EXPERT VIEW/REVIEW PAPER

COVID-19 and Obstructive Sleep Apnea

Arup K Halder

Abstract

Obstructive sleep apnea (OSA) is a disease that manifests with snoring, excessive daytime sleepiness, and fatigue. OSA is the mother of many diseases. COVID-19 is such a disease that can cause greater harm to the patients with OSA. The prevalence of clinically significant OSA where an urgent intervention was required was 6–17% in the adult population, whereas the prevalence was as high as 49% in the advanced age-group. The prevalence of OSA is always more in adult men than in adult women. Expressions of COVID-19 among different peoples are varied. But four main determinants are the following: (1) renin–angiotensin–aldosterone system (RAAS), (2) oxidative stress of the individual, (3) endothelial dysfunction, and (4) immune responses. All of these four systems are in deranged state in OSA patients; they are already in the hyperactive states due to intermittent hypoxia, sympathetic activation, and poor sleep quality. So any acute insult like COVID-19 may throw these systems out of control. The acute "happy hypoxia" of COVID-19 can really be dangerous in the presence of "chronic intermittent happy hypoxia" of OSA.

Keywords: COVID-19, Endothelial dysfunction, Happy hypoxia, OSA, Oxidative stress, RAAS.

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Introduction

Obstructive sleep apnea (OSA) is a disease that manifests with snoring, excessive daytime sleepiness, and fatigue. In this disease, there is a repeated upper airway collapses or closures during sleep, which results in drop in oxygen saturation, frequent arousal and repeated sympathetic stimulation, loss of deep stages of sleep, swing in arterial blood gas, and repeated changes in intrathoracic pressures. All these lead to a proinflammatory state and invite many diseases like hypertension, cardiovascular disorders, neurological diseases, diabetes, metabolic syndrome, and obesity. So OSA is the mother of many diseases. Unfortunately, the awareness of the disease among the general population and even among medical professionals is very poor. So a lot of OSA patients remain undiagnosed and untreated. A pool of patients are at reduced physiological reserve and any acute insult can jeopardize their health. COVID-19 is such a disease that can cause greater harm to the patients with OSA. But the unfortunate saga continues in this context also, and OSA is often overlooked as a potential comorbidity in most of the population. Here in this article, we will look for the connection between COVID-19 and OSA, try to analyze the prevalence of this combo, and try to formulate plans to mitigate the problem.

Obstructive Sleep Apnea: A Common Condition

The OSA is a rare condition currently because of the rare awareness. In fact, it is a very common condition with a very high prevalence. However, there is a heterogeneity of the prevalence in different populations, which is probably ascribed due to heterogeneity of the criteria used to define OSA.[1] The prevalence of clinically significant OSA, where an urgent intervention was required, was 6[2]–17%[3] in the adult population, whereas the prevalence was as high as 49% in the advanced age group.[4] If the mild OSA groups are also included in the study, the prevalence rate increases further. Two studies have shown a prevalence rate of OSA as 88% in men aged 65–69 years[5] and 90% in men aged 60–85 years.[4] The prevalence of OSA is always more in adult men than adult women.

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A Sharing Common Pathway of COVID-19 and OSA Pathophysiology

Expressions of COVID-19 among different people are varied. They may be completely asymptomatic in few people but may be severe in others. The underlying host response determines the outcome of the disease. The host response depends on multiple factors. But four main determinants are the following:

- Renin–angiotensin–aldosterone system (RAAS)
- Oxidative stress of the individual
- Endothelial dysfunction
- Immune responses.

All of these four systems are in deranged state in OSA patients; they are already in the hyperactive states due to intermittent hypoxia, sympathetic activation, and poor sleep quality. So any acute insult like COVID-19 may throw these systems out of control. The pieces of evidence are pretty convincing that these systems are already in accelerated phase in OSA. Let us scrutinize them sequentially.

Renin–Angiotensin–Aldosterone System

Renin–angiotensin–aldosterone system is one of the prime regulators of cardiovascular and various other functions.[6] Altered activation of RAAS is attributed to pathogenesis of many diseases such as hypertension, myocardial infarction, heart failure, diabetes,

and inflammatory lung disease. Renin acts on angiotensinogen and converts it to angiotensinogen I. Angiotensinogen-converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor and proinflammatory.[7] But this effect is counterbalanced by another enzyme called angiotensin-converting enzyme 2 (ACE2). ACE2 was discovered by two independent research groups in 2000. ACE2 also acts on angiotensin I and converts into angiotensin (1–7), which is vasodilator and anti-inflammatory. So ACE2 counters the activity of ACE by reducing the amount of angiotensin II and increasing angiotensin (1–7), acting as a negative regulator of RAAS. So ACE2 exhibits a protective action on cardiovascular and respiratory systems. So any downregulation of ACE2 translates into more angiotensin II.

The classical pathway is activated by OSA. It produces more angiotensin II, which is proinflammatory. It causes vasoconstriction, vascular remodeling, and a prothrombotic state. This is often manifested as hypertension and cardiovascular disorders. The following pieces of evidence support this idea.

- In a meta-analysis, OSA was associated with a higher level of angiotensin II and aldosterone, particularly in patients with hypertension.[8]
- In another study, increased ACE activity was highlighted in untreated OSA patients regardless of hypertension.[9]
- Further, the severity of nocturnal hypoxemia in OSA augments RAAS activity.[8,9]
- Obesity is a significant comorbidity in OSA and also affects the RAAS activity.[10]

Similarly, in COVID-19 the RAAS pathway is activated. After the initial engagement of COVID-19 spike protein with ACE2 receptor, there is subsequent downregulation of ACE2 abundance on cell surfaces.[11] Continued viral infection and replication contribute to reduced membrane ACE2 expression. This leads to increased activity of the vasoconstrictor and proliferative axis (angiotensin II/ACE) and downregulation of protective axis (ACE2/angiotensin 1–17). This in turn is associated with higher risks of acute thrombosis, destabilization of atherosclerotic plaques, enhanced platelet activity, and coagulation.

We still do not have any solid evidence on how differently the RAAS is activated in COVID-19 patients in OSA than non-OSA patients. But an acute on chronic activation in COVID-19–OSA combo should certainly bring more damage, than in either disease alone.

Oxidative Stress

The oxidative stress is actually the defensive mechanism of the body that is meant to kill the non-self protein. It is mediated by superoxide radicals, also known as reactive oxygen species (ROS). But overwhelmed ROS can also damage any cells containing DNA or RNA. So it is kept in check with a simultaneous action of two systems—the damaging pro-oxidant (PO) system and the balancing antioxidant system (AO).

Various studies have shown an oxidative stress increase in OSA. This is due to multiple reasons as follows.

- Enhanced release of superoxide from leukocytes: The circulating neutrophils and monocytes of OSA patients exhibited markedly enhanced *in vitro* release of superoxide radical anions. This is mainly due to the activation of NADPH oxidase (NOX). This is a major superoxide-generating enzyme and its expression is unregulated in OSA.
- Reduced bioavailability of nitric oxide (NO): Through various pathways, oxidative stress can reduce the NO bioavailability in OSA and this is the cause of endothelial dysfunction (described later).
- Increased oxidation of lipids, proteins, and DNA: The excessively generated ROS may lead to increased oxidation of biological compounds such as lipids, proteins, and DNA. This is often the cause of atherosclerosis.[12]
- Reduced AO capacity: The effects of oxidative stress can be counteracted by AO system. But this AO system is impaired in untreated OSA.[13] Lower levels of superoxide dismutase (SOD) have been described in OSA,[14] which is one of the key AO enzymes.

In COVID-19, the oxidative stress occurs through the following pathway: Both viral infection and RAAS activation produce ROS leading to oxidative burst. After viral entry macrophages are activated by Toll-like receptors, there is a secretion of tumor necrosis factor alpha (TNF-α), which in turn activates NADPH oxidase. NADPH oxidase is the main enzyme that stimulates the production of ROS. The resulting ROS targets the virus. But NADPH being overused by inflammation also brings certain challenges to AO system.[15]

There is an acute or chronic rise of the oxidative stress, with reduced AO reserve; the COVID-19–OSA combo has the potential to bring more damages.

Endothelial Dysfunction

In COVID-19: The beginning of endothelial dysfunction in COVID-19 is perhaps the trigger to complications. The main causes of endothelial dysfunction are reduced activity of ACE2/angiotensin (1–7) axis with enhanced activity of ACE/angiotensin II axis in the presence of oxidative stress. This leads to imbalance between two systems of NO synthesis. It decreases the endothelial NO synthase (eNOS) that is anti-inflammatory, but increases the inducible NO synthase (iNOS) that is proinflammatory, and produces NO radicals. This imbalance between AO and PO system results in destruction of endothelial cells and pro-thrombotic states. This causes blockage of small vessels and hypoxic environment. In the hypoxic situation, there are ROS generation and hypoxia–inducible factor 1 alpha (HIF-1α) activation.[15] Consequently, it induces the expression of furic enzymes and further viral activation.

In OSA: Several studies have suggested impaired endothelial functions in OSA.[16,17] The three potential etiologies include hypoxemia, oxidative stress, and systemic inflammation. Endothelial injury results in the alteration of endothelial hormones that are responsible for maintaining vascular tone and prevention of abnormal cell proliferation, increasing coagulopathy and altered leukocyte trafficking. This also exposes subendothelial structures to diverse growth factors in the blood.[18] The resultant vasoconstriction, vascular smooth muscle proliferation, and hyper-coagulability may lead to adverse cardiovascular consequences associated with OSA, such as hypertension, cardiovascular disorders, and stroke.

Immune Dysfunction, Cytokine Storm, and Acute Respiratory Distress Syndrome (ARDS) in COVID-19

In COVID-19: In COVID-19 pneumonia, the aberrant release of proinflammatory cytokines leads to lung injury by damaging the epithelial and endothelial barriers, microvascular leakage,

alveolar edema, and hypoxia.[5] The antigen-presenting cells (APCs) including macrophages present COVID-19 antigen to T cells. T cells are activated to produce various cytokines via Th17 and others by a positive feedback loop.[15] Also during viral replication, nuclear factor-kappa beta (NF-kβ) pathway is activated. The uncontrolled release of proinflammatory factors like IL-6, IL-8, IL-1β, GM-CSF, and chemokines like CCL-2, CCL-5, CCL-3, together with ROS, causes ARDS leading to pulmonary fibrosis and death.[15]

In OSA: The chances of ARDS and pulmonary complications are more in OSA. This was nicely depicted by one study which is evaluated the chances of peri- and postoperative pulmonary complications in surgical and orthopedic patients.[19] They selected these groups to avoid or reduce the potential biases of medical diseases contributing to ARDS and other complications. The study was conducted from 1998–2007 and recruited 2,610,441 postoperative orthopedic patients and 3,441,262 surgical postoperative patients. Of those, 2.52 and 1.4% had OSA, respectively. The following table shows the rate of postoperative complications among OSA and non-OSA patients (Table 1).

From the above table, the researchers concluded that OSA is an independent risk factor for perioperative pulmonary complications. Therefore, it is a piece of indirect evidence that OSA patients are at increased risk of pulmonary complications when confronted with any acute insults.

From the above discussions, it is evident that COVID-19 and OSA follow the same pathways in different time frames. The already overwhelming pathways in OSA should respond in a more deadly manner during the acute insults.

The pathophysiological manifestations of OSA are poor sleep and obstructive respiratory events during sleep. So sleep *per se* is also an important determinant of cellular events. Sleep deprivation from any cause, be it OSA, or other causes, will jeopardize the body milieu. So the following section is devoted to the effect of sleep deprivation on immunity. This sleep deprivation can occur in OSA, shift work, or due to other causes.

Sleep and Immunity[20]

Many studies have suggested that total sleep deprivation and rapid eye movement (REM) sleep deprivation modify various components of the immune system, such as the percentage of cell populations, like CD4+, CD8+, and NK cells.[21] Alternatively, sleep patterns are also altered during acute infections. So there is a bidirectional relationship between sleep and immunity. In this regard, two cytokines deserve a special mention—TNF-α and IL-6.

TNF-α: It is a classic proinflammatory cytokine that has also been implicated in the regulation of sleep.[22] Systemic administration of TNF-α promotes both duration and depth of non-rapid eye movement (NREM) sleep. The level of TNF-α is often enhanced following sleep deprivation.[23] TNF-α leads to the activation of NF-kβ pathways that in turn activates NOS, cyclooxygenase 2, and adenosine receptors, all of which are implicated in sleep regulation.[24,25] In OSA, patients with excessive daytime sleepiness TNF-α concentrations are found to be elevated.[26]

IL-6: It is also a classic proinflammatory cytokine that has also been implicated in the regulation of sleep. It produces similar effects like TNF-α, in animal models. Intermittent hypoxia in OSA induces a polarization of macrophages along with increased production of IL-6.[27] OSA patients with excessive daytime sleepiness also exhibit increased IL-6 levels.[28] During acute infections, the secretion of IL-1, IL-6, IL-10, IL-12, and TNF-α peaks. The hypothalamus, hippocampus, brainstem, and cortex contain receptors for IL-1 and TNF-α.[29] This induces excessive sleepiness during acute infections. This may be an adaptive response to such adverse circumstances and devotes more of its energy to the immune system.

In COVID-19, the TNF-α and IL-6 both are increased. So there may be excessive sleepiness and fatigue. Sleep deprivation from any prior cause will just add to these cytokine levels further in acute infections.

Prevalence of COVID-19–OSA Combo

In one of the largest case series of 5,700 patients admitted in 12 different New York hospitals with a median age of 63 years (IQR 52–75), the commonest comorbidity was hypertension (56.6%), but they also stated that they had 41.7% obese patients and 2.9% patients with OSA.[30] A recent Finnish study evaluated the existence of OSA in COVID-19 patients.[31] They found that OSA was present in 29% of the patients of hospitalized COVID-19, being almost 10 times higher than its prevalence. Other small studies have shown that OSA was present in 21% of the patients in a case series in Seattle and 28.6% of the critically ill COVID-19 patients in Washington.[32,33] The ongoing OSA–COVID-19 study (NCT 04363333) will throw further light into the association of COVID-19 and OSA.

Conclusion

The OSA is a serious comorbidity that can lead to an acute complication in COVID-19. Just an awareness about this condition can save many lives. All COVID-19 patients should be scrutinized for this condition like other comorbidities. Few simple questions or questionnaires like STOP BANG or BERLIN may easily screen the suspected patients. Polysomnography, which is a gold standard for diagnosis of this condition, should not be done in acute conditions. It should be reserved for future, after recovery from infection, for highly suspected patients. If OSA is diagnosed clinically in a COVID-19 patient, they should be closely monitored for complications. They also require monitoring of oxygen saturation during sleep as an acute desaturation in COVID-19 in the presence of OSA-induced oxygen desaturation may be dangerous. No other diseases apart from OSA can cause such a dangerous level of decrease in oxygen saturation in the absence of the patient's knowledge. So the acute "happy hypoxia" of COVID-19 can really

Table 1: Pulmonary complications of surgical patients with OSA

Pulmonary complications	*Orthopedic with OSA*	*Orthopedic without OSA*	*Surgical with OSA*	*Surgical without OSA*
Aspiration pneumonia	1.18%	0.84%	2.79%	2.05%
ARDS	1.06%	0.45%	3.79%	2.44%
Mechanical ventilation	3.99%	0.79%	10.8%	5.94%
Pulmonary thromboembolism	0.51%	0.42%	0.45%	0.49%

be dangerous in the presence of "chronic intermittent happy hypoxia" of OSA.

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References

1. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev 2017;34:70–81. DOI: 10.1016/j.smrv.2016.07.002.
2. Reddy EV, Kadhiravan T, Mishra HK, et al. Prevalence and risk factors of obstructive sleep apnea among middle-aged urban Indians: a community-based study. Sleep Med 2009;10(8):913–918. DOI: 10.1016/j.sleep.2008.08.011.
3. Tufik S, Santos-Silva R, Taddei JA, et al. Obstructive sleep apnea syndrome in the Sao Paulo epidemiologic sleep study. Sleep Med 2010;11(5):441–446. DOI: 10.1016/j.sleep.2009.10.005.
4. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3(4):310–318. DOI: 10.1016/S2213-2600(15)00043-0.
5. Lee SD, Kang SH, Ju G, et al. The prevalence of and risk factors for sleep-disordered breathing in an elderly Korean population. Respiration 2014;87(5):372–378. DOI: 10.1159/000358442.
6. Ekiz T, İnönü Köseoğlu H, Pazarlı AC. Obstructive sleep apnea, renin-angiotensin system, and COVID-19: possible interactions. J Clin Sleep Med 2020;16(8):1403–1404. DOI: 10.5664/jcsm.8576.
7. Fraga-Silva RA, Sorg BS, Wankhede M, et al. ACE2 activation promotes antithrombotic activity. Mol Med 2010;16(5–6):210–215. DOI: 10.2119/molmed.2009.00160.
8. Jin ZN, Wei YX. Meta-analysis of effects of obstructive sleep apnea on the renin-angiotensin-aldosterone system. J Geriatr Cardiol 2016;13(4):333–343. DOI: 10.11909/j.issn.1671-5411.2016.03.020.
9. Barceló A, Elorza MA, Barbé F, et al. Angiotensin converting enzyme in patients with sleep apnoea syndrome: plasma activity and gene polymorphisms. Eur Respir J 2001;17(4):728–732. DOI: 10.1183/09031936.01.17407280.
10. McSharry D, Malhotra A. Potential influences of obstructive sleep apnea and obesity on COVID-19 severity. J Clin Sleep Med 2020;16(9):1645. DOI: 10.5664/jcsm.8538.
11. Vaduganathan M, Vardeny O, Michel T, et al. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382(17):1653–1659. DOI: 10.1056/NEJMsr2005760.
12. Bauters F, Rietzschel ER, Hertegonne KB, et al. The link between obstructive sleep apnea and cardiovascular disease. Curr Atheroscler Rep 2016;18(1):1. DOI: 10.1007/s11883-015-0556-z.
13. Vicente E, Marin JM, Carrizo SJ, et al. Upper airway and systemic inflammation in obstructive sleep apnoea. Eur Respir J 2016;48(4):1108–1117. DOI: 10.1183/13993003.00234-2016.
14. DeMartino T, Ghoul RE, Wang L, et al. Oxidative stress and inflammation differentially elevated in objective versus habitual subjective reduced sleep duration in obstructive sleep apnea. Sleep 2016;39(7):1361–1369. DOI: 10.5665/sleep.5964.
15. Delgado-Rochea L, Mestab F. Oxidative stress as key player in severe acute respiratory syndrome coronavirus (SARS-CoV) infection. Arch Med Res 2020;51(5):384–387. DOI: 10.1016/j.arcmed.2020.04.019.
16. Budhiraja R, Parthasarathy S, Quan SF. Endothelial dysfunction in obstructive sleep apnea. J Clin Sleep Med 2007;3(4):409.
17. Ip MS, Tse HF, Lam B, et al. Endothelial function in obstructive sleep apnea and response to treatment. Am J Respir Crit Care Med 2004;169(3):348–353. DOI: 10.1164/rccm.200306-767OC.
18. Budhiraja R, Tuder RM, Hassoun PM. Endothelial dysfunction in pulmonary hypertension. Circulation 2004;109(2):159–165. DOI: 10.1161/01.CIR.0000102381.57477.50.
19. Memtsoudis S, Liu SS, Ma Y, et al. Perioperative pulmonary outcomes in patients with sleep apnea after noncardiac surgery. Anesth Analg 2011;112(1):113–121. DOI: 10.1213/ANE.0b013e3182009abf.
20. Ibarra-Coronado EG, Pantaleón-Martínez AM, Velazquéz-Moctezuma J. The bidirectional relationship between sleep and immunity against infections. J Immunol Res 2015;2015. Article ID 678164, 14 p. DOI: 10.1155/2015/678164.
21. Dimitrov S, Lange T, Nohroudi K, et al. Number and function of circulating human antigen presenting cells regulated by sleep. Sleep 2007;30(4):401–411. DOI: 10.1093/sleep/30.4.401.
22. Kheirandish-Gozal L, Gozal D. Obstructive sleep apnea and inflammation: proof of concept based on two illustrative cytokines. Int J Mol Sci 2019;20(3):459. DOI: 10.3390/ijms20030459.
23. De Araújo Freitas IG, de Bruin PF, Bittencourt L, et al. What can blood biomarkers tell us about cardiovascular risk in obstructive sleep apnea? Sleep Breath 2015;19(3):755–768. DOI: 10.1007/s11325-015-1143-9.
24. Churchill L, Rector DM, Yasuda K, et al. Tumor necrosis factor alpha: activity dependent expression and promotion of cortical column sleep in rats. Neuroscience 2008;156(1):71–80. DOI: 10.1016/j.neuroscience.2008.06.066.
25. Krueger JM, Opp MR. Sleep and microbes. Int Rev Neurobiol 2016;131:207–225. DOI: 10.1016/bs.irn.2016.07.003.
26. Gozal D, Kheirandish-Gozal L. Obesity and excessive daytime sleepiness in prepubertal children with obstructive sleep apnea. Pediatrics 2009;123(1):13–18. DOI: 10.1542/peds.2008-0228.
27. Li Y, Vgontzas AN, Fernandez-Mendoza J, et al. Objective, but not subjective, sleepiness is associated with inflammation in sleep apnea. Sleep 2017;40(2):zsw033. DOI: 10.1093/sleep/zsw033.
28. Van Eyck A, Van Hoorenbeeck K, De Winter BY, et al. Sleep-disordered breathing, systemic adipokine secretion, and metabolic dysregulation in overweight and obese children and adolescents. Sleep Med 2017;30:52–56. DOI: 10.1016/j.sleep.2015.11.014.
29. Bhattacharjee R, Kim J, Kheirandish-Gozal L, et al. Obesity and obstructive sleep apnea syndrome in children: a tale of inflammatory cascades. Pediatr Pulmonol 2011;46(4):313–323. DOI: 10.1002/ppul.21370.
30. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323(20):2052–2059. DOI: 10.1001/jama.2020.6775.
31. Feuth T, Saaresranta T, Karlsson A, et al. Is sleep apnoea a risk factor for Covid-19? Findings from a retrospective cohort study. medRxiv. DOI: 10.1101/2020.05.14.20098319.
32. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region – case series. N Engl J Med 2020;382(21):2012–2022. DOI: 10.1056/NEJMoa2004500.
33. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020;323(16):1612–1614. DOI: 10.1001/jama.2020.4326.