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# OBSTRUCTIVE SLEEP APNEA *in* PULMONARY CRITICAL CARE

## Essential Ventilatory Approach

ANTONIO M. ESQUINAS
TAKATOSHI KASAI
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# Obstructive Sleep Apnea in Pulmonary Critical Care

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*To our patients and their families*

# Contents

# Preface

There is a significant prevalence of OSA disease in the current population with a great impact on the development of complications when these patients require hospital admission. The status of this patients is more vulnerable in critical situations when they require invasive or non-invasive ventilatory support in intensive care units or serious surgical procedures. In many of these cases, the development of infectious or non-infectious complications aggravates the prognosis. In these situations, precise knowledge of the pathophysiological aspects and the development of preventive actions and early treatment are required as it acts in the most vulnerable phase of this disease.

This book describes all the actions that are required as well as possible scenarios that the hospitalized patient with OSA may require.

The book has been structured from the analysis of epidemiology, comorbidities, Pharmacological data, and a description of all the Ventilatory Management Options (High Flow Nasal Oxygen in Sleep-Disordered Breathing, Invasive Mechanical Ventilation), details of essential aspects in Monitoring in Critical Care and a whole analysis of situations such as Hypercapnic. OSA and COPD: The Overlap Syndrome, Asthma. Overlap Syndrome: Concept and Ventilatory Modes, Severe Acute Pneumonia, Acute Heart Failure, Neurological Diseases, Interstitial Lung Diseases: Pathophysiology and Treatment.

We have analyzed an essential aspect such as weaning Mechanical Ventilation, extubation Period: Clinical and Practical Implications and all the situations of greatest risk in Anesthesiology-Perioperative Medicine (Pathophysiology, Diagnosis and Treatment).

Finally, it has been considered that it is essential to complete this study with a design of how to carry out the preparation of these patients in the

discharge from Intensive Care Unit, determinants in Mortality and Outcome, Telemedicine: Clinical and social Life Effects.

We hope that this book may help in the complexity of OSA in critical care.

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# Chapter1

# Epidemiology

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## Abstract

Obstructive sleep apnea (OSA) is a chronic condition characterized by at least five obstructive events (apneas and hypopneas) per hour during sleep due to an intermittent, complete, or partial, upper airway obstruction. OSA is related to various diseases determining an admission to intensive care unit (ICU) and poor outcome. Some articles have shown increased risk of poor outcomes and higher mortality and higher risk of admission to ICU in patients with hypercapnic acute respiratory failure with OSA compared to non-OSA patients. Thus, there is the necessity of earlier diagnosis for OSA patients in ICU and earlier treatment to improve the outcome. Their management in ICU must be individualized to increase the odds of discharge and to avoid the complications. The aim of this chapter is to describe the OSA in intensive care unit, its prevalence and what kind of complications OSA patients have.

**Keywords:** comorbidities, intensive care unit, hypercapnic acute respiratory failure, mortality, obstructive sleep apnea, outcome

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## Introduction

Obstructive sleep apnea (OSA) is nowadays considered as one of the most frequent chronic diseases, with multi-organ consequences and a high societal burden. OSA is characterized by at least five obstructive events (apnoea and hypopnoea) per hour during sleep due to an intermittent, complete, or partial, upper airway obstruction. Most of the time, the respiratory events are associated with snoring, oxygen desaturations and brief arousal from sleep with a BMI ≥ 40 kg/m2. The global prevalence of OSA in the middle-aged population is above 20% [1]. This prevalence has substantially increased over the last few decades owing to the parallel epidemics of obesity and type 2 diabetes [2]. OSA prevalence is even higher in patients suffering from cardiovascular diseases, reaching 50% in hypertension, arrhythmia, or stroke patients [3].

The combination of OSA and morbid obesity might be associated with some specific frailties and a relatively high risk of cardiovascular and metabolic comorbidities, along with an increased risk of mortality.

OSA patients often present multiple comorbidities, such as obesity, diabetes, hypertension, ischemic heart disease, heart failure and/or stroke, which are also frequently the underlying causes for intensive care unit (ICU) admission [4-7]. Sleep disordered breathing has also been identified as a common contributing cause of hypercapnic respiratory failure in obese patients admitted to the ICU [8]. In addition, patients with OSA often have co-morbidities, such as chronic obstructive pulmonary disease (COPD) and asthma [9], and these would aggravate and complicate the pulmonary conditions when OSA patients develop acute respiratory failure [10].

The prevalence of OSA in the ICU population has been reported as being between 7.8% and 10.3% according to two retrospective American surveys [11, 12]. OSA prevalence certainly appears to differ from one ICU to another depending on the predominant ICU activity (i.e., surgical versus medical, pediatric neurological or trauma oriented ICU). In a study the physician-reported prevalence of OSA of only 5.6% reflects a massive under-diagnosis of OSA in ICU patients [7] while, studies implementing polysomnographic assessment of ICU survivors reported a much higher OSA prevalence [13, 14]. A study assessing the prevalence and severity of OSA in patients surviving acute hypercapnic respiratory failure (AHRF) in the ICU by sleep studies, observed a much higher than expected prevalence of moderate to severe OSA and severe OSA for both COPD and non-COPD groups[14]. For patients admitted and surviving acute hypercapnic respiratory failure the prevalence of

OSA increases to 65%% [13, 14]. Extensive data have demonstrated that undiagnosed OSA syndrome is associated with an increased risk of poor outcomes and higher mortality in the postoperative period [15, 16].

Patients presenting with OSA at ICU admission were older, with a higher BMI and a larger number of comorbidities than non-OSA patients [17].

The most common reasons for first-time ICU admission in critically ill OSA patients were cardiovascular events, followed by respiratory events, cerebrovascular events, and infectious events [18]. Hang et al., [18] found that the clinical variables of the patients admitted due to respiratory, cerebrovascular, and cardiovascular events showed no significant differences in age, gender, BMI, apnoea-hypopnoea index (AHI), mean oxygen saturation ($SaO_2$), minimum ($SaO_2$), laboratory data, length of ICU stay and in-hospital and two-year mortality rate. However, patients admitted due to respiratory events had significantly higher APACHE II scores, lower arterial blood gas pH levels and higher PaCO2 than patients admitted due to cardiovascular and cerebrovascular events. There was no difference in short- and long-term mortality but patients admitted due to respiratory had a significantly higher incidence of requiring NIV after extubation and higher ICU readmission rates [18].

Obese patients admitted to an ICU require more complex management and those with OSA often need continuous positive airway pressure (CPAP) treatment [19].

OSA is known to be associated with renal decline [20, 21] and it has been reported that OSA is linked with a higher risk of acute kidney damage in critically ill patients [22]. Also, sleep apnea and deterioration in sleep quality might impair immune responses and protection against infections [23]; e.g., for influenza patients with exacerbation OSA was a significant contributor to the reasons for ICU admission [24]. Moreover, OSA patients are more sensitive to opioids developing central apneas after extubation [25]. Intravenous fluid loading also influences OSA severity [26]. Taken together, these reports advocate that, as for obese individuals, the detection of underlying OSA should impact ICU management.

Combining OSA with other comorbidities may be associated with an effect on the impact of hospital-free survival [14]. A retrospective observation designed to identify novel risk factors associated with readmission after hospitalization for acute exacerbation of COPD identified sleep apnea among other comorbid conditions, as a novel risk factor for readmission [27].

It has been assumed that OSA patients have increased morbidity and mortality when admitted to an ICU. A study found that OSA patients were

more likely to require ICU transfer and intubation or noninvasive positive pressure ventilation after surgery [28].

Recently, studies are being focused on the association between OSA status and the prognosis of critically ill patients, but with controversial results [7, 11]. One found that OSA was associated with decreased mortality [11] but the other did not identify such benefit [7]. A retrospective cohort study by Lin et al., found that compared with those without OSA, patients with OSA had a significantly lower risk of ICU- and in-hospital mortality [17]. After adjusted for age, gender, weight, SAPS II scores, sequential organ failure assessment (SOFA) score, comorbidities, and laboratory tests, OSA was still associated with decreased risk of mortality, which indicated that OSA itself might be a protective factor for mortality. Several factors could explain the protective effect of OSA in critical care patients. First, in this study, patients without OSA were older and had higher SAPS II scores, indicated that patients without OSA had greater severity of illness.

Second, long-term adaptation to hypoxia might cause ischemic preconditioning due to the nocturnal cycles of hypoxia-reoxygenation, which might alleviate the acute stress response and protect the cardiocirculatory system against infarction and further ischemic insults [29]. Furthermore, the mobilization, proliferative and angiogenic capacities of endothelial progenitor cells were heightened in patients with OSA, indicating that vascular endothelial cell repair might also be involved in the mechanism of cardiovascular protection [30]. Another mechanism by which OSA might reduce mortality was the development of coronary collaterals. OSA might promote angiogenesis through oxidative stress and upregulation of vascular endothelial growth factor in patients with coronary artery disease, which might trigger the development of coronary collaterals and improve blood supply to the heart [31].This adaptive change in the cardiovascular system might increase myocardial oxygen and reduce cardiovascular risk among patients with serious illnesses [32].

The prevalence of OSA in patients with severe Coronavirus Disease 2019 (COVID-19) has been subject of debate [33]. A study by Maas et al., found a prevalence of 6.3% in patients with COVID-19 in their cohort from the USA [34]. This is in concordance with the results of Voncken et al., [35], as well as with estimations of the worldwide prevalence of OSA between 3 and 7%.

There is a strong association of OSA with increased mortality in COVID-19 patients. A brief report studying 4,668 COVID-19 patients from an electronic patient registry from New England, USA, showed an increased all-cause mortality rate (11.7%) compared with controls (6.9%) [36]. Maas et al.,

[34] showed that OSA was associated with increased risk for hospitalization (OR 1.65) and respiratory failure (OR 1.98).

Several pathophysiological mechanisms may help to explain the increased mortality risk in COVID-19 patients with OSA. One frequently suggested mechanism is an increased risk of aspiration. This theory is supported by an overall higher incidence of pneumonia in OSA patients [37]. The mechanism may be related to laryngeal sensory dysfunction, laryngeal adductor reflection attenuation, impaired cough reflexes (during REM sleep) and/ or gastroesophageal reflux, which have all been described in patients with OSA [38]. In addition, gasping is a common phenomenon in patients with OSA and gasping may predispose to aspiration of virus particles [39]. Furthermore, also other mechanical problems in OSA contribute to less effective ventilation treatment, including a higher risk of difficult intubation and non-invasive ventilation may be less effective due to the intermittent airway obstruction episodes [40]. In addition, higher levels of inflammatory markers have been reported in OSA patients compared to patients without OSA. This could increase the risk for overproduction of prompt response proinflammatory cytokines which could increase chances of developing Cytokine Storm Syndrome (CSS) [41].

## Conclusion

Patients with OSA in ICU represent a big challenge. Known OSA is not demonstrated to be an independent risk factor for adverse outcomes in ICU patients.

## References

[1] Ogna A., Tobback N., Andries D., Preisig M., Vollenweider P., Waeber G., Marques-Vidal P., Haba-Rubio J., Heinzer R. Prevalence of sleep-disordered breathing in the general population: THE HypnoLaus study. *Lancet Respir. Med.* (2015) doi:10.1016/S2213-2600(15)00043-0.

[2] Reilly, J. J., El-Hamdouchi, A., Diouf, A., Monyeki, A. & Somda, S. A. Determining the worldwide prevalence of obesity. *The Lancet* (2018) doi:10.1016/S0140-6736(18)30794-3.

[3] Shahrokh Javaheri, Ferran Barbe, Francisco Campos-Rodriguez, Jerome A. Dempsey, Rami Khayat, Sogol Javaheri, Atul Malhotra, Miguel A. Martinez-Garcia, Reena Mehra, Allan I. Pack, sevolod Y. Polotsky, Susan Redline, Virend K. Somers.

Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. *Journal of the American College of Cardiology* (2017) doi:10.1016/j.jacc.2016.11.069.

[4] Zamarron, C., Vanesa García Paz & Riveiro, A. Obstructive sleep apnea syndrome is a systemic disease. Current evidence. *European Journal of Internal Medicine* (2008) doi:10.1016/j.ejim.2007.12.006.

[5] Reutrakul, S. & Mokhlesi, B. Obstructive Sleep Apnea and Diabetes: A State of the Art Review. *Chest* (2017) doi:10.1016/j.chest.2017.05.009.

[6] [Richards, K. C., Anderson, W. M. D., Chesson, A. L. & Nagel, C. L. Sleep-related breathing disorders in patients who are critically ill. *J. Cardiovasc. Nurs.* (2002) doi:10.1097/00005082-200210000-00005.

[7] Sébastien Bailly, Louis-Marie Galerneau, Stéphane Ruckly, Alexandre Seiller, Nicolas Terzi, Carole Schwebel, Claire Dupuis, Renaud Tamisier, Bernard Mourvillier, Jean-Louis Pepin, Jean-François Timsit. Impact of obstructive sleep apnea on the obesity paradox in critically ill patients. *J. Crit. Care* (2020) doi:10.1016/j.jcrc.2019.12.016.

[8] BaHammam, A., Syed, S. & Al-Mughairy, A. Sleep-related breathing disorders in obese patients presenting with acute respiratory failure. *Respir. Med.* (2005) doi:10.1016/j.rmed.2004.10.021.

[9] Karachaliou, F., Kostikas, K., Pastaka, C., Bagiatis, V. & Gourgoulianis, K. I. Prevalence of sleep-related symptoms in a primary care population - Their relation to asthma and COPD. *Prim. Care Respir. J.* (2007) doi:10.3132/pcrj.2007.00045.

[10] Fletcher, E. C., Shah, A., Qian, W. & Miller, C. C. "Near miss" death in obstructive sleep apnea: A critical care syndrome. *Crit. Care Med.* (1991) doi:10.1097/0000 3246-199109000-00011.

[11] Bolona, E., Hahn, P. Y. & Afessa, B. Intensive care unit and hospital mortality in patients with obstructive sleep apnea. *J. Crit. Care* (2015) doi:10.1016/j.jcrc.2014.10.001.

[12] Jean, R. E., Gibson, C. D., Jean, R. A. & Ochieng, P. Obstructive sleep apnea and acute respiratory failure: An analysis of mortality risk in patients with pneumonia requiring invasive mechanical ventilation. *J. Crit. Care* (2015) doi:10.1016/j.jcrc.2015.03.016.

[13] Arnaud W. Thille, Ana Córdoba-Izquierdo, Bernard Maitre, Laurent Boyer, Laurent Brochard, Xavier Drouot. High prevalence of sleep apnea syndrome in patients admitted to ICU for acute hypercapnic respiratory failure: a preliminary study. *Intensive Care Medicine* (2018) doi:10.1007/s00134-017-4998-3.

[14] Dan Adler, Jean-Louis Pépin, Elise Dupuis-Lozeron, Katerina Espa-Cervena, Roselyne Merlet-Violet, Hajo Muller, Jean-Paul Janssens, Laurent Brochard. Comorbidities and subgroups of patients surviving severe acute hypercapnic respiratory failure in the intensive care unit. *Am. J. Respir. Crit. Care Med.* (2017) doi:10.1164/rccm.201608-1666OC.

[15] Matthew T. V. Chan, Chew Yin Wang, Edwin Seet, Stanley Tam, Hou Yee Lai, Eleanor F. F. Chew, William K. K. Wu, Benny C. P. Cheng, Carmen K. M. Lam, Timothy G. Short, David S. C. Hui, Frances Chung, Postoperative Vascular Complications in Unrecognized Obstructive Sleep Apnea (POSA) Study

Investigators. Association of Unrecognized Obstructive Sleep Apnea with Postoperative Cardiovascular Events in Patients Undergoing Major Noncardiac Surgery. *JAMA - J. Am. Med. Assoc.* (2019) doi:10.1001/jama.2019.4783.

[16] Ana Fernandez-Bustamante, Karsten Bartels, Claudia Clavijo, Benjamin K. Scott, Rachel Kacmar, Kenneth Bullard, Angela F. D. Moss, William Henderson, Elizabeth Juarez-Colunga, Leslie Jameson. Preoperatively Screened Obstructive Sleep Apnea is Associated with Worse Postoperative Outcomes Than Previously Diagnosed Obstructive Sleep Apnea. *Anesth. Analg.* (2017) doi:10.1213/ANE.0000000000002241.

[17] Lin, P., Li, X., Zhang, J. & Liang, Z. Association between obstructive sleep apnea and reduced mortality in critically ill patients: A propensity score-based analysis. *Int. J. Gen. Med.* (2021) doi:10.2147/IJGM.S330752.

[18] Hang L. W., W. Chen, S. J. Liang, Y. C. Lin, C. Y. Tu, H. J. Chen, K. L. Chiu. Clinical characteristics and outcomes of patients with obstructive sleep apnoea requiring intensive care. *Anaesth. Intensive Care* (2010) doi:10.1177/0310057x1003800315.

[19] Lee, C. K., Tefera, E. & Colice, G. The effect of obesity on outcomes in mechanically ventilated patients in a medical intensive care unit. *Respiration* (2014) doi:10.1159/000357317.

[20] Oreste Marrone, Salvatore Battaglia, Paschalis Steiropoulos, Ozen K Basoglu, John A. Kvamme, Silke Ryan, Jean-Louis Pepin, Johan Verbraecken, Ludger Grote, Jan Hedner, Maria R. Bonsignore, ESADA study group. Chronic kidney disease in European patients with obstructive sleep apnea: the ESADA cohort study. *J. Sleep Res.* (2016) doi:10.1111/jsr.12426.

[21] Oreste Marrone, Fabio Cibella, Jean-Louis Pépin, Ludger Grote, Johan Verbraecken, Tarja Saaresranta, John A Kvamme, Ozen K Basoglu, Carolina Lombardi, Walter T. McNicholas, Jan Hedner, Maria R. Bonsignore, ESADA Network. Fixed But Not Autoadjusting Positive Airway Pressure Attenuates the Time-dependent Decline in Glomerular Filtration Rate in Patients With OSA. *Chest* (2018) doi:10.1016/j.chest.2018.04.020.

[22] Lin Dou, Haitao Lan, Daniel J. Reynolds, Tina M. Gunderson, Rahul Kashyap, Ognjen Gajic, Sean Caples, Guangxi Li, Kianoush B. Kashani. Association between Obstructive Sleep Apnea and Acute Kidney Injury in Critically Ill Patients: A Propensity-Matched Study. *Nephron* (2017) doi:10.1159/000453367.

[23] Besedovsky, L. & Born, J. Sleep, Don't Sneeze: Longer Sleep Reduces the Risk of Catching a Cold. *Sleep* (2015) doi:10.5665/sleep.4958.

[24] Beumer M. C., R. M. Koch, D. van Beuningen, A. M. OudeLashof, F. L. van de Veerdonk, E. Kolwijck, J. G. van der Hoeven, D. C. Bergmans, C W E Hoedemaekers. Influenza virus and factors that are associated with ICU admission, pulmonary co-infections and ICU mortality. *J. Crit. Care* (2019) doi:10.1016/j.jcrc.2018.11.013.

[25] Chung, F., Liao, P., Elsaid, H., Shapiro, C. M. & Kang, W. Factors associated with postoperative exacerbation of sleep-disordered breathing. *Anesthesiology* (2014) doi:10.1097/ALN.0000000000000041.

[26] Azadeh Yadollahi, Joseph M. Gabriel, Laura H. White, Luigi Taranto Montemurro, Takatoshi Kasai, T. Douglas Bradley. A randomized, double crossover study to investigate the influence of saline infusion on sleep apnea severity in men. *Sleep* (2014) doi:10.5665/sleep.4084.

[27] Glaser, J. B. & El-Haddad, H. Exploring novel medicare readmission risk variables in chronic obstructive pulmonary disease patients at high risk of readmission within 30 days of hospital discharge. *Ann. Am. Thorac. Soc.* (2015) doi:10.1513/Annals ATS.201504-228OC.

[28] Gupta, R. M., Parvizi, J., Hanssen, A. D. & Gay, P. C. Postoperative complications in patients with obstructive sleep apnea syndrome undergoing hip or knee replacement: A case-control study. *Mayo Clin. Proc.* (2001) doi:10.4065/76.9.897.

[29] Lavie, L. & Lavie, P. Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea. *Med. Hypotheses* (2006) doi:10.1016/j. mehy.2005.10.033.

[30] Berger, S., Aronson, D., Lavie, P. & Lavie, L. Endothelial progenitor cells in acute myocardial infarction and sleep-disordered breathing. *Am. J. Respir. Crit. Care Med.* (2013) doi:10.1164/rccm.201206-1144OC.

[31] Steiner, S., Schueller, P. O., Schulze, V. & Strauer, B. E. Occurrence of coronary collateral vessels in patients with sleep apnea and total coronary occlusion. *Chest* (2010) doi:10.1378/chest.09-1136.

[32] Lavie, L. & Lavie, P. Coronary collateral circulation in sleep apnea: A cardioprotective mechanism? *Chest* (2010) doi:10.1378/chest.09-2657.

[33] de Kruif, M. D., Voncken, S. F. J., Laven, S. A. J. S., Feron, T. M. H. & Kolfoort-Otte, A. A. B. Obstructive sleep apnea and risk of COVID-19 infection, hospitalization and respiratory failure. *Sleep and Breathing* (2021) doi:10.1007/ s11325-020-02271-2.

[34] Maas, M. B., Kim, M., Malkani, R. G., Abbott, S. M. & Zee, P. C. Obstructive Sleep Apnea and Risk of COVID-19 Infection, Hospitalization and Respiratory Failure. *Sleep Breath.* (2021) doi:10.1007/s11325-020-02203-0.

[35] Voncken S. F. J., T. M. H. Feron, S. A. J. S. Laven, U. Karaca, K. Beerhorst, P. Klarenbeek, J. M. J. A. A. Straetmans, G. J. de Vries, A. A. B. Kolfoort-Otte, M D de Kruif. Impact of obstructive sleep apnea on clinical outcomes in patients hospitalized with COVID-19. *Sleep Breath.* (2022) doi:10.1007/s11325-021-02476-z.

[36] Cade, B. E., Dashti, H. S., Hassan, S. M., Redline, S. & Karlson, E. W. Sleep apnea and COVID-19 mortality and hospitalization. *American Journal of Respiratory and Critical Care Medicine* (2020) doi:10.1164/rccm.202006-2252LE.

[37] Vincent Yi-Fong Su, Chia-Jen Liu, Hsin-Kai Wang, Li-An Wu, Shi-Chuan Chang, Diahn-Warng Perng, Wei-Juin Su, Yuh-Min Chen, Elizabeth Ya-Hsuan Lin, Tzeng-Ji Chen, Kun-Ta Chou. Sleep apnea and risk of pneumonia: A nationwide population-based study. *C. Can. Med. Assoc. J.* (2014) doi:10.1503/cmaj.131547.

[38] Eusebi Chiner, Mónica Llombart, Joan Valls, Esther Pastor, José N. Sancho-Chust, Ada Luz Andreu, Manuel Sánchez-de-la-Torre, Ferran Barbé. Association between obstructive sleep apnea and community-acquired pneumonia. *PLoS One* (2016) doi:10.1371/journal.pone.0152749.

[39] Michael Beal, Andrew Chesson, Thomas Garcia, Gloria Caldito, Fred Stucker, Cherie-Ann Nathan. A pilot study of quantitative aspiration in patients with symptoms of obstructive sleep apnea: Comparison to a historic control group. *Laryngoscope* (2004) doi:10.1097/00005537-200406000-00002.

[40] Mahesh Nagappa, David T Wong, Crispiana Cozowicz, Satya Krishna Ramachandran, Stavros G Memtsoudis, Frances Chung. Is obstructive sleep apnea associated with difficult airway? Evidence from a systematic review and meta-analysis of prospective and retrospective cohort studies. *PLoS One* (2018) doi:10.1371/journal.pone.0204904.

[41] Sefer Elezkurtaj, Selina Greuel, Jana Ihlow, Edward Georg Michaelis, Philip Bischoff, Catarina Alisa Kunze, Bruno Valentin Sinn, Manuela Gerhold, Kathrin Hauptmann, Barbara Ingold-Heppner, Florian Miller, Hermann Herbst, Victor Max Corman, Hubert Martin, Helena Radbruch, Frank L Heppner, David Horst. Causes of death and comorbidities in hospitalized patients with COVID-19. *Sci. Rep.* (2021) doi:10.1038/s41598-021-82862-5.

# Chapter 2

# Comorbidities: Key Practical Recommendations

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## Abstract

Obstructive sleep apnea (OSA) is a common sleep-disordered breathing associated with repetitive apneas, hypopneas, or respiratory effort-related arousals. OSA is associated with increased prevalence of many comorbidities including cardiovascular diseases like arrhythmias particularly atrial fibrillation, heart failure, stroke, pulmonary hypertension, and metabolic disturbance including diabetes mellitus and dyslipidemia. Depression and mood changes are also common in OSA. Furthermore, there are overlaps in the clinical presentations of some of these comorbidities and OSA symptoms making the possibility of underdiagnoses of OSA or its comorbidities. Some of these comorbidities are a physiological sequela of OSA. Though some comorbidities could be linked to obesity, there is growing evidence of OSA as an independent risk factor. Continuous positive airway pressure (CPAP) has been proven to alleviate some of these comorbidities or their severity while additional detailed studies are required to further characterize benefits in some others.

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**Keywords**: obstructive sleep apnea, comorbidities, cardiovascular diseases, continuous positive airway pressure, sleep-disordered breathing

## Introduction

The incidence of cardiovascular diseases and cardiovascular events has increased in OSA patients. Similarly, there is a proportional relationship between all-cause mortality and the severity of OSA [1]. The current available data suggests that CPAP therapy is ineffective as a secondary prevention of cardiovascular diseases or cardiovascular events [2], however, there are many limitations in the current available evidence urging further randomized controlled trials. Many other cardiovascular diseases are associated with OSA including systemic hypertension, ischemic heart disease, arrhythmias particularly atrial fibrillation, heart failure, stroke, and pulmonary hypertension. Depression and metabolic disturbance including diabetes mellitus are also associated with OSA. While CPAP can be effective on reducing some of these comorbidities, still there is a gap in the knowledge of CPAP efficacy on others. Further studies targeting OSA phenotypes might be the key to answer many questions.

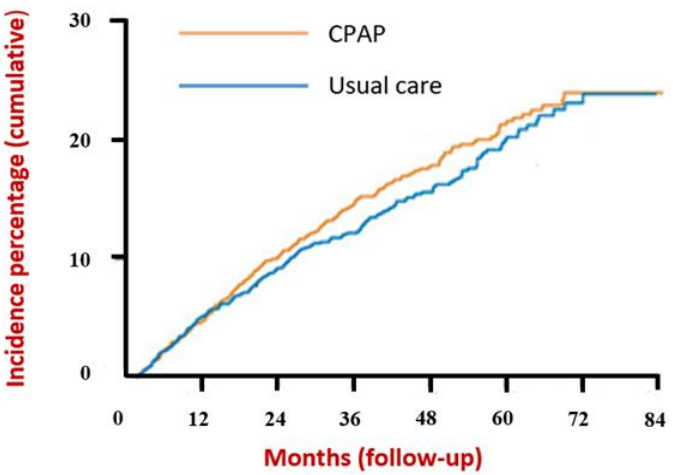


**Figure 1.** Cumulative incidence of the primary endpoint comparing CPAP group (CPAP plus usual care) and usual care group (usual care alone). N Engl J Med 2016; 375:919-93.

## OSA and Cardiovascular Diseases

### Cardiovascular Events

Observational studies have shown that OSA is associated with increased cardiovascular disease and increased morbidity and mortality. Sleep-disordered breathing increases all-cause mortality in proportion to the severity of sleep-disordered breathing as classified by apnea/hypopnea index (AHI) with hazard ratios of 0.93, 1.17, and 1.46 for mild, moderate, and severe OSA respectively [1]. This risk is particularly worse in men aged forty to seventy and coronary artery disease follows the same pattern as all-cause mortality [1].

The Sleep Apnea Cardiovascular Endpoints (SAVE) study which was one of the largest randomized controlled trials to investigate the benefit of CPAP in preventing cardiovascular events revealed that CPAP did not prevent cardiovascular events in those with moderate to severe OSA and existing cardiovascular diseases or coronary artery disease (Figure 1). These cardiovascular events include cardiovascular deaths, stroke, myocardial infarction, hospitalizations for unstable angina, transient ischemic attack, or heart failure [2]. However, there are many limitations in this study which include the exclusion of the sleepy population with an Epworth sleepiness score (ESS) of 15 (range of 0-24), or severely hypoxic patients (oxygen saturation <80% for more than 10% of recorded time) and those who are at elevated risk of road traffic accident. Furthermore, the study was conducted on patients with already established cardiovascular disease (i.e., not primary prevention). In addition, the diagnosis of OSA in the studied population was made by Apnea Link (automated oximetry) rather than full polysomnography and the adherence to CPAP was poor (mean of 3.3 hours per night). All these limitations constrain the generalization of these results. Several meta-analyses of RCT showed comparable results [3] with different OSA severity and duration of treatment. Further RCTs are required to indicate CPAP benefit on OSA patients according to patient characteristics or phenotypes (e.g., sleep vs non-sleepy patients).

### Coronary Artery Disease

There is convincing evidence that untreated men with severe OSA (mean AHI of 45 events/hour) are associated with increased non-fatal cardiovascular

events including stroke, myocardial infarction, and acute coronary syndrome, as well as fatal cardiovascular events irrespective of confounding factors including obesity when it is compared with patient with mild to moderate OSA [4]. This reflects the importance of CPAP treatment. Further RCTs are needed to prove the CPAP effect on cardiovascular outcomes.

## Hypertension

There is a well-known association between OSA and hypertension with close to fifty percent of OSA patients being hypertensive. Furthermore, there is an increased prevalence of OSA in patients with resistant hypertension. OSA is also linked to non-dipping nocturnal blood pressure, particularly in those who have cardiovascular risk and moderate to severe OSA [5]. A prospective population-based study for patients with OSA found that after four years of follow-up, there was a proportional relationship between the severity of OSA and the presence of hypertension with an odds ratio of 2.03 and 2.89 for mild and moderate-severe OSA respectively after adjustment for other risk factors [6]. One meta-analysis has shown that using CPAP is associated with a small reduction in systolic blood pressure (mean of 2.6 mmHg) [7]. This little reduction is clinically important as it can lessen cardiovascular risk. Additional studies are required to further characterized benefits in certain groups of OSA patients like sleepy patients and to investigate benefits according to the severity of OSA. Moreover, more evidence is required to examine the effect of withdrawal of CPAP on blood pressure control, the effect on diastolic blood pressure, the effect of CPAP when it is compared to antihypertensive agents, duration of CPAP usage to see the effect and alternative treatment to CPAP and their effect on blood pressure.

## Atrial Fibrillation and Other Arrhythmias

Arrhythmias in general and particularly atrial fibrillation are associated with OSA. These arrhythmias were attributed to several physiological changes in OSA which include hypoxia and it is associated with delayed depolarization, fluctuated autonomic system, and respiratory acidosis. The prevalence of atrial fibrillation (AF) in OSA patients is variable from 2% to 5% independent of other risk factors and it is three to four folds higher than the general population. Outcomes of sleep disorders in older men (MrOS) study revealed that the

prevalence of atrial fibrillation and complex ventricular ectopy (CVE) are proportionally correlated to the severity of sleep-disordered breathing (SDB) measured by respiratory disturbance index (RDI) in older men. Though this study also showed that CVE is more prevalent in obstructive sleep apnea as compared with AF which was more common in central sleep apnea [8].

Patients with OSA have an elevated risk of recurrent AF after ablation compared with non-OSA patients close to 31%. This risk can increase to 57% if CPAP therapy is not used. Furthermore, CPAP can reduce AF recurrence at a rate close to the non-OSA patient [9].

Other arrhythmias like conduction delay including sinus pause, asystole, and atrioventricular block were reported in old literature but have never been proven in large studies. Ventricular arrhythmia, on the other hand, has been linked to OSA as well [10], yet large RCTs are still required to determine the utility of CPAP or alternative therapy to prevent or reduce the recurrent rate.

## Stroke

There is growing evidence of an increased incidence of stroke in OSA patients. Several hypotheses have been proposed as mechanisms for increasing stroke risk. Firstly, OSA is associated with an increase in other cardiovascular risks including diabetes mellitus and insulin resistance, hypertension, heart diseases, and atrial fibrillation. Furthermore, there might be a reduction in cerebral flow velocity secondary to increased intrathoracic pressure because of the obstructive events. Moreover, intermittent hypoxia can attenuate the cerebral vasodilatory response. Similarly, endothelial dysfunction secondary to oxidant stress and an increase in sympathetic drive all can play a role in the pathogenesis of stroke. Likewise, OSA can result in pulmonary hypertension which could lead to right to left shunt in patients with patent foramen ovale (PFO) and therefore possible paradoxical embolism and stroke. The hazard ratio (HR) is 2.89 in one observational study irrespective of confounding factors like diabetes mellitus, hypertension, previous stroke, atrial fibrillation, smoking history, body mass index, age, or gender. This risk corresponds proportionally to the severity of OSA with hazard ratios of 2.44 and 3.56 in patients with AHI (5-15) and >15 events per hour respectively [11]. Using CPAP may alleviate some of the proposed risk factors for stroke like improving blood pressure. Though some RCTs have shown no proven effect on the rate of stroke after CPAP therapy [2]. However large detailed RCTs to investigate the benefit of CPAP in reducing stroke incidence are lacking.

## Heart Failure

The prevalence of heart failure in OSA patients is variable in the literature between 50% to 75%. Many physiological changes could explain this correlation which includes reduced preload and increased afterload because of increased negative intrathoracic pressure during obstructive respiratory events. Similarly, increasing sympathetic drive could increase heart failure recurrence. In addition, some of the OSA's symptoms can be confused with heart failure symptoms like paroxysmal nocturnal dyspnea and nocturia due to diuresis which can lead to under recognition of OSA. On other hand, heart failure is proposed as a risk to worsen OSA, particularly in supine positions due to neck edema.

The risk to develop heart failure is worse in men and those with severe OSA. The risk is approximately 59% compared with subjects with no OSA [12]. CPAP therapy reduces the incidence of heart failure in those more than 60 years of age [13].

## Pulmonary Hypertension

Pulmonary hypertension due to OSA belongs to group 3 according to the clinical classification of pulmonary hypertension (i.e., pulmonary hypertension due to lung disease and/or hypoxia). The severity of pulmonary hypertension in OSA patients is usually mild if there is no coexisting other potential etiology for pulmonary hypertension. Pulmonary hypertension can also be a prognostic factor in OSA patients. CPAP therapy has been proven to improve systolic pulmonary arterial pressure and pulmonary vascular resistance after a few months of treatment.

## OSA and Metabolic Disturbance

Diabetes and insulin resistance are proven in cross-sectional studies to be associated with OSA. Similarly, increasing OSA severity is associated with increasing type 2 diabetes incidence independent of possible confounding factors like body mass index, age, race, gender, and baseline fasting glucose. This risk is less in those who use CPAP [14]. OSA not only leads to an increased risk of diabetes, but it is associated with other metabolic disturbances which can lead to metabolic syndrome. This is attributed to the