from the identification of the first case as "Pneumonia of unknown etiology" in December 2019 until January 13, 2020, when infections were found in people outside Wuhan. This phase is characterized by direct infection from animals as zoonotic vectors and the initial transmission from person to person. Secondly, rapid Spread through Nosocomial Infections and Close Contact Transmission. In the second phase, there was rapid spread through nosocomial infections (hospital-acquired infections) and increased close contact transmission, including within families (Chan et al., 2020). Transmission increased by 20 times compared to the first phase. During this phase, Wuhan underwent its first lockdown to contain the virus. However, around the Chinese New Year on January 25, 2020, approximately 5 million people had already left Wuhan out of 8.5 million. Thirdly, Increase in Cluster Cases and Uncontrolled Spread. The third phase began around January 26, 2020, with a rapid increase in COVID-19 cases not only in Wuhan but also in other regions of the People's Republic of China and several other countries. On January 30, 2020, the WHO declared COVID-19 a Public Health Emergency of International Concern (PHEIC) that had spread worldwide (Chan et al., 2020). Later, on March 30, 2020, the WHO announced that COVID-19 had become a global pandemic (Cucinotta and Vanelli, 2020). As of the writing of this proposal, according to the WHO Coronavirus Dashboard, there are more than 545 million confirmed cases worldwide (WHO, 2022). The virus has spread to every country globally, making it the 21st-century global pandemic.

SARS-CoV-2 possesses four structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N). The protruding spike (S) protein from the virus's surface is crucial for the virus's penetration into the host cell. ACE-2 receptor has been identified as the entry point for SARS-CoV-2, predominantly found in lung epithelial cells. After the virus binds to the ACE-2 receptor, the S1 protein subunit undergoes cleavage to expose the S2 subunit, leading to conformational changes that result in virus-cell fusion (Parasher, 2021). Following fusion, the virus replicates by creating a negative-sense RNA based on the single positive-sense RNA it carries, through the RNA polymerase process (transcription). This negative-sense RNA then serves as a template for the synthesis of new proteins in the host cell cytoplasm (translation). This process is followed by the virus's M protein facilitating the attachment of the translated proteins to the endoplasmic reticulum of the host cell. After being in the endoplasmic reticulum, the translated products are transported by the Golgi vesicles to the cell membrane and released from the cell through exocytosis. The newly formed virus is then ready to infect the surrounding lung epithelial cells (Parasher, 2021).

2.2 Pneumonia and ARDS in COVID-19

The clinical course of COVID-19 can be divided into four stages (Parasher, 2021). First phase is asymptomatic phase. This phase begins with the binding of SARS-CoV-2 to ACE2 receptors on nasal epithelial cells. During this phase, there is local virus propagation. The immune response generated in this phase is limited but detectable through nasal swab tests. Despite being an early phase with a low viral load, individuals infected with COVID-19 in this phase can still spread the SARS-CoV-2 virus (Parasher, 2021).

Second phase is Upper Respiratory Tract Infection Phase. In this phase, the virus migrates from nasal epithelial cells to the upper respiratory tract. Symptoms such as fever, fatigue, and dry cough appear during this phase. There is an increased immune response characterized by the production of Interferon Beta (IFN-β), Interferon Lambda (IFN-λ), and C-X-C motif chemokine ligand 10 (CXCL10) from infected cells. For the majority of patients, COVID-19 progresses only to this phase and does not advance to the next due to an adequate immune response (Parasher, 2021). Third phase is Lower Respiratory Tract Infection Phase. About 20 percent of infected patients progress to this phase, experiencing more severe symptoms. The virus infects type 2 alveolar epithelial cells via the ACE2 receptor (Mason and Health, 2020). This triggers the release of various cytokines and inflammatory markers on a larger scale, such as Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-α (TNF-α), Interferon Gamma (IFN-γ), Interferon Beta (IFN-β), Interferon Lambda (IFN-λ), and C-X-C motif chemokine ligand 10 (CXCL10) (Yuki et al., 2020). The presence of a "Cytokine Storm" acts as an attractant for CD4 Helper T cells and CD8 Cytotoxic T cells, playing a crucial role in fighting the virus but also causing inflammation and pneumocyte apoptosis. Repeated inflammation and apoptosis lead to lung tissue damage, resulting in ARDS and Pneumonia (Parasher, 2021). Pneumonia is defined as acute inflammation of the lungs with alveolar infiltrates. Acute Respiratory Distress Syndrome (ARDS) is a condition characterized by reduced lung oxygenation and decreased lung compliance. In patients with severe inflammation, lung compliance drops below 40 ml/cmH2O, contrasting with the physiological condition where compliance is around 50 ml/cmH2O (Gattinoni et al., 2020). Reduced compliance is marked by hypoxia and a decrease in the tidal volume of the patient's breathing.

2.3 Therapy of COVID-19

According to the COVID-19 Management Guidelines by the Five Colleges, COVID-19 patients are categorized into five severity levels as follows (Burhan et al., 2022). Asymptomatic (this condition is the mildest, where patients show no symptoms), mild (patients exhibit symptoms without evidence of pneumonia and hypoxia. Typically, these patients experience fever, cough, fatigue, and myalgia. Oxygen saturation (SpO2) in this category is > 95% with room air), moderate (patients display clinical signs of pneumonia such as fever, cough, shortness of breath, and rapid breathing, but without severe pneumonia indicated by an oxygen saturation (SpO2) > 93% with room air), severe (patients exhibit clinical signs of pneumonia like fever, cough, shortness of breath, and rapid breathing), and critical (patients with Acute Respiratory Distress Syndrome (ARDS), sepsis, septic shock, or other conditions requiring life support measures such as mechanical ventilation or vasopressor therapy.

COVID-19 therapy, as per the COVID-19 Management Guidelines by the Five Colleges, is tailored to the severity of the illness and encompasses three types: isolation and monitoring, non-pharmacological interventions, and pharmacological approaches. For asymptomatic cases, patients undergo self-isolation for 10 days, coupled with education on preventive measures and optional pharmacological support involving Vitamin C and D. Mild cases involve similar protocols, with the addition of antiviral medications like Favipiravir, Molnupiravir, or Nirmatrelvir/Ritonavir. Moderate cases require hospitalization, with comprehensive non-pharmacological care and pharmacological interventions such as intravenous Vitamin C and continued Vitamin D supplementation. The severity levels, ranging from asymptomatic to critical, dictate the nuanced approach to therapy, ensuring a tailored response to each patient's condition (Burhan et al., 2022).

Antiviral treatment includes Remdesivir (200 mg IV drip on day 1, followed by 1x100 mg IV drip on day 2-5 or day 2-10). If Remdesivir is unavailable, alternative antivirals may be administered based on drug availability in respective healthcare facilities, including Favipiravir, Molnupiravir, or Nirmatrelvir/Ritonavir. Symptomatic and comorbid treatments, as well as anticoagulation, are instituted based on evaluation. For severe and critical cases, patients are isolated in Intensive Care Units (ICU) or High Care Units (HCU) with

escalated non-pharmacological interventions, including continuous monitoring and oxygen therapy. Pharmacological interventions involve intravenous Vitamin C and D supplementation, antiviral treatment, corticosteroids like Dexamethasone, Tocilizumab administration, and additional treatments based on comorbidities and symptoms. The comprehensive therapeutic strategy aims to address the diverse clinical presentations of COVID-19 (Burhan et al., 2022).

Blood Gas Analysis (BGA) or Analisis Gas Darah (AGD) is a common diagnostic tool used to evaluate the partial pressures of gases in the blood and the acid-base conditions of the blood (Castro et al., 2021). The following are some components typically examined using blood gas analysis along with their normal ranges such as pH (7.35-7.45), PaO2 (75-100 mmHg), PaCO2 (35-45 mmHg), HCO3 (22-26 meq/L), and SaO2 (95-100%). Blood gas analysis can be performed on blood from arteries, veins, or capillaries. Normally, blood gas analysis is conducted in the upper extremities by drawing blood from the radial artery. In cases where radial artery puncture is not feasible, blood can be drawn from the femoral artery. In AGD, arterial blood is preferred over venous blood because venous blood shows differences in blood pH and pCO2 due to local organ and tissue activity and the flow rate around the venous blood vessels (Nigam, 2016). Blood Gas Analysis is crucial for understanding a patient's oxygenation, ventilation, and acid-base status. While non-invasive measures like pulse oximetry exist, Blood Gas Analysis remains a standard test for assessing these components. It serves as a confirmation of pulse oximetry results (Castro et al., 2021).

2.4 Relationship between Hypoxia and Hypoxemia

Hypoxia, characterized by oxygen levels in the blood falling below physiological norms, results from either insufficient blood flow to the tissues or a reduced oxygen content in the blood (hypoxemia) (Bhutta et al., 2022). The two primary causes of hypoxia encompass a lack of blood flow to the tissues and a diminished oxygen quantity in the blood. Conditions leading to decreased blood flow include right-to-left shunt, peripheral artery disease (PAD), blood clots, and heart failure (Bhutta et al., 2022). Hypoxemia can arise from various factors, such as anemia, asthma, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), pneumonia, pneumothorax, and decreased oxygen pressure (Mayo Clinic, 2018). Understanding these causes is crucial for addressing hypoxia and tailoring appropriate interventions based on the specific contributing factors. Hypoxia has several effects on the human body, predominantly leading to pathological outcomes, but it also plays a role in certain physiological processes such as increased ventilation and cardiac output when the respiratory center in the medulla and pons detects a decrease in oxygen partial pressure (Chen et al., 2020). Additionally, hypoxia plays a crucial role in the inflammation process through the "hypoxia signaling pathway" regulated by hypoxia-inducible factor (HIF). Hypoxia can result in heart failure. Hypoxia-induced heart failure occurs due to factors such as increased heart rate, elevated systolic pressure, and disturbances in the heart's conduction system. This condition is particularly dangerous in COVID-19 patients because low blood oxygen levels exacerbate circulatory failure, hindering oxygen delivery. Brain tissue damage during hypoxia is caused by vasodilation of cerebral blood vessels leading to edema and oxygen deficiency in brain tissues. Vasodilation of brain blood vessels due to hypoxia is caused by the production of vasodilators such as hydrogen ions, potassium, adenosine, and prostaglandins. Hypoxia also prompts the endothelial layer of cerebral arteries to release vasodilation markers like prostacyclin and nitric oxide. Continuous vasodilation leads to cerebral artery leakage and reduced fluid absorption, filling the brain space. Prolonged occurrences may result in brain edema. Hypoxia in the brain can also cause the death of brain cells due to ischemia or apoptosis, contributing to brain edema (O'Neill et al., 2022). Oxygen deprivation for the brain for 1-2 minutes leads to neurological disturbances, and within 3-5 minutes, it causes permanent brain damage. Under normoxic conditions, the HIF subunit is hydroxylated by oxygen-dependent prolyl-4-hydroxylase (PHD). Hydroxylated HIF binds to Von Hippel-Lindau protein (pVHL), a component marking the E3 ubiquitin ligase complex that degrades HIF via proteasomes. The degraded HIF remnants are

further degraded by factor inhibiting HIF (FIH) (Lee et al., 2019). During hypoxia, PHD and FIH activities are suppressed, allowing HIF-α subunits to translocate into the nucleus to bind with HIF-1β, promoting the upregulation of transcription for genes active in hypoxic conditions (Lee et al., 2019). In addition to its role in HIF, hypoxia also significantly influences Nuclear Factor κB (NF-κB). NF-κB is a family of transcription factors that regulate inflammation and the body's immune response. Hypoxia enhances the activation of NF-κB, leading to increased production of Tumor Necrosis Factor α (TNF-α), a proinflammatory cytokines. This activation of HIF by hypoxia has adverse effects on COVID-19 patients because HIF functions as an inflammation trigger. The physiological inflammation in COVID-19 patients, aimed at combating virus replication, worsens due to additional inflammation from HIF activation. Excessive inflammation can have detrimental effects on patient safety. Hypoxic conditions can be managed in several ways such as airway maintenance, increasing inhalation fraction of O2 (FiO2), and positive Pressure Ventilation (Bhutta et al., 2022).

Although hypoxemia and hypoxia are often used interchangeably, there is a definitional difference between the two conditions. As previously mentioned, hypoxia is a condition where tissue oxygen is below normal, while hypoxemia is a condition where arterial oxygen pressure is below the physiological level (80-100 mmHg). According to Samuel's 2008 study, hypoxemia is the most common cause of tissue hypoxia. Generally, hypoxemia is a sign of hypoxic conditions (Samuel and Franklin, 2008).

2.5 Relationship between Hyperoxia and Hyperoxemia

Hyperoxia is a condition where tissue oxygen levels are higher than physiological conditions, clinically significant when PaO2 levels exceed 120 mmHg (de Graaff et al., 2011). Hyperoxia is rarely a natural occurrence. Common causes of hyperoxia include inhaling air with higher oxygen concentrations, causing the Inspiratory Oxygen Fraction (FiO2) to exceed the normal condition of 0.21 (Brugniaux et al., 2018) and being in a high-pressure environment (hyperbaric), which can occur naturally, such as deep-sea diving, or artificially, like being in a hyperbaric chamber used by athletes for recovery. In clinical therapy, these conditions are often combined for optimal results. Increasing blood oxygen levels are much more potent in hyperbaric therapy than hyperoxia due to the ideal gas law (Tenny and Cooper, 2021). The law states that a multiple-fold increase in pressure will linearly increase the amount of oxygen, whereas high-concentration oxygen therapy can only be administered up to 100% pure oxygen (Brugniaux et al., 2018). Oxygen, since its discovery in medical applications, is considered a double-edged sword. On one side, oxygen plays an integral role in Adenosine Triphosphate (ATP) synthesis. On the other side, oxygen also has the potential to damage crucial biological molecules in the body due to the formation of Reactive Oxygen Species (ROS). Hyperoxic conditions in the respiratory system are referred to as the "Lorrain-Smith Effect." In this condition, inflammation of the upper respiratory tract, such as tracheobronchitis, is observed. If hyperoxia is not promptly addressed, alveolar damage and Acute Respiratory Distress Syndrome (ARDS) can occur within 24 hours. Over a more extended period, these symptoms may manifest as atelectasis. The Lorrain-Smith Effect is hazardous for COVID-19 patients because COVID-19 manifestations themselves cause ARDS and inflammation of lung tissue, exacerbating the patient's symptoms. Hyperoxic conditions can also cause damage to the nervous system, known as the "Paul-Bert Effect." This effect manifests as changes in vision, such as tunnel vision, tinnitus, facial twitching, changes in behavior, and tonic-clonic seizures. Tonic-clonic seizures are particularly dangerous for COVID-19 patients because strong stimuli can cause the patient's respiratory muscles to press forcefully on the lungs during the tonic phase, leading to respiratory arrest. Apart from respiratory disruption, tonic-clonic seizures are also feared to cause Sudden Unexpected Death in Epilepsy (SUDEP), with the highest incidence in tonic-clonic seizures (Paige and Cavanna, 2022). The production of ROS is a crucial indicator of inflammatory diseases. In the body's physiological condition, ROS is produced by cells involved in the body's defense, such as Polymorphonuclear Neutrophils (PMNs). ROS serves as an excellent mediator of inflammation. ROS significantly influences the regulation of Nuclear

Factor κB (NF-κB), which plays a vital role in TNF-α production, triggering apoptosis. In patients experiencing hyperoxia, managing this condition involves reducing the high oxygen levels experienced by the patient. This can be achieved by identifying the underlying cause of hyperoxia. For example, hyperoxia caused by high fractional inspiratory oxygen can be addressed by lowering the patient's fractional inspiratory oxygen. Hyperoxia caused by high pressure can be managed by gradually reducing the pressure experienced by the patient until they reach atmospheric pressure (Cooper et al., 2022).

Hyperoxia is a condition where the amount of oxygen in tissues is above normal physiological conditions, while hyperoxemia is a condition where arterial oxygen partial pressure is above normal in arteries. In this study, the impact of oxygen therapy on hyperoxic conditions will be examined. According to Singer's 2021 study, oxygen supplementation (FiO2 >0.21) causes hyperoxemia, and hyperoxemia itself aligns with hyperoxia because the increase in arterial oxygen partial pressure will also increase the amount of oxygen in tissues (Singer et al., 2021).

3. Conclusion

In conclusion, this comprehensive review provides valuable insights into the complex interplay between oxygen levels and the pathological mechanisms associated with COVID-19. The findings underscore the significance of considering oxygen dynamics in the diagnosis and treatment of the disease. By unraveling the relationships between hypoxia, hypoxemia, hyperoxia, and hyperoxemia, this study aims to inform clinicians, researchers, and healthcare practitioners, offering a holistic understanding of the dynamic nature of oxygen regulation in the context of COVID-19.

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