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Obstructive Sleep Apnea and Cardiovascular Diseases

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Abstract:

Background: Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder characterized by recurrent episodes of partial or complete upper airway obstruction during sleep, leading to intermittent hypoxia, hypercapnia, and sleep fragmentation. These pathophysiological changes trigger sympathetic nervous system activation, oxidative stress, systemic inflammation, and endothelial dysfunction, all of which contribute to cardiovascular morbidity. Increasing evidence links OSA to hypertension, arrhythmias, coronary artery disease, heart failure, stroke, and sudden cardiac death. Despite its high prevalence, OSA remains underdiagnosed, and untreated cases may accelerate the progression of cardiovascular disease (CVD) and worsen outcomes.

Keywords: Obstructive sleep apnea; Cardiovascular disease; Hypertension; Arrhythmia; Heart failure; Stroke; Endothelial dysfunction; Intermittent hypoxia.

Introduction:

Obstructive sleep apnea (OSA) is a highly prevalent sleep disorder characterized by recurrent episodes of upper airway obstruction during sleep, resulting in intermittent hypoxia, hypercapnia, and sleep fragmentation. Global prevalence estimates suggest that OSA affects up to one billion people, with higher rates observed among obese individuals, older adults, and men **(1).**

The pathophysiological mechanisms linking OSA to cardiovascular disease (CVD) are multifactorial. Repetitive cycles of oxygen desaturation and reoxygenation lead to oxidative stress, systemic inflammation, and endothelial dysfunction, which promote atherosclerosis and vascular remodeling **(2).**

Clinical and epidemiological studies have established OSA as an independent risk factor for several cardiovascular conditions, including hypertension, arrhythmias, coronary artery disease, heart failure, and stroke. These associations remain significant even after adjusting for traditional cardiovascular risk factors, underscoring the importance of OSA as a modifiable contributor to CVD burden **(3).**

Treatment of OSA, particularly with continuous positive airway pressure (CPAP) therapy, has been shown to improve daytime symptoms and certain cardiovascular parameters. However, evidence regarding its long-term effect on major adverse cardiovascular events remains mixed, highlighting the need for further large-scale randomized controlled trials to guide optimal management strategies **(4).**

Obstructive sleep apnea (OSA), which causes sleep deprivation, intermittent hypoxia, and negative intrathoracic pressure swings, can be accompanied by other harmful pathophysiologies relating to cardiovascular diseases (CVD), including sudden death, atrial fibrillation, stroke, and coronary artery disease leading to heart failure **(5)**.

Endothelial dysfunction can be caused by oxidative stress, systemic inflammation, and sympathetic nervous activation. These factors are affected by SDB, such as intermittent hypoxia, sleep deprivation, and arousal). Inflammatory pathways triggered by intermittent hypoxia in OSA might also contribute to the development and progression of atherosclerosis. SDB severity is reportedly associated with endothelial dysfunction determined by flow-mediated dilatation or arterial stiffness determined by cardio-ankle vascular index. With regard to cerebral artery, SDB-related oxidative stress and systemic inflammation promote increased intima-media thickness. Markers of oxidative stress and inflammation are associated with SDB-related hypoxia and intima-media thickness **(6)**.

Patients with OSA without other known risk factors for arteriosclerosis have increased intima-media thickness compared with those without OSA, and intima- media thickness is related to nocturnal hypoxia severity. Doubling of the AHI was associated with a 19% increase in coronary artery calcium in men aged < 65 years, and a 17% increase of the same parameter in women of all ages. It has been reported that SDB severity is significantly associated with coronary atherosclerotic burden severity (Gensini score), and reflected elevated troponin T as silent myocardial ischemia and minute myocardial injury, even in patients with stable CAD **(7, 8)**.

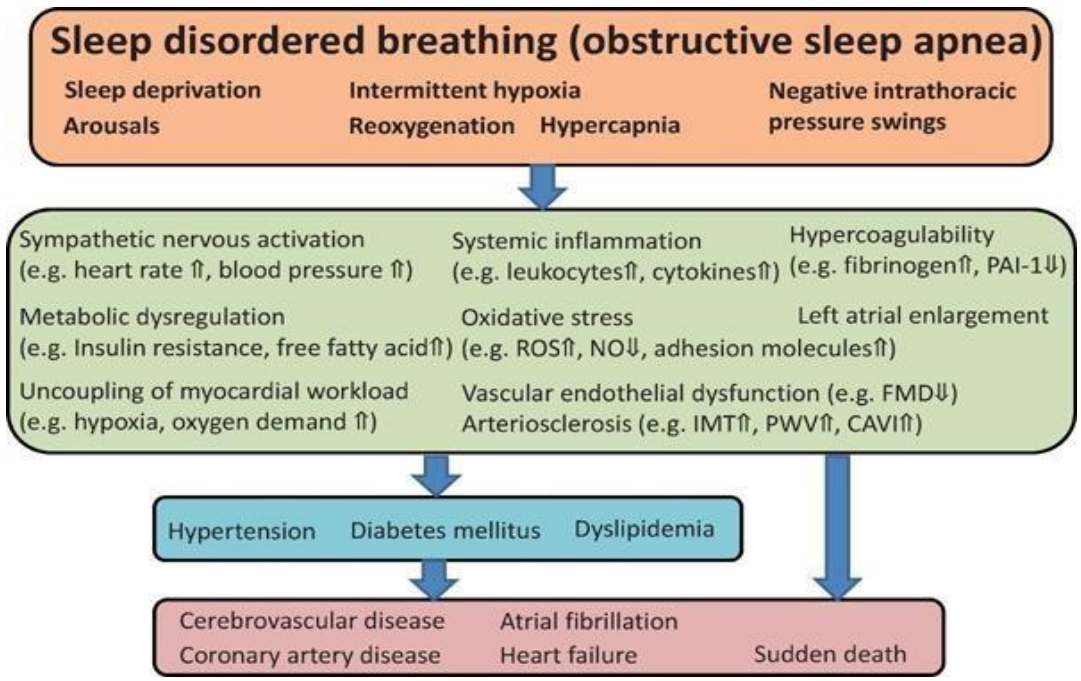

Fig. (1): Pathophysiology of the impact of sleep disordered breathing, OSA, on cardiovascular disease **(9)**.

PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; NO, nitric oxide; FMD, flow-mediated dilatation; IMT, intima-media thickness; PWV, pulse wave velocity; CAVI, cardio- ankle vascular index.

Hypertension

Up to 50% of OSA patients may have hypertension, and 30% of hypertensive patients will likely have OSA. Patients with untreated OSA followed over 4 years have a 2- to 3-fold increased risk of developing incident hypertension. OSA has been recognized as a particularly important likely causal factor in resistant hypertension and this may be important in those of African ancestry, a population with a high prevalence of unrecognized OSA, poorly controlled hypertension, and hypertensive complications **(10)**. A recent systematic review and meta-analysis reported a significant association of essential hypertension with mild, moderate and severe OSA ($p<0.05$) **(11)**.

Cardiac arrhythmia

The complex and dynamic substrate for arrhythmias induced by OSA, which is characterized by structural remodeling as well as transient apnea-associated electrophysiological changes, is summarized in **Figure 2 (12)**.

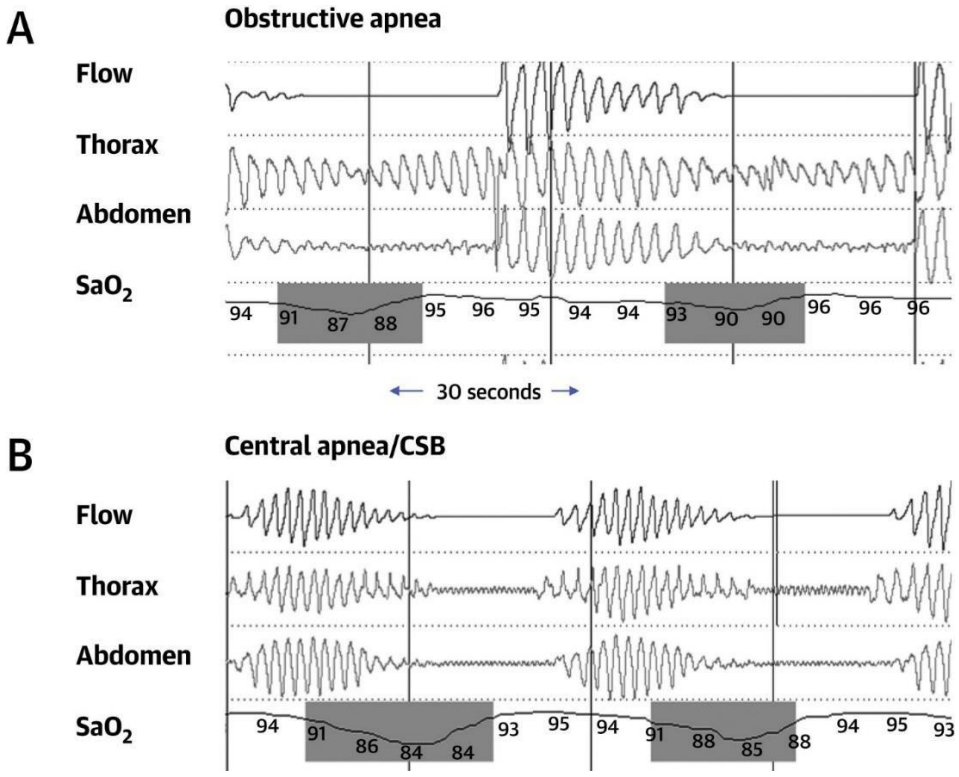

Fig. (2): Characteristic Home Sleep Apnea Testing Traces **(A)** Patient with OSA; **(B)** a patient with CSA, showing airflow, thoracic and abdominal wall movements, and Pa02 (partial pressure of arterial oxygen). Note: desaturation is delayed in CSA because of long circulation time in heart failure **(5)**.

Atrial fibrillation

Patients with OSA show marked atrial structural changes and conduction abnormalities, without any changes in atrial refractoriness. OSA may also increase AF trigger formation in the pulmonary veins and elsewhere. Additionally, obstructive respiratory events may result in transient electrophysiological arrhythmogenic changes, which may explain the increased risk of nocturnal AF paroxysms temporally related to such events **(13)**. In the VARIOSA- AF (Night-to-Night Variability in Severity of Sleep Apnea and Daily Dynamic Atrial Fibrillation Risk) study (**Figure 3**), the nights with more severe sleep apnea conferred a 2.3-fold increased risk of ≥1 h of AF during the same day compared with the best sleep nights (**Figure 4**) **(14, 15)**.

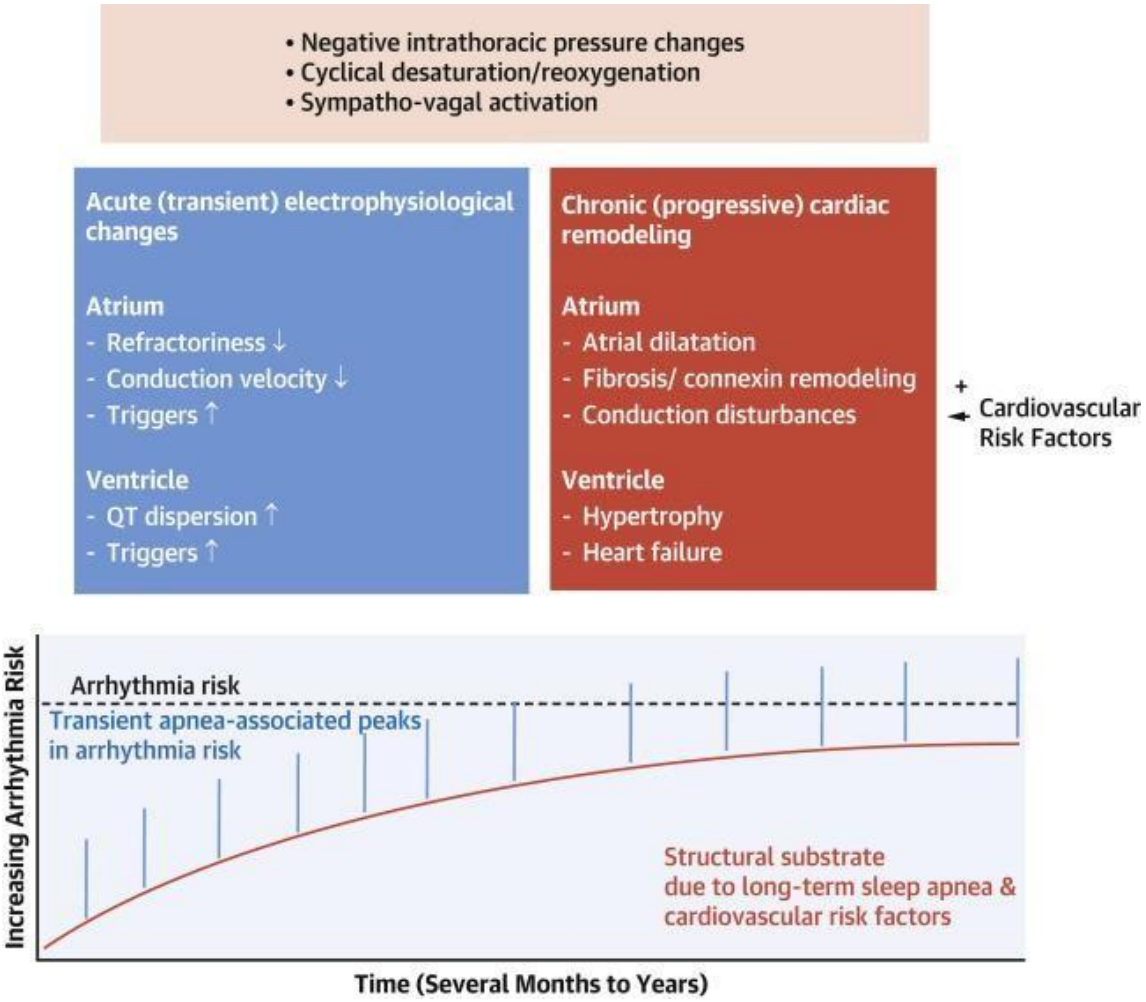

Fig. (3): The Complex and Dynamic Substrate for Arrhythmia Induced by Sleep Apnea. **(Top)** Sleep apnea–related pathophysiological changes resulting in acute transient electrophysiological changes **(blue box)** and chronic progressive cardiac remodeling processes **(red box)**. **(Bottom)** Individual acute sleep apnea episodes cause transient apnea-associated peaks in arrhythmia risk **(blue lines)**, but in the absence of an underlying structural substrate, the threshold necessary to trigger an arrhythmia **(dashed black line)** cannot be reached. However, in the presence of structural remodeling due to long-term sleep apnea and cardiovascular risk factors **(red line)**, acute sleep apnea episodes can trigger arrhythmia **(5)**.

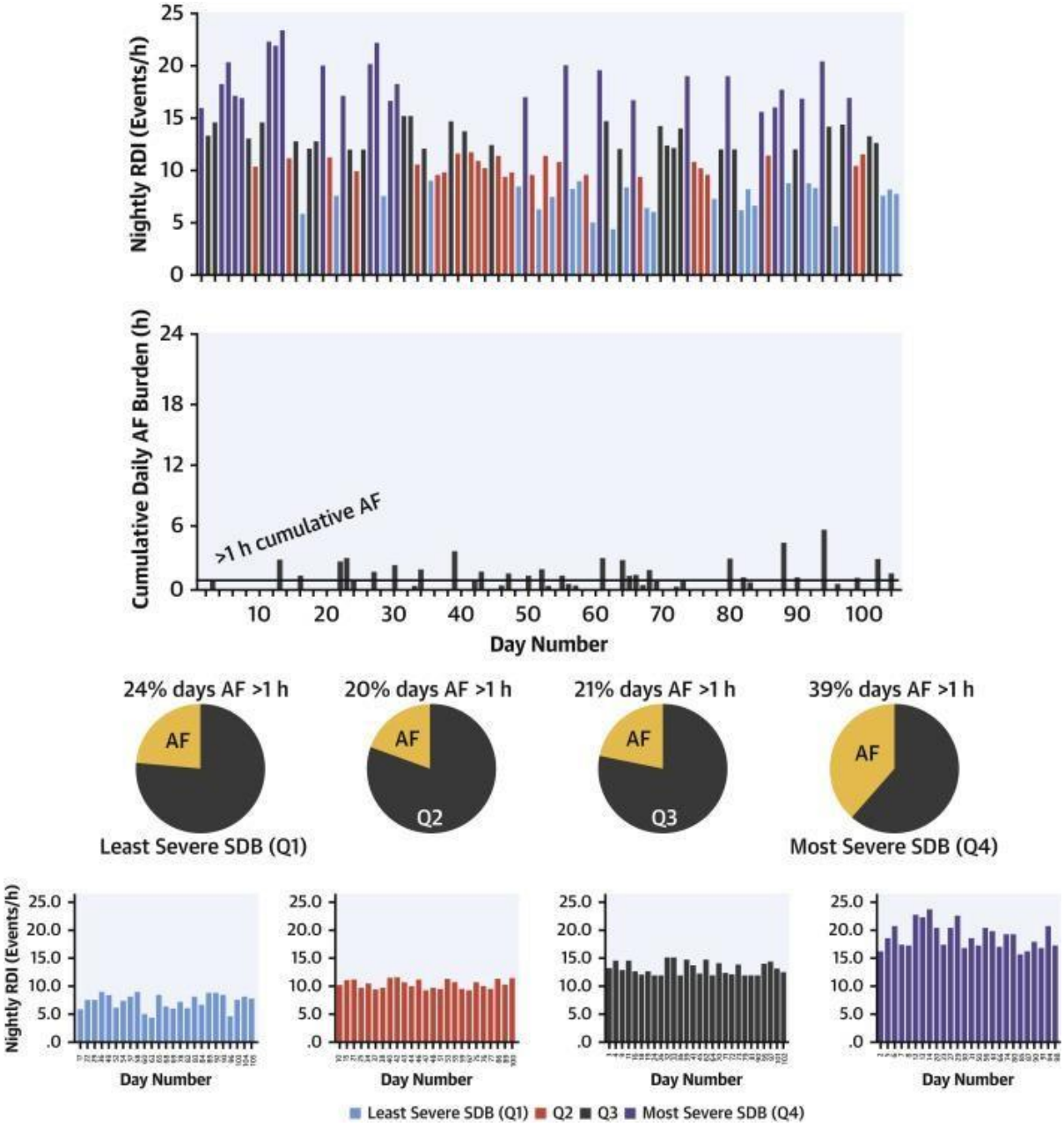

Fig. (4): Simultaneous Long-Term Day-by-Day Variation in Sleep Apnea and Episodes of AF. Patients with implanted pacemakers showed considerable night-to- night variation in sleep apnea severity, with a higher respiratory disturbance index (RDI) associated with an increasing risk of atrial fibrillation (AF) during the same day **(15)**.

The prevalence of SDB in patients with AF is higher (21%-74%) than in control subjects without AF (3%-49%). Also, severe OSA is associated with a lower response rate to antiarrhythmic drug therapy. OSA have a 31% greater AF- recurrence rate after pulmonary vein isolation than those without OSA. Moreover, CPAP use was associated with lower AF recurrences after cardioversion and lower AF recurrence rate after pulmonary vein isolation. Non-CPAP interventions may also be effective in reducing AF recurrence. Weight loss by behavioral changes or bariatric surgery, as well as alcohol abstinence, have beneficial effects

on OSA and have been shown to also promote the maintenance of sinus rhythm. AF may predispose to CSB through mechanisms similar to those in HF (with raised pulmonary vascular pressure triggering hyperventilation and hypocapnia through stimulation of pulmonary vagal irritant receptors, leading to respiratory system instability), or CSB may increase the propensity to AF by hypocapnia and increased electrical instability. Alternatively, autonomic dysfunction may predispose to both CSB and AF, as can be found in idiopathic CSB **(16, 17).**

Ventricular arrhythmia

Intrathoracic pressure swings during obstructive apneas contribute to changes in ventricular repolarization, and this along with sympathetic activation may represent mechanisms for increased risk of sudden cardiac death in OSA. An AHI of 20/h was an independent risk factor for incident sudden cardiac death in a study of more than 10,000 patients referred for polysomnography. Coexisting HF and sleep apnea increase the risk of developing malignant ventricular arrhythmia **(18)**. Severe OSA also increases the risk of ventricular premature beats and nonsustained ventricular tachycardia, and nocturnal sudden cardiac death. Registry data show that treatment of CSB with servoassisted ventilation in HF patients with implantable cardioverter defibrillator devices decreases the use of implantable cardioverter- defibrillator therapies, although CVD (and all-cause) mortality was increased in a large randomized trial of this therapy **(19, 20)**.

Coronary artery disease

OSA is associated with increased risk of coronary events. In an observational cohort of more than 1,400 patients, and after adjustment for traditional risk factors, OSA was associated with a 2-fold increase in risk of CVD events or death. The prevalence of undiagnosed severe OSA in patients with ST-segment elevation myocardial infarction (MI) was about 40%. In patients admitted with an MI without a prior diagnosis of OSA, those with OSA were far more likely to have had their MI during the nighttime, presumably because of the acute nocturnal hypoxic, adrenergic, and hemodynamic stress induced by obstructive apneas **(20, 21)**. In a 4-year follow-up of patients after MI, independent predictors of major adverse cardiovascular events (MACE) included severity of nocturnal hypoxemia and EDS. Patients with OSA have evidence of increased arterial stiffness, early atherosclerosis, coronary artery calcification, coronary plaque instability, and increased plaque vulnerability **(21).**

Severity of coronary artery disease increased in those with moderate-to-severe OSA, independent of other risk factors. Acute pressor surges, hypoxemia, and adrenergic activation during apneic events may be implicated as triggers of cardiac ischemia or plaque rupture. There is a close temporal relationship between the hypoxemia of an obstructive apnea and the development of ST-segment changes and chest pain waking a patient from sleep **(22)**. Rather than the AHI, it is the severity of nocturnal oxygen desaturation that appears to most strongly predict the development of nocturnal ST-segment depression in OSA patients. OSA is associated with increased mortality after an MI and with heightened CVD risk after coronary intervention. In more than 1,300 patients who underwent polysomnography, more than 45% had an AHI ≥15/h. OSA was independently associated with an increased risk of MACE. In a

subsequent meta-analysis of effects of OSA after percutaneous coronary intervention, OSA was found to increase the risk of MACE, but not of readmission for HF or of stroke **(23)**.

Heart failure

SDB is common in HF, with prevalence rates of 50%-75% in HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction. In acute decompensated HF, the prevalence is between 44% and 97%. Patients with HFrEF showed a strong association between SDB (either OSA or CSA) and obesity, male sex, AF, age, and poorer left ventricular (LV) systolic function. The prevalence of CSA increases as the symptomatic severity of the HF syndrome increases, and the severity mirrors underlying cardiac dysfunction. SDB is independently associated with increased mortality **(24-26)**.

Pulmonary arterial hypertension

Acute hypoxia during episodes of OSA may increase pulmonary artery pressures transiently due to hypoxic vasoconstriction. To what extent these transient increases in pulmonary vascular resistance carry over into sustained vasoconstriction remains unclear. Although OSA may often coexist with pulmonary (or systemic) hypertension, it is unclear the extent to which the OSA drives this association. Nevertheless, it is important to identify pulmonary hypertension in patients with OSA, because such patients are at risk for increased mortality. The prevalence of pulmonary hypertension (pulmonary artery pressures ≥20 mm Hg) in patients with OSA has been reported to be around 20% in those regardless of coexisting lung disease **(27, 28)**.

Chronic thromboembolic pulmonary hypertension: (29)

OSA promotes the release of inflammatory markers and activates the coagulation cascade, which increase the risk of acute thromboembolic events, and also predisposes patients to the development of CTEPH (chronic thromboembolic pulmonary hypertension). There is increased prevalence of sleep apnea in patients with acute pulmonary embolism and/or deep vein thrombosis.

Obstructive sleep apnea-related hemodynamic alterations may result in venous stasis, increased thrombogenicity (on a vascular and molecular level), increased inflammatory insult and injury so fulfilling the criteria for the nomenclature of Virchow's triad

The development of CTEPH may be promoted by the persistence of thrombotic material in the circulation, stemming from inadequate/incomplete thrombus resolution. Chronic hypoxia and hypercapnia in OSA impair thrombus resolution due to inadequate fibrinolysis, persistent inflammation, vascular smooth muscle activation, accelerated adhesion molecule expression and platelet activation.

OSA and right cardiac structure and function

Obstructive sleep apnea syndrome can directly cause right ventricle (RV) systolic and diastolic dysfunction**. (30)**

Hypoxia is a strong stimulus to pulmonary artery vasoconstriction, which causes increased pulmonary artery pressure and pulmonary vascular resistance and leads to adaptive changes of

RV. **(31)**

RV diastolic dysfunction often occurs earlier than RV systolic dysfunction, dilation, and hypertrophy.

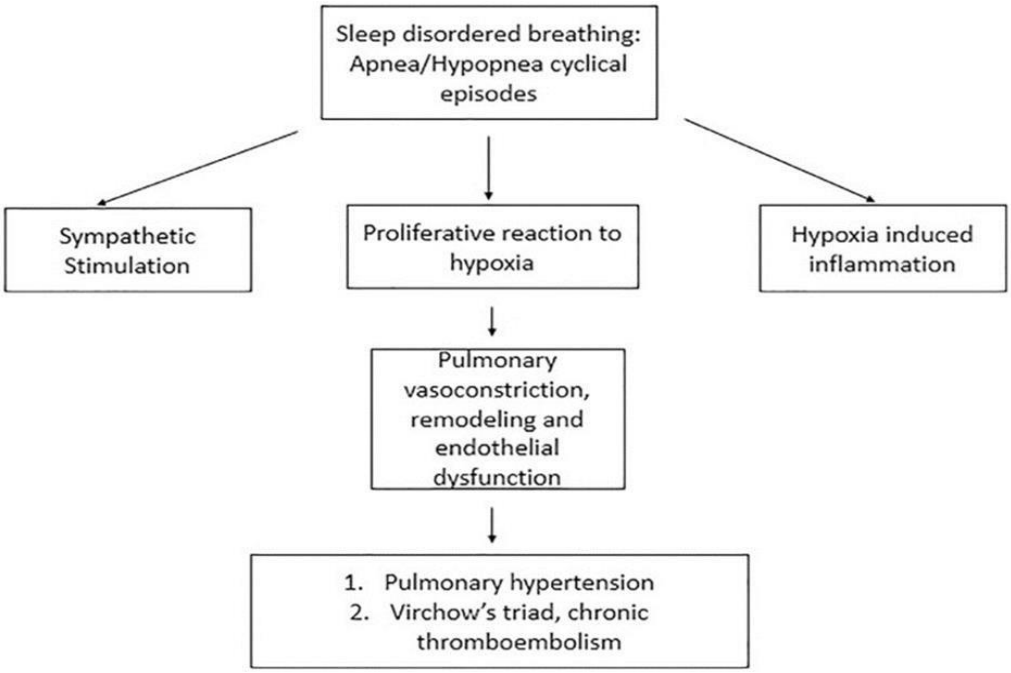

Fig (5): Summary of the three main factors believed responsible for the increase the PAP observed in sleep apnea.

Mortality

Physician diagnosis of OSA predicted a 2.4 increase in mortality, and a higher CVD incidence, over 7.5 years in more than 5,000 participants in the MESA study (Multi-Ethnic Study of Atherosclerosis) who were free of known CVD at baseline. Associations are stronger for an AHI >30, with weaker or inconsistent associations for milder OSA **(32)**. Among men, untreated severe OSA is associated with a 2.9-fold increased risk of fatal CVD events compared with untreated patients with mild or moderate OSA. Among women, the mortality rate was 3.5-fold higher in severe untreated OSA than in female control patients **(33)**. Individuals with severe OSA had a 3-fold increased HR for all-cause mortality compared with those with no OSA, with somewhat higher estimates for CVD mortality **(5)**.

Predictive markers

Several studies have reported that measures of overnight hypoxemia better predict mortality than the AHI—findings consistent with a central role of cyclical changes in oxygen saturation in contributing to inflammation, oxidative stress, and sympathetic nervous system activation. Polysomnographic parameters, such as the oxygen desaturation index (ODI), total sleep time, diastolic dipping of blood pressure, time of sleep below 90% saturation (T<90%), arousal index, and pulse rate variability per hour, play a pivotal role in the comprehensive assessment of

cardiovascular complications in patients with sleep-disordered breathing **(34-36)**.

Oxygen desaturation index (ODI) represents a measure of the frequency and severity of oxygen desaturation events during sleep. It quantifies the number of times per hour of sleep that the oxygen saturation drops by a certain percentage from the baseline. Higher ODI values indicate a greater burden of oxygen desaturation events and are associated with an increased risk of cardiovascular complications, including hypertension, coronary artery disease, and stroke **(37, 38)**.

Total sleep time refers to the duration of sleep during the PSG study. Inadequate or disrupted sleep due to SDB can have negative effects on cardiovascular health. Sleep deprivation and poor sleep quality are associated with increased sympathetic activity, inflammation, and endothelial dysfunction, which contribute to cardiovascular complications **(39, 40)**.

Furthermore, Diastolic dipping of blood pressure refers to the physiological decrease in blood pressure during sleep compared to wakefulness. Impaired blood pressure dipping during sleep is commonly observed in individuals with SDB. Non- dipping or reverse dipping patterns, where blood pressure remains elevated during sleep, are associated with an increased risk of cardiovascular diseases, including hypertension, left ventricular hypertrophy, and stroke **(41, 42)**.

T<90% represents the duration of time spent with oxygen saturation below 90% during sleep. Prolonged periods of oxygen deprivation during sleep can lead to oxidative stress, endothelial dysfunction, and increased sympathetic activity, all of which contribute to cardiovascular complications. Monitoring T<90% helps assess the severity of hypoxemia and its potential impact on cardiovascular health **(43)**. Moreover, the arousal index measures the frequency of arousals from sleep caused by respiratory events, limb movements, or other disruptions. In patients with SDB, frequent arousals disrupt sleep architecture, impair sleep quality, and contribute to cardiovascular complications. Sleep fragmentation due to frequent arousals is associated with increased sympathetic activity, inflammation, endothelial dysfunction, and metabolic abnormalities **(43, 44)**.

Pulse rate variability (PRV) measures the variation in heart rate intervals. Increased PRV is observed in patients with SDB and is associated with autonomic dysfunction. PRV reflects the balance between sympathetic and parasympathetic activity. In individuals with SDB, the recurrent apnea and hypopnea events lead to sympathetic activation and fluctuations in heart rate. Increased PRV is a marker of increased sympathetic tone and is linked to cardiovascular morbidity and mortality **(45-48)**.

In over 10,000 Canadian patients followed for a median of 68 months, AHI did not predict mortality; but by contrast, a 58% increased mortality was associated with T<90 of 9 min compared with 0 min. Mortality was also associated with other indices of sleep disruption, including periodic leg movements, numbers of awakenings, and a short sleep time **(49)**. In a prospective analysis of more than 10,000 individuals in another cohort followed for an average of 5.3 years, patients with significant nocturnal hypoxemia had a nearly 2-fold increase in the risk of sudden cardiac death after potential confounders had been considered **(50)**.

Another large prospective study of older men demonstrated, not only that increased T<90 predicted mortality, but that this association was partially mediated by an elevation in inflammatory mediators **(51)**. Other indices of hypoxemia during sleep also have been identified as potentially potent predictors of mortality, supporting the use of oximetry-based measures for risk stratification **(35, 52, 53)**.

Analyzing these PSG parameters with a focus on ODI, total sleep time, diastolic dipping of blood pressure, T<90%, arousal index, and pulse rate variability per hour allows for a comprehensive assessment of cardiovascular complications in patients with SDB. These parameters provide insights into the severity of SDB, the degree of hypoxemia and sleep disruption, and the impact on cardiovascular health **(35, 36, 43, 54).**

References:

1. Benjafield, A. V., Ayas, N. T., Eastwood, P. R., Heinzer, R., Ip, M. S. M., Morrell, M. J., Malhotra, A., Almeida, F., Andara, C., Antic, N. A., Arias, M. A., Arzt, M., Atkins, M., Barbé, F., Barnes, M., Barrera, F., Beecroft, J., Benjafield, J., Bittencourt, L., ... McEvoy, R. D. (2019). Estimation of the global prevalence and burden of obstructive sleep apnoea: A literature-based analysis. The Lancet Respiratory Medicine, 7(8), 687–698. https://doi.org/10.1016/S2213-2600(19)30198-5
2. Ryan, S., Cummins, E. P., Taylor, C. T., & McNicholas, W. T. (2023). Intermittent hypoxia and inflammation in OSA: Potential pathways to cardiovascular disease. European Respiratory Review, 32(168), 230009. https://doi.org/10.1183/16000617.0009-2023
3. Peker, Y., Glantz, H., Eulenburg, C., Wegscheider, K., Herlitz, J., & Thunström, E. (2022). Impact of obstructive sleep apnea on cardiovascular disease: A systematic review and meta-analysis. Sleep Medicine Reviews, 63, 101621. https://doi.org/10.1016/j.smrv.2022.101621
4. McEvoy, R. D., Antic, N. A., Heeley, E., Anderson, C. S., Barbe, F., Bassetti, C. L., Billot, L., Bittencourt, L., Bourke, D., Bratton, D. J., Brown, S., Chai-Coetzer, C. L., Chen, R., Cheng, D. C., Chen, G., Choi, S. J., Choi, Y. J., Colquhoun, D., ... Neal, B. (2023). CPAP for prevention of cardiovascular events in obstructive sleep apnea. The New England Journal of Medicine, 388(10), 889–898. https://doi.org/10.1056/NEJMoa1606599
5. Cowie, M. R., Linz, D., Redline, S., Somers, V. K., & Simonds, A. K. (2021). Sleep disordered breathing and cardiovascular disease: JACC state-of-the-art review. Journal of the American College of Cardiology, 78(6), 608-624.
6. Chen, J., Lin, S., & Zeng, Y. (2021). An update on obstructive sleep apnea for atherosclerosis: mechanism, diagnosis, and treatment. Frontiers in cardiovascular medicine, 8, 647071.
7. Faria, A., Macedo, A., Castro, C., Valle, E., Lacerda, R., Ayas, N., & Laher, I. (2022). Impact of sleep apnea and treatments on cardiovascular disease. Sleep Science, 15(2), 250.

8. Kidawara, Y., Kadoya, M., Morimoto, A., Daimon, T., Kakutani-Hatayama, M., Kosaka-Hamamoto, K., Miyoshi, A., Konishi, K., Kusunoki, Y., & Shoji, T. (2022). Sleep Apnea and Physical Movement During Sleep, But Not Sleep Duration, Are Independently Associated With Progression of Left Ventricular Diastolic Dysfunction: Prospective Hyogo Sleep Cardio-Autonomic Atherosclerosis Cohort Study. Journal of the American Heart Association, 11(19), e024948.
9. Yoshihisa, A., & Takeishi, Y. (2019). Sleep disordered breathing and cardiovascular diseases. Journal of atherosclerosis and thrombosis, 26(4), 315-327.
10. Johnson, D. A., Thomas, S. J., Abdalla, M., Guo, N., Yano, Y., Rueschman, M., Tanner, R. M., Mittleman, M. A., Calhoun, D. A., & Wilson, J. G. (2019). Association between sleep apnea and blood pressure control among blacks: Jackson Heart Sleep Study. Circulation, 139(10), 1275-1284.
11. Hou, H., Zhao, Y., Yu, W., Dong, H., Xue, X., Ding, J., Xing, W., & Wang, W. (2018). Association of obstructive sleep apnea with hypertension: a systematic review and meta-analysis. Journal of global health, 8(1).
12. Linz, D., McEvoy, R. D., Cowie, M. R., Somers, V. K., Nattel, S., Lévy, P., Kalman, J. M., & Sanders, P. (2018). Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: a review. JAMA cardiology, 3(6), 532-540.
13. Anter, E., Di Biase, L., Contreras-Valdes, F. M., Gianni, C., Mohanty, S., Tschabrunn, C. M., Viles-Gonzalez, J. F., Leshem, E., Buxton, A. E., & Kulbak, G. (2017). Atrial substrate and triggers of paroxysmal atrial fibrillation in patients with obstructive sleep apnea. Circulation: Arrhythmia and Electrophysiology, 10(11), e005407.
14. Linz, D., Brooks, A. G., Elliott, A. D., Kalman, J. M., McEvoy, R. D., Lau, D. H., & Sanders, P. (2018). Nightly variation in sleep apnea severity as atrial fibrillation risk. Journal of the American College of Cardiology, 72(19), 2406-2407.).
15. Linz, D., Brooks, A. G., Elliott, A. D., Nalliah, C. J., Hendriks, J. M., Middeldorp, M. E., Gallagher, C., Mahajan, R., Kalman, J. M., & McEvoy, R. D. (2019). Variability of sleep apnea severity and risk of atrial fibrillation: the VARIOSA-AF study. JACC: Clinical Electrophysiology, 5(6), 692-701.
16. Linz, D., Baumert, M., Desteghe, L., Kadhim, K., Vernooy, K., Kalman, J. M., Dobrev, D., Arzt, M., Sastry, M., & Crijns, H. J. (2019). Nightly sleep apnea severity in patients with atrial fibrillation: potential applications of long-term sleep apnea monitoring. IJC Heart & Vasculature, 24, 100424.
17. Moula, A. I., Parrini, I., Tetta, C., Lucà, F., Parise, G., Rao, C. M., Mauro, E., Parise, O., Matteucci, F., & Gulizia, M. M. (2022). Obstructive sleep apnea and atrial fibrillation. Journal of Clinical Medicine, 11(5), 1242.

18. Mehra, R., Chung, M. K., Olshansky, B., Dobrev, D., Jackson, C. L., Kundel, V., Linz, D., Redeker, N. S., Redline, S., & Sanders, P. (2022). Sleep-disordered breathing and cardiac arrhythmias in adults: mechanistic insights and clinical implications: a scientific statement from the american heart association. Circulation, 146(9), e119-e136.

19. Acharya, R., Basnet, S., Tharu, B., Koirala, A., Dhital, R., Shrestha, P., Poudel, D., Ghimire, S., & Kafle, S. (2020). Obstructive sleep apnea: risk factor for arrhythmias, conduction disorders, and cardiac arrest. Cureus, 12(8).

20. Di Fusco, S. A., Pignalberi, C., Santini, L., Colivicchi, F., & Santini, M. (2020). Arrhythmias and sleep apnea: physiopathologic link and clinical implications. Journal of Interventional Cardiac Electrophysiology, 57(3), 387-397.

21. Konishi, T., Kashiwagi, Y., Funayama, N., Yamamoto, T., Murakami, H., Hotta, D., & Tanaka, S. (2019). Obstructive sleep apnea is associated with increased coronary plaque instability: an optical frequency domain imaging study. Heart and vessels, 34(8), 1266-1279.

22. Ishiwata, S., Tomita, Y., Ishiwata, S., Narui, K., Daida, H., & Kasai, T. (2020). Association between obstructive sleep apnea and SYNTAX score. Journal of Clinical Medicine, 9(10), 3314.

23. Qu, H., Guo, M., Zhang, Y., & Shi, D.-z. (2018). Obstructive sleep apnea increases the risk of cardiac events after percutaneous coronary intervention: a meta-analysis of prospective cohort studies. Sleep and Breathing, 22, 33-40.

24. Pak, V. M., Strouss, L., Yaggi, H. K., Redeker, N. S., Mohsenin, V., & Riegel, B. (2019). Mechanisms of reduced sleepiness symptoms in heart failure and obstructive sleep apnea. Journal of Sleep Research, 28(5), e12778.

25. Coniglio, A. C., & Mentz, R. J. (2022). Sleep breathing disorders in heart failure. Cardiology Clinics, 40(2), 183-189.

26. Javaheri, S., & Javaheri, S. (2022). Obstructive Sleep Apnea in Heart Failure: Current Knowledge and Future Directions. Journal of Clinical Medicine, 11(12), 3458.

27. Adir, Y., Humbert, M., & Chaouat, A. (2021). Sleep-related breathing disorders and pulmonary hypertension. European Respiratory Journal, 57(1).

28. Duan, A., Huang, Z., Hu, M., Zhao, Z., Zhao, Q., Jin, Q., Yan, L., Zhang, Y., Li, X., & An, C. (2023). The comorbidity burden and disease phenotype in pre-capillary pulmonary hypertension: The contributing role of obstructive sleep apnea. Sleep Medicine, 101, 146-153.

29. Abbasi A. , Gupta S.S , Sabharwal N. , Meghrajani V., Shaurya S.Sharma 1, Kamholz S. et al (2021)A comprehensive review of obstructive sleep apnea Sleep Sci, Apr-Jun;14(2):142–154. doi: 10.5935/1984-0063.20200056

30. Tadic, M., & Cuspidi, C. (2023). Obstructive sleep apnea and right ventricular remodeling: Do we have all the answers? Journal of Clinical Medicine, 12(6), 2421. https://doi.org/10.3390/jcm12062421

31. Waypa G.B and Schumacker P.T (2010) .HYPOXIA-INDUCED CHANGES IN PULMONARY AND SYSTEMIC VASCULAR RESISTANCE: WHERE IS THE O2 SENSOR? : Respir Physiol Neurobiol. Aug 14;174(3):201–211. doi: 10.1016/j.resp.2010.08.007

32. Xie, C., Zhu, R., Tian, Y., & Wang, K. (2017). Association of obstructive sleep apnoea with the risk of vascular outcomes and all-cause mortality: a meta-analysis. BMJ open, 7(12), e013983.

33. Campos-Rodriguez, F., Martinez-Garcia, M. A., Reyes-Nuñez, N., Caballero-Martinez, I., Catalan-Serra, P., & Almeida-Gonzalez, C. V. (2014). Role of sleep apnea and continuous positive airway pressure therapy in the incidence of stroke or coronary heart disease in women. American journal of respiratory and critical care medicine, 189(12), 1544-1550.

34. Azarbarzin, A., Sands, S. A., Stone, K. L., Taranto-Montemurro, L., Messineo, L., Terrill, P. I., Ancoli-Israel, S., Ensrud, K., Purcell, S., & White, D. P. (2019). The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. European heart journal, 40(14), 1149-1157.

35. Ma, C., Zhang, Y., Liu, J., & Sun, G. (2021). A novel parameter is better than the AHI to assess nocturnal hypoxaemia and excessive daytime sleepiness in obstructive sleep apnoea. Scientific Reports, 11(1), 4702.

36. Cao, W., Luo, J., Huang, R., & Xiao, Y. (2023). Implication of a novel measure of obstructive sleep apnea severity for cardiovascular morbidity. Sleep Medicine, 103, 204-210.

37. Sunkonkit, K., Alzaid, M., Al-Saleh, S., & Amin, R. (2022). The Clinical Utility of the Oxygen Desaturation Index to Predict Sleep-Disordered Breathing in Children. In B49. SLEEP, CHEST WALL, AND NEUROMUSCULAR-OH MY! (pp. A2992-A2992). American Thoracic Society.

38. Wang, L., Ou, Q., Shan, G., Lao, M., Pei, G., Xu, Y., Huang, J., Tan, J., Chen, W., & Lu, B. (2022). Independent Association Between Oxygen Desaturation Index and Cardiovascular Disease in Non-Sleepy Sleep-Disordered Breathing Subtype: A Chinese Community-Based Study. Nature and Science of Sleep, 1397-1406.

39. Sreedharan, S. E., Agrawal, P., Rajith, R. S., Nair, S., Sarma, S. P., & Radhakrishnan, A. (2016). Clinical and polysomnographic predictors of severe obstructive sleep apnea in the South Indian population. Annals of Indian Academy of Neurology, 19(2), 216.

40. Rundo, J. V., & Downey III, R. (2019). Polysomnography. Handbook of clinical neurology, 160, 381-392.

41. Mokhlesi, B., Hagen, E. W., Finn, L. A., Hla, K. M., Carter, J. R., & Peppard, P. E. (2015). Obstructive sleep apnoea during REM sleep and incident non-dipping of nocturnal blood pressure: a longitudinal analysis of the Wisconsin Sleep Cohort. Thorax, 70(11), 1062-1069.

42. Khoshkish, S., Hohl, M., Linz, B., Arzt, M., Mahfoud, F., Baumert, M., Schöpe, J., Böhm, M., & Linz, D. (2018). The association between different features of sleep-disordered breathing and blood pressure: a cross-sectional study. The Journal of Clinical Hypertension, 20(3), 575-581.

43. Wali, S. O., Abaalkhail, B., AlQassas, I., Alhejaili, F., Spence, D. W., & Pandi-Perumal, S. R. (2020). The correlation between oxygen saturation indices and the standard obstructive sleep apnea severity. Annals of thoracic medicine, 15(2), 70.

44. Kim, J. B., Seo, B. S., & Kim, J. H. (2019). Effect of arousal on sympathetic overactivity in patients with obstructive sleep apnea. Sleep Medicine, 62, 86-91.

45. Sequeira, V. C. C., Bandeira, P. M., & Azevedo, J. C. M. (2019). Heart rate variability in adults with obstructive sleep apnea: a systematic review. Sleep Science, 12(3), 214.

46. Mejía-Mejía, E., May, J. M., Torres, R., & Kyriacou, P. A. (2020). Pulse rate variability in cardiovascular health: A review on its applications and relationship with heart rate variability. Physiological Measurement, 41(7), 07TR01

47. Blanchard, M., Gerves-Pinquie, C., Feuilloy, M., Le Vaillant, M., Trzepizur, W., Meslier, N., Paris, A., Pigeanne, T., Racineux, J.-L., & Balusson, F. (2021). Association of nocturnal hypoxemia and pulse rate variability with incident atrial fibrillation in patients investigated for obstructive sleep apnea. Annals of the American Thoracic Society, 18(6), 1043-1051.

48. Sabil, A., Gervès-Pinquié, C., Blanchard, M., Feuilloy, M., Trzepizur, W., Goupil, F., Pigeanne, T., Oger, E., Girault, J.-M., & Gagnadoux, F. (2021). Overnight Oximetry–derived Pulse Rate Variability Predicts Stroke Risk in Patients with Obstructive Sleep Apnea. American journal of respiratory and critical care medicine, 204(1), 106-109.

49. Kendzerska, T., Gershon, A. S., Hawker, G., Leung, R. S., & Tomlinson, G. (2014). Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study. PLoS medicine, 11(2), e1001599.

50. Gami, A. S., Olson, E. J., Shen, W. K., Wright, R. S., Ballman, K. V., Hodge, D. O., Herges, R. M., Howard, D. E., & Somers, V. K. (2013). Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10,701 adults. Journal of the American College of Cardiology, 62(7), 610-616.

51. Smagula, S. F., Stone, K. L., Redline, S., Ancoli-Israel, S., Barrett-Connor, E., Lane, N. E., Orwoll, E., & Cauley, J. A. (2016). Actigraphy and polysomnography measured sleep disturbances, inflammation, and mortality among older men. Psychosomatic medicine, 78(6), 686

52. Wang, Q., Zhang, C., Jia, P., Zhang, J., Feng, L., Wei, S., Luo, Y., Su, L., Zhao, C., & Dong, H. (2014). The association between the phenotype of excessive daytime sleepiness and blood pressure in patients with obstructive sleep apnea-hypopnea syndrome. International journal of medical sciences, 11(7), 713.

53. Fazeli, M. A., Najafi, T., & Ghadami, M. R. (2022). Polysomnographic characteristics in patients with obstructive sleep apnea with blood pressure" dipping" and" non-dipping" pattern. Scandinavia Journal of Sleep Medicine, 2(1).

54. Varghese, L., Rebekah, G., Priya, N., Oliver, A., & Kurien, R. (2022). Oxygen desaturation index as alternative parameter in screening patients with severe obstructive sleep apnea. Sleep Science, 15(Spec 1), 224.