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Continuous positive air pressure (CPAP) should be used in all COVID-19 patients when the first and mild respiratory symptoms commence

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Abstract

The most awful complication COVID-19 is hypoxemia due to respiratory failure. The mechanisms of lung damage and hypoxemia in COVID-19 include ventilation/perfusion mismatch, loss of hypoxic vasoconstriction and increased coagulopathy. Hence, it is of particular attention that acute lung injury, hypoxemia, systemic inflammatory response syndrome, acute respiratory distress syndrome (ARDS) occurs after SARS-CoV-2 infection. Cytokine storm in COVID-19 patients is centrally involved in the aggravation of symptoms and disease development, and denotes a key factor contributing to ARDS and mortality. Indeed, there is a close relationship between lung damage, hypoxemia and the cytokine storm. Other important issue is to consider the possible presence of happy of silent hypoxemia, which is described in patients with pronounced arterial hypoxemia who don't express a sense of dyspnea. Moreover, pulse oximetry (PO) should be interpreted with caution, because due to left-sided shifting of the oxyhemoglobin dissociation curve during hypocapnia periods, PO might measure a normal oxygen saturation in spite of very low PaO2. Continuous positive air pressure (CPAP) is nowadays the preferred method of non-invasive ventilation (NIV) management of COVID-19 patients, has significant and helpful role in Covid-19 management, mainly if it is used in an early phase of the disease, because it may prevent clinical deterioration and reduce the need for invasive ventilation at all. We strongly recommend to early use CPAP in all Covid-19 patient who present the first mild respiratory symptoms, such as cough, or light tachypnea and hyperpnea, etc., when they are still outside the ICUs, i.e. in regular wards or at patient's homes. This method would prevent periods of hypopnea and hypoxia which can stimulate the synthesis of ACE in lung endothelial cells, leading to cytokine storm, which can cause ARDS, multi-organ failure, and death.

Introduction

One of the gravest complications of SARS-CoV-2 infection is the development of an atypical upper respiratory tract pneumonia that enforces a major challenge to clinicians in terms of disease management [1]. A substantial proportion of patients who are admitted to intensive care units (UCIs) worsen in a short period of time, leakproof clinical states, and die from acute respiratory distress syndrome (ARDS) [2-10].

The most awful complication COVID 19 is hypoxemia due to respiratory failure. The mechanisms of lung damage and hypoxemia in COVID 19 include ventilation/perfusion mismatch, loss of hypoxic vasoconstriction and increased coagulopathy. Hence, it is of particular attention that acute lung injury, hypoxemia, systemic inflammatory response syndrome (SIRS), and ARDS occur after SARS-CoV-2 infection [9,10,11-14].

An abnormal and uncontrolled production of cytokines has been observed in critically ill patients with COVID-19 pneumonia. The subsequent uncontrolled cytokine storm in COVID-19 patients is centrally involved in the aggravation of symptoms and disease development, and denotes a key factor contributing to ARDS and mortality [15-21]. Indeed, there is a close inter-relationship between of lung damage, hypoxemia and the cytokine storm [11,22-30]. According to the current WHO guidance, supportive therapy remains the most significant management strategy for this disease, including supplemental oxygen therapy, conservative fluid management and empiric antimicrobial application. Furthermore, new treatment protocols need to be established in order to control the prolonged and progressive hypoxia of COVID-19 patients [31].

The treatment for severe respiratory failure in Covid-19 patients have included early intubation and invasive ventilation, as this was deemed preferable to be more effective than Non-Invasive Ventilation (NIV). Nevertheless, NIV may have a more significant and helpful role than firstly thought, mainly if it is used in an early phase of the disease. NIV avoids the need for sedation, allows easier communication with patient, and requires less intensive nursing care [32-35].

Hypoxia, cytokine storm and inflammation

The SARS-CoV-2 virus binds and infects the cells via utilizing angiotensin converting enzyme 2 (ACE-2) as a receptor, which is widely found in tissues of the organism. It has been suggested that increased levels of ACE-2 were positively associated with COVID- 19 infection. There are two types of ACE (ACE-1 and ACE-2) acting oppositely in pulmonary endothelium; ACE-2 functions as a vasodepressor whereas ACE-1 functions as a vasoconstrictor. Under physiological conditions, there is a dynamic equilibrium between ACE-1 and ACE-2. Though, in conditions of hypoxemia like in COVID-19 infection, ACE-1 is

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upregulated by the hypoxia-inducible factor-1 (HIF-1); meanwhile the expression of ACE-2 is noticeably reduced. Subsequently, both hypoxemia and related ACE-2 upregulation may deteriorate clinical outcomes in COVID-19 [11,36-45].

The immune system has an exquisite mechanism capable of responding to various pathogens. Normal anti-viral immune response necessitates the activation of the inflammatory pathways of the immune system. Nevertheless, aberrant or exaggerated response of the host's immune system can cause severe disease if remains uncontrolled [46-50].

The cytokine storm is an activation cascade of auto-amplifying cytokine production due to unregulated host immune response to dissimilar triggers. The term cytokine storm calls up bright images of an immune system gone awry and an inflammatory response burst out of control. The cytokine storm is a systemic inflammatory response to infections and drugs leading to excessive activation of immune cells and generating pro-inflammatory cytokines. Cytokines are an indispensable part of the inflammatory process. Cytokines are produced by several immune cells including the innate macrophages, dendritic cells, natural killer cells and the adaptive T and B lymphocytes [16,51-58].

Due to rapid endothelial dysfunction in the lungs, microthrombi may occur by activation of the coagulation system, resulting in drastic changes in blood rheology and causing organ failure due to hypoperfusion or misperfusion. In Covid-19, the aberrant release of pro-inflammatory factors leads to lung epithelial and endothelial cell apoptosis which damages the lung microvascular and alveolar epithelial cell barrier, leading to vascular leakage, alveolar edema and hypoxia [59-69]. Cytokine mediated injury of lung endothelial and epithelial cells may damage the integrity of blood/air barrier, thus promoting vascular permeability in addition to alveolar edema, infiltration by inflammatory cells (i.e. neutrophils and macrophages) and hypoxia. Certain kinds of cytokines trigger cell death, causing that a lot of tissue can die. In COVID-19, that tissue is mostly in the lung. As the tissue breaks down, the walls of the lungs' tiny air sacs become leaky and fill with fluid, causing pneumonia and starving the blood of oxygen [24,68,70,71]. These phenomena also lead to lack of oxygen supply in the tissues or organs due to hypoperfusion of blood. Moreover, proinflammatory cytokines suppress the oxygen utilization of mitochondria, resulting in a change of metabolic pathway from oxidative phosphorylation to glycolysis, thus causing cells to change their mode of metabolism to glycolytic or anaerobic. Increased oxygen demands of infiltrated immune cells, reduced supply of metabolic substrates by blood clots and compression of blood vessels, and atelectasis of lung contribute to tissue hypoxia during inflammation, inducing hypoxemia, and triggering more proinflammatory cytokines [72-82].

Tissue hypoxia during inflammation is not just a simple passerby process, but can significantly affect the development or attenuation of inflammation by causing the regulation of hypoxia-dependent gene expression. Several studies analyzing cytokine profiles from COVID-19 patients have suggested that the cytokine storm correlated directly with lung injury, hypoxemia, multi-organ failure, and unfavorable prognosis of severe COVID-19 [28,83-88].The exposure to hypoxia promotes several transcription factors, which plays a central role in stimulating the proinflammatory cytokines TNF-α and IL-6. Hypoxia is a microenvironmental feature of chronically inflamed tissues which can impact upon the progression of inflammation in a number of ways. HIF and NF-κB are two hypoxia- responsive transcription factors which, as well as controlling independent cohorts of adaptive and inflammatory genes, demonstrate a high degree of interdependence. Central to the activation of both the HIF and NF-κB pathways in hypoxia appear to be the oxygen- sensing hydroxylases. Certainly, the study of transcriptionally regulated tissue adaptation to hypoxia necessitates further research to help control hypoxia-induced inflammation and multiple organ failure [28,57,89-100]. Inflammatory cytokines. Cytokines are an indispensable part of the inflammatory process. Cytokines are produced by several immune cells including the innate macrophages, dendritic cells, natural killer cells and the adaptive T and B lymphocytes [16,51-58].

Happy or silent hypoxemia

Other very important issue to consider is the possible presence of "happy or silent hypoxemia". One of the aspects perplexing clinicians who take care of COVID-19 patients with pronounced arterial hypoxemia, yet without proportional signs of respiratory distress, with even deceiving cyanosis, is that they don't even express a sense of dyspnea. This phenomenon is referred as 'happy or silent hypoxemia". For clinicians the presence of happy or silent hypoxemia in Covid-19 patients, in spite of pronounced arterial hypoxemia, can erroneously lead to the conclusion that the patient is not in a critical condition. Those cases can quickly leapfrog clinical evolution stages and suffer ARDS, with concomitant cardiorespiratory arrest and death [59,101,105].

Pulse oximetry: changes in oxyhemoglobin dissociation curve

Pulse oximetry which measures oxygen saturation (SpO2) is very often used to detect hypoxemia. Nevertheless, SpO2 should be carefully interpreted in COVID-19. The sigmoid shaped oxyhemoglobin dissociation curve seems to shift to the left, due to induced respiratory alkalosis (drop in PaCO2) because of hypoxemia-driven tachypnea and hyperpnea. During hypocapnic periods, the affinity of hemoglobin for oxygen and thus oxygen saturation rises for a specified degree of PaO2, explaining why SpO2 can be well-preserved in the face of a profoundly low PaO2. In high altitude hypoxemia, hypocapnia significantly changes the oxygen-hemoglobin dissociation curve and recovers blood oxygen saturation. The alveolar gas equation also predicts that hyperventilation and the resulting drop in the alveolar partial pressure of CO2 produces an increment in the alveolar partial pressure of oxygen and finally lead to a raise in SpO2 [103,106].

Invasive or non-invasive ventilation in Covid-19 patients

Over the past decade, the use of noninvasive ventilation (NIV) in the setting of acute exacerbations of chronic obstructive pulmonary disease has gained popularity [32,107,108].The treatment for severe respiratory failure in Covid-19 patients have included early intubation and invasive ventilation, as this was deemed preferable to be more effective than Non-Invasive Ventilation (NIV). Nevertheless, evolving evidence has shown that NIV may have a more significant and helpful role than it was firstly considered. NIV avoids the need for sedation, allows easier communication with patient, and requires less intensive nursing care [32-35].

There are three types of NIV: High Flow Nasal Oxygen (HFNO), Continuous Positive Aire Pressure (CPAP) and BiPAP (Bi-Level Positive Airway Pressure) [32].

High Flow Nasal Oxygen (HFNO)

HFNO therapy through a nasal cannula is a technique whereby heated and humidified oxygen is delivered to the nose at high flow rates. These high flow rates generate low level of positive pressure in the upper airways, and the fraction of inspired oxygen (FIO2) can be attuned by varying the fraction of oxygen in the driving gas. The high flow rates may also reduce physiological dead space by flushing expired CO2 from the upper airway, a process that possibly explains the observed decrement in the process of breathing. In patients with acute respiratory failure of various origins, high flow oxygen has been shown to result in better comfort and oxygenation than standard oxygen therapy delivered through a face mask [35,109]. Nonetheless, the use of HFVO remains controversial in suspected and confirmed severe cases of COVID-19 disease. As a result, currently in the UK, the national guidance does not recommend HFNO in COVID-19 because for the lack of evidence of efficacy, the high oxygen usage, and risk of infection spread [8,14,35,110].

Bilevel positive airway pressure (BiPAP)

BiPAP is commonly used in the care of patients with chronic respiratory disease, so it may be useful in COVID-19 patients. In COVID-19, BiPAP may have a clinical use to improve the work of breathing. However, it carries a risk that inappropriate settings may allow the patient to take an excessively large tidal volume causing baro and volutrauma. BiPAP allows for a high driving pressure coupled with a low driving pressure. Prior to commencing BiPAP, the patient must be assessed for a pneumothorax, ideally by a chest X-Ray or ultrasound. Due to the need for chest auscultation for COVID-19 patients, is not recommended as it increases the risk of transmission to the healthcare professional [8,111,112].

Continuous Positive Airway Pressure (CPAP)

CPAP is nowadays the preferred form of NIV in the management of COVID-19 patients. With improved and commercial available CPAP equipment, there is now growing evidence that it may be of benefit to patients in the disease process, avoiding hypoxia, and then may preventing deterioration and reducing the need for invasive ventilation at all [113-116]. CPAP is usually commenced at a higher level than normal intrinsic pressure around 5 cm H2O. For most patients with ARDS, it is secondary to conditions which either collapse the alveolar or widen the gap between the alveolar and the blood vessels that surround them thereby reducing gaseous exchange. The application of Positive End Expiratory Pressure (PEEP) assists in maintaining the patient's airway pressure prevents alveolar collapse, in turn increasing lung volumes and distends them to reduce the distance between the alveolar and the blood vessels to improve gaseous exchange. In severe COVID-19, initial CPAP setting have been suggested 10 cm H2O and 60% oxygen [14,110,112,116-122].

Conclusion

We strongly recommend to early use CPAP in all Covid-19 patient who present the first mild respiratory symptoms, such as cough, or light tachypnea and hyperpnea, etc., when they are still outside the ICUs, i.e. in regular wards or at patient's homes. This method would prevent periods of hypopnea and hypoxia which can stimulate the synthesis of ACE in lung endothelial cells, finally leading to cytokine storm, which can cause ARDS and multi-organ failure [9,14,110,112,116,118].

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