



Obstructive Sleep Apnea Syndrome as an Important Risk Factor in Severe Covid-19 Disease

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Abstract

OSAS has been considered by some authors an important risk factor for severe Covid-19. Risk factors for mortality in COVID-19, such as cardiovascular and cerebrovascular complications or comorbidities, for example hypertension, heart failure, coronary artery disease, cerebrovascular diseases, diabetes mellitus, and obesity are commonly seen in OSAS patients. SARS-CoV-2 uses the ACE2 receptor for host cell entry, and augmented expression of ACE and dysregulation of the renin-angiotensin system in untreated OSAS patients, due to chronic intermittent hypoxia, has been shown. Angiotensin converting enzyme (ACE) abnormalities have been implicated in the pathogenesis of cardiovascular and cerebrovascular diseases. Therefore, it is suspected that OSAS (particularly with concurrent obesity) could potentially contribute to worsening hypoxemia leading to the cytokine storm that typically occurs in patients with COVID-19, which can cause acute respiratory distress syndrome (ARDS) and multiorgan failure. Happy or silent hypoxemia in OSAS patients can even induce more confusion to clinicians in patients who can speedily jump clinical evolution stages and suffer ARDS. Evolving evidence has shown that Non-Invasive Ventilation (NIV) may have a more significant and helpful role than firstly thought, mainly if it is used in an early phase of Covid-19, when the first respiratory symptoms appear. CPAP is nowadays the preferred form of NIV in the management of the hypoxemic COVID-19 patient. With improved and enhanced CPAP equipment, there is now growing evidence that it may be of benefit to patients early in the disease process, may prevent deterioration to ARDS reducing the need for invasive ventilation at all.

Keywords

Covid-19, Obstructive sleep apnea syndrome (OSAS), SARS-CoV-2, Acute respiratory distress syndrome (ARDS), Non-invasive ventilation, CPAP

Introduction

According the recent publications, agedness, hypertension, cardiovascular diseases, lung diseases, and diabetes mellitus seem to be the main risk factors for mortality in COVID-19 [1-10]. Nevertheless, publications about the possible association between obstructive sleep apnea syndrome (OSAS) and COVID-19 are relatively scarce [11-15].

OSAS has been considered by some authors an important risk factor for severe Covid-19 [16,17]. The prevalence of several cardiovascular diseases is increased with OSAS with still unclear reasons. Bhatraju, et al. evaluated 24 patients with COVID-19 in an ICU in Washington State, and they revealed that 21% had OSA [18]. Additionally, Arentz, et al. evaluated 21 patients with COVID-19 in an ICU and observed that 28.6% complained [19].

Risk factors for mortality in COVID-19, such as cardiovascular and cerebrovascular complications or comorbidities, for example hypertension, heart failure, coronary artery disease,

cerebrovascular diseases, diabetes mellitus, and obesity are commonly seen in OSAS patients [4,9,20-22]. Fibrotic changes can also be seen after COVID-19, and fibrosis was previously shown to be a risk factor for OSAS [23].

Worth mentioning, the augmented expression of ACE and dysregulation of renin-angiotensin system in untreated OSAS patients due to chronic intermittent hypoxia has been shown. Angiotensin converting enzyme (ACE) abnormalities have been implicated in the pathogenesis of cardiovascular

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Accepted: December 21, 2020

Published online: December 23, 2020

Citation: Machado C, DeFina PA, Machado Y, et al. (2020) Obstructive Sleep Apnea Syndrome as an Important Risk Factor in Severe Covid-19 Disease. *J Clin Anesth Pain Manag* 4(2):150-155

and cerebrovascular diseases [24-27].

SARS-CoV-2 uses the ACE2 receptor for host cell entry. The angiotensin converting enzyme (ACE) is a zinc metallo-peptidase, whose main functions are to convert angiotensin I into angiotensin II (a vasoactive peptide) and to inactivate bradykinin. Because of its effects upon vascular tone and the formation of the atherosclerotic plaque, alterations in ACE production have been implicated in the pathogenesis of various cardiovascular and cerebrovascular diseases [28-30].

Barcelo, et al. concluded that the plasma activity of ACE is significantly increased in patients with untreated OSAS, which is independent of the presence of arterial hypertension. These authors ruled out that different genotype distributions can result in different ACE activity levels, because no different distribution or allelic frequency was found between OSAS patients and healthy subjects [31].

OSAS leads to repetitive airway collapse with apnea/hypopnea and hypoxia during sleep. It is important to emphasize that these episodes of hypoxia/reoxygenation that occur during each episode of apnea in OSAS patients can stimulate the synthesis of ACE in endothelial cells, inducing a higher ACE activity, contributing to the increased prevalence of cardiovascular and cerebrovascular diseases reported in OSAS patients [31,32].

Therefore, it is suspected that OSAS (particularly with concurrent obesity) could potentially contribute to worsening hypoxemia and the cytokine storm that occurs in patients with COVID-19. Obesity likely contributes to hypoxemia by reducing end-expiratory lung volume and by contributing to positive pleural pressures at end-exhalation. Both OSAS and obesity hypoventilation can cause important hypoxemia, which could worsen hypoxemia in COVID-19 pneumonia. Additionally, both OSAS and obesity could exacerbate the cytokine storm that can happen in with SARS-CoV-2 infection, which can cause acute respiratory distress syndrome (ARDS) and multiorgan failure, given that both OSAS and obesity may be proinflammatory conditions [33-37].

OSAS has been found to be an independent risk factor for post-obstructive pulmonary edema in patients requiring tracheostomy [38,39]. Patients with OSAS requiring surgery have been shown to have a higher rate of pulmonary complications with hypoxemia being most common, even following adjustment for body mass index [40-43].

Clinicians must consider the diagnosis of OSAS in Covid-19 patients. A simple questionnaire, without the needs for a polysomnography study, might give a high level of confidence that that the patient is complaining OSAS [44-48].

OSAS patients may experience such alterations in pulmonary mechanics as airflow obstruction, decreased lung volumes, and impaired gas exchange, all of which may predispose them to develop ARDS [49].

Our hypothesis is that episodes of sleep apnea in Covid-19 patients can provoke a speedy progress to acute distress respiratory syndrome (ARDS), requiring mechanical ventilation [50-52].

Acute Respiratory Distress Syndrome and Happy or Silent Hypoxemia in Covid-19 Patients Complaining OSAS

The most characteristic and challenging symptoms of Covid-19 are related to acute respiratory distress syndrome (ARDS) [53-56]. Wang, et al. reported that about 46% to 65% of the patients admitted in the intensive care units (ICUs) required mechanical ventilation in a brief period of time and died because of respiratory distress. According to these data, about 89% of the patients in intensive care units (ICUs) could not breathe by their own, worsening in a short period of time and dying due to respiratory failure [2,57]. ARDS remains a common cause of respiratory failure in ICUs with estimated mortality rate of over 40% [50].

Moreover, 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. Nonetheless, these patients very frequently rapidly progress to ARDS, requiring mechanical ventilation. This phenomenon is referred as silent or 'happy or silent hypoxemia' [58-62].

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 [63,64].

Hence, happy or silent hypoxemia in OSAS patients can even induce more confusion to clinicians in patients who can speedily jump clinical evolution stages and suffer ARDS [50,63,64].

Pulse oximetry which measures oxygen saturation (SpO_2) is often used to detect hypoxemia. Nevertheless, SpO_2 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 $PaCO_2$) 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 PaO_2 , explaining why SpO_2 can be well-preserved in the face of a profoundly low PaO_2 . 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 CO_2 produces an increment in the alveolar partial pressure of oxygen and finally lead to a raise in SpO_2 [50,59,63,65,66].

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 [67-69]. 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 firstly thought, mainly if it is used in an early phase of the disease when the first respiratory symptoms appear. NIV avoids the need for sedation, allows easier communication with patient, and requires less intensive nursing care [16,67,70,71].

There are three types of NIV: High Flow Nasal Oxygen (HFNO), Continuous Positive Airway Pressure (CPAP) and BiPAP (Bi-Level Positive Airway Pressure) [67].

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 levels of positive pressure in the upper airways, and the fraction of inspired oxygen (FiO_2) 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 CO_2 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 [71,72].

Nonetheless, the use of HFNO 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 [71,73-75].

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 [75-77].

Continuous positive airway pressure (CPAP)

CPAP is nowadays the preferred form of NIV in the management of COVID-19 patients. With improved and enhanced CPAP equipment, there is now growing evidence that it may be of benefit to patients early in the disease process, may prevent deterioration and reduce the need for invasive ventilation at all.

CPAP is usually commenced at a higher level than normal intrinsic pressure around 5 cmH_2O . 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 settings have been suggested 10 cmH_2O and 60% oxygen [12,15,73,74,77-82].

It is also recommended to early use CPAP in all Covid-19 patient, even without complaining OSAS, when the first respiratory symptoms appear, 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 stimu-

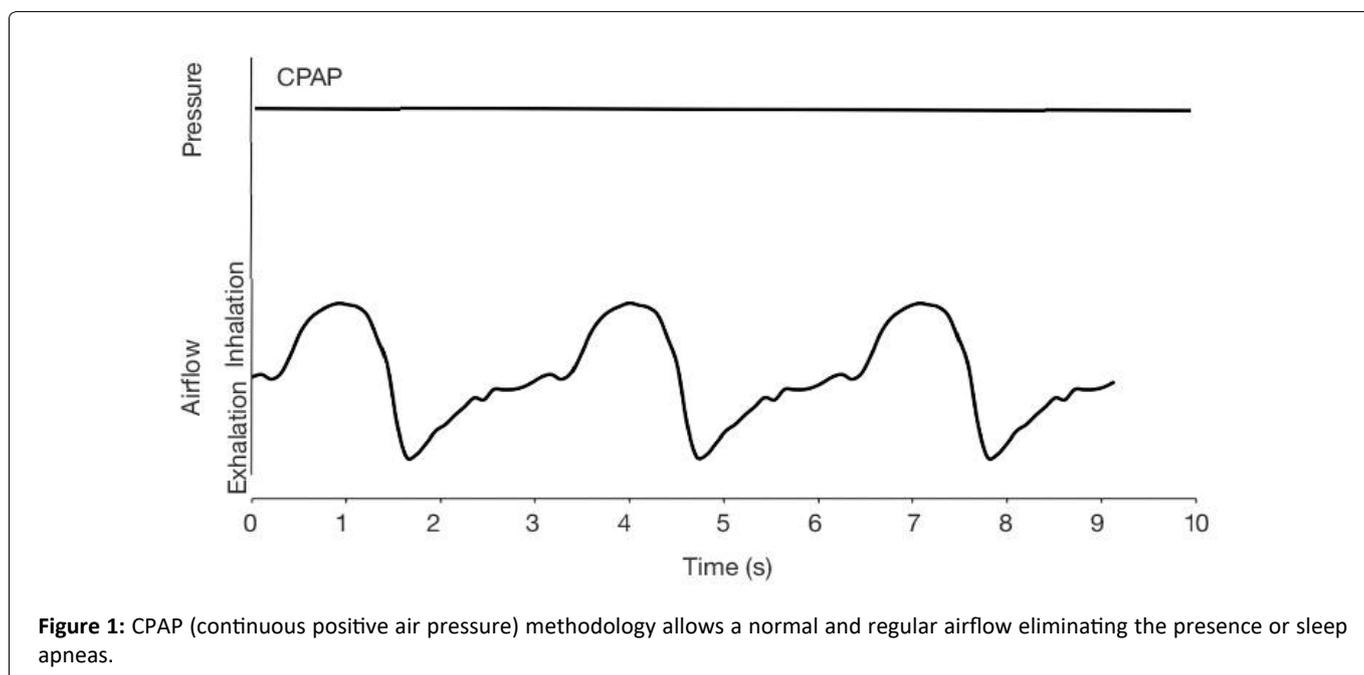


Figure 1: CPAP (continuous positive air pressure) methodology allows a normal and regular airflow eliminating the presence or sleep apneas.

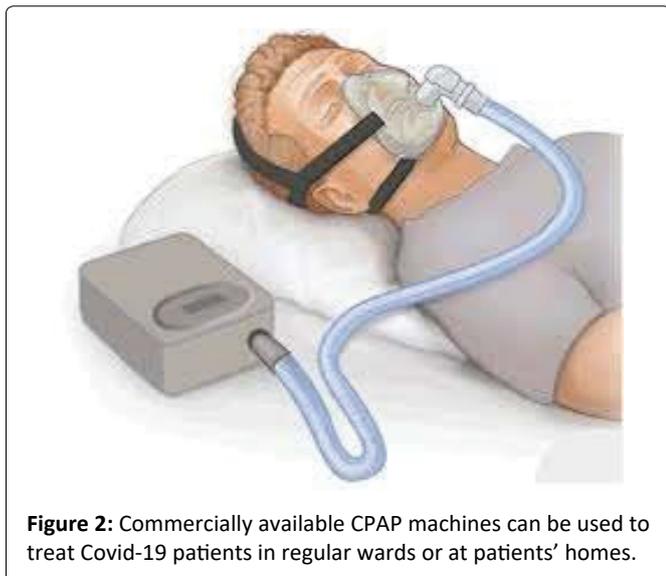


Figure 2: Commercially available CPAP machines can be used to treat Covid-19 patients in regular wards or at patients' homes.

late the synthesis of ACE in endothelial cells, finally leading to cytokine storm, which can cause ARDS and multiorgan failure [50,73,74,77,79,80] (Figure 1 and Figure 2).

Conclusion

1. OSAS should be considered as an important risk factor for severe Covid-19.
2. Clinicians must consider the diagnosis of OSAS in Covid-19 patients. A simple questionnaire, without the needs for a polysomnography study, might give a high level of confidence that the Covid-19 patient is complaining OSAS.
3. Clinicians should suspect the possibility of happy or silent hypoxemia presence, even with SpO₂ normal values, measured by pulse oximeter. SpO₂ can be well-preserved in the face of a profoundly low PaO₂. It is important to remark that patients with happy or silent hypoxemia don't express sense of dyspnea.
4. NIV using CPAP must be used very early in OSAS patients, not only in ICUs, but in regular wards or at patient's homes.
5. We also recommend to early use CPAP in any Covid-19 patient, even without complaining OSAS, when the first respiratory symptoms appear, such as cough, or even light tachypnea and hyperpnea, etc., even outside ICUs, i.e. in regular wards or at patient's homes.

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DOI: 10.36959/377/347