



The Relationship Between Slow Wave Sleep and Blood Oxygen Saturation Among Patients With Apnea: Retrospective Study

Ebrahim Norouzi, PhD¹, Ali Zakei, PhD¹, Alexandra J. Bratty, PhD², Habibolah Khazaie, MD¹

¹Sleep Disorders Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

²AB Research Consulting, Las Vegas, NV, USA

Received: May 11, 2023

Revised: June 17, 2023

Accepted: August 14, 2023

Corresponding Authors

Ebrahim Norouzi, PhD
Sleep Disorders Research Center,
Farabi Medical Education Center,
Dolat-Abad Boulevard, Isa Square,
Kermanshah, Iran
Tel +98-9129469087
Fax +98-8338265255
E-mail ebrahim.norouzi68@gmail.com

Habibolah Khazaie, MD
Sleep Disorders Research Center,
Kermanshah University
of Medical Sciences,
Kermanshah, Iran
Tel +98-9129469087
Fax +98-8338265255
E-mail hakhazaie@gmail.com

ORCID iDs

Ebrahim Norouzi 
<https://orcid.org/0000-0003-1091-9371>
Ali Zakei 
<https://orcid.org/0000-0002-5259-6104>
Alexandra J. Bratty 
<https://orcid.org/0000-0002-4318-3164>
Habibolah Khazaie 
<https://orcid.org/0000-0002-8066-9753>

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background and Objective Prior research suggests that slow wave sleep (SWS) is disrupted in people with obstructive sleep apnea (OSA). However, it was not clear whether the reduction in SWS is related to abnormal breathing or the extent of OSA as determined by the minimum oxygen saturation. Further, there is limited research on the relationship between oxygen saturation and SWS. The present study examined the relationship between SWS and minimum oxygen saturation levels in patients with OSA.

Methods The sample consisted of 589 patients with OSA (mean age: 48.54 years) who completed full-night polysomnography.

Results Results showed that there was a significant difference in SWS scores across three apnea-hypopnea index (AHI) groups (AHI score 5–15 for mild apnea, 16–30 for moderate apnea, and >30 for severe apnea). Lower SWS scores were observed in the severe apnea group. Additionally, results indicated that as oxygen saturation decreased, the SWS scores decreased.

Conclusions Results from this study indicate that oxygen saturation significantly predicts SWS amounts. These findings suggest that interventions for low oxygen saturation could enhance the amounts of SWS. The clinical ramifications of these findings are worthy of consideration.

Sleep Med Res 2023;14(3):149-154

Keywords Sleep medicine; Slow wave sleep; Apnea; Delta sleep; Oxygen desaturation.

INTRODUCTION

There are two basic categories of sleep: non-rapid eye movement (NREM) and rapid eye movement (REM). NREM is composed of three stages, with each stage representing progressively deeper sleep. Slow wave sleep (SWS) is defined as the sum of stage 3 and stage 4 NREM sleep and is characterized by highvoltage, synchronized electroencephalographic (EEG) waveforms, often measured as slow wave activity [1]. SWS plays an important role in cerebral restoration and recovery in humans and is involved in the maintenance and consolidation of sleep [2]. SWS is also essential for homeostasis and feeling revitalized upon waking. It serves as a restorative factor in the central nervous system [3] and facilitates the clearance of metabolites [4]. During SWS, slow fluctuating neural oscillations/brain waves are followed by combined waves of blood and cerebrospinal fluid, impacting neural activity [5]. Indeed, sleep and particularly SWS is important for cognitive function [6]. Additionally, SWS can increase the level of arousal-promoting neuromodulators and decrease accumulated metabolites [7].

However, the exact nature and roles of SWS are not clearly understood and there is still much to learn about SWS generation and its physiologic functions. Tononi and Cirelli [8] examined the electrophysiologic character of SWS and demonstrated its important role in

synaptic strength, leading to improved memory and cognitive processing [9,10]. Still, information regarding the prevalence of SWS in different populations, especially patient populations, is incomplete and scarce [11,12].

SWS deficits have been observed in patients with schizophrenia [13], major depression disorders [14], fibromyalgia [15], post-traumatic stress disorder [16] and people with generalized anxiety disorder [17]. The reduction of SWS has also been observed among older people [18] and those with insomnia [19]. However, few studies have examined the prevalence of SWS in people with obstructive sleep apnea (OSA), who often complain about non-deep sleep and exhaustion. Though Afifi et al. [20] found abnormalities in cortical arousal activity in people with OSA, they did not assess SWS. Catcheside and Jordan [21] found that the respiratory arousals (RAs) from a state of sleep to wakefulness during SWS were strongly correlated with the oxygen desaturation index. Additionally, Ren et al. [22] showed that patients with OSA experienced less SWS. However, it was not clear whether the reduction in SWS was related to abnormal breathing or the extent of OSA as determined by the minimum oxygen saturation.

In general, the two broad areas of abnormalities studied in OSA include cognitive function and psychomotor performance [23], while the relationship between oxygen saturation and SWS has received less attention. Previous research indicated that compared to healthy people, those with OSA exhibited some abnormality in brain activity during NREM and REM sleep. Moreover, brain activity was positively correlated with apnea-hypopnea index (AHI) and oxygen desaturation index [24]. In a meta-analysis, Mullins et al. [25] claimed that while findings were inconsistent, overall, OSA patients had fewer and slower sleep spindle frequency activities compared with the controls.

To our knowledge, there is no study that has investigated the relationship between SWS and minimum oxygen saturation in OSA despite documented associations between brain activity and AHI [26]. Therefore, the present study aimed to examine the relationship between SWS and minimum oxygen saturation in patients with OSA based on the polysomnography (PSG) scores. It was hypothesized that 1) there will be a significant difference in SWS scores across mild, moderate, and severe apnea cohorts, 2) there will be a positive correlation between SWS and oxygen saturation, and 3) oxygen saturation will predict SWS.

METHODS

Participants

The participants were 589 Iranian adults with OSA who were patients at the Sleep Disorders Research Center (SDRC), Farabi Hospital, Kermanshah University of Medical Sciences (Kermanshah, Iran). They underwent PSG to evaluate abnormalities of sleep and/or wakefulness and other physiologic disorders. The

inclusion criteria were: 1) AHI score ≥ 5 , 2) ages < 65 years, and 3) adults living in Iran. Exclusion criteria were: 1) personality disorders, 2) substance use disorders, 3) patients treated with benzodiazepines, GABA-receptor agonists, or opiates, 4) narcolepsy, 5) hypersomnia, 6) chronic fatigue syndrome, and 7) severe bipolarity with psychotic symptoms, suicidal ideation and intent, or severe sensorimotor injury (Fig. 1). The exclusion criteria were designed to mitigate the possibility of recruiting participants with depression, insomnia, and other related conditions that could have confounded the study analysis.

Procedure

Full-night PSG recordings of 589 patients with sleep-disordered breathing (SDB) who had been studied between April 2019 and June 2022 were retrospectively analyzed. The sample comprised 210 females and 379 males; with a mean age of 48.54 years (SD = 13.61). Patient data included weight, height, body mass index, respiratory disturbance index (RDI), AHI, arousal index, total sleep time, and periodic leg movements. Like the AHI, RDI reports on respiratory distress events during sleep, but unlike the AHI, it also includes respiratory-effort related arousals.

A full-night PSG was performed in the SDRC at Kermanshah University of Medical Sciences (Kermanshah, Iran). Patients' charts and permission to use this data for research purposes were provided by the local Institutional Review Board, provided that patient confidentiality would be strictly respected (Ethical Approval ID: IR.KUMS.REC.1401.360). The research presented in this manuscript was conducted according to the principles of the Declaration of Helsinki [27].

All individuals had undergone overnight PSG with recordings of EEG, electrooculogram, bilateral pretibial electromyogram, and electrocardiogram. Nasal airflow was measured via impact pressure through a nasal sensor in which pressure fluctuations of the breathed air stream were determined.

Thoracic and abdominal excursions, oxyhemoglobin satura-

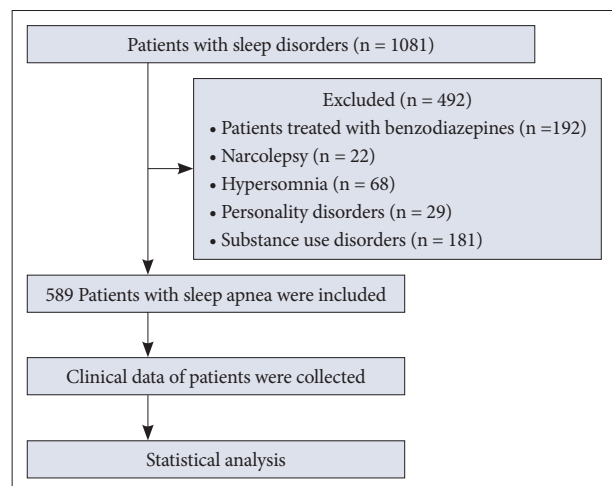


Fig. 1. Flow diagram for consolidated standards of reporting trials.

tion (pulse oximeter), and body position were simultaneously recorded. The polysomnographic recordings were performed using the Alice-LE-Diagnostic Sleep System (SOMNOmedics GmbH, Randersacker, Germany). For each patient, PSG was performed in a standard way between 10 PM and 6 AM. In the morning, following the night of study, sleep stages and sleep-related respiratory events were manually scored according to the American Academy of Sleep Medicine 2012 guidelines [28].

A nasal airflow amplitude reduction greater than 90%, lasting for at least 10 s, was defined as apnea. Hypopnea was defined as an airflow reduction between 50% and 90% with an associated 3% reduction of blood oxygen saturation (SpO₂). Further classification in obstructive, central, or mixed respiratory apnea events was based on simultaneous evaluation of nasal airflow and thoracic and abdominal excursion.

The AHI is an index used to indicate the severity of sleep apnea. It represents the number of apnea and hypopnea events per hour of sleep. An apnea is a pause in breathing that lasts at least 10 s. Hypopnea is a period of shallow breathing or decreased airflow. The AHI is calculated by dividing the number of apnea events plus hypopnea events by the total number of minutes of sleep, then multiplying this number by 60 to get an hourly rate. The severity of sleep apnea is classified based on AHI as follows: normal sleep, AHI < 5; mild sleep apnea, AHI ≥ 5 but < 15; moderate sleep apnea, AHI ≥ 15 but < 30; severe sleep apnea, AHI ≥ 30. Consequently, in this study, there were three analysis AHI groups (AHI score 5–15 for mild apnea group, 16–30 for moderate apnea group, and > 30 for severe apnea group). Using the PSG device software, the RA number during each individual's sleep period as well as the duration and amplitude of each RA were visually registered; like the AHI, it reports on respiratory distress events during sleep, but unlike the AHI, it also includes respiratory-effort related arousals. RAs were detected in 30-s epochs and were scored using the American Academy of Sleep Medicine criteria. Intraclass correlations for both SWS duration and AHI intensity were calculated.

Statistical Analysis

We compared PSG data and demographic information between the three groups via a series of independent one-way analysis of variance (ANOVA) tests. Moreover, the relationships between SWS and minimum oxygen saturation were examined via a series of Pearson's correlations and a multiple linear regression test. All statistical analyses were conducted with SPSS version 25 for Windows (IBM Corp., Armonk, NY, USA). Statistical significance (*p* value) was set at $\alpha < 0.05$.

RESULTS

Table 1 provides an overview of the demographic background of the participants for the three identified AHI cohorts: mild,

moderate, and severe apnea (AHI score 5–15 for mild, 16–30 for moderate, and > 30 for severe). Additionally, the one-way ANOVA results are provided, indicating significant differences across groups for virtually all variables, except height, total time of sleep, wake index, and periodic leg movements, and arousal.

To test the first hypothesis, the mean score for SWS, which is a percentage of the total sleep time was examined across the three sleep apnea cohorts. As highlighted in Table 2, ANOVA results suggested there was a significant difference across the three groups ($p = 0.05$). The highest SWS mean score (15.70) was observed in the moderate apnea group. The second-highest SWS score (13.59) was observed in the mild apnea group, and the lowest SWS score (11.75) was observed in the severe apnea cohort. However, post-hoc calculations (Bonferroni tests) showed a significant difference only between the moderate and severe groups (mean difference = 3.95, $p = 0.04$).

The second hypothesis, that there would be a positive association between SWS and oxygen saturation, was tested using a Pearson's correlation coefficient, and revealed a significant relationship ($r = 0.23$, $p < 0.001$). Finally, for the third hypothesis, that oxygen saturation would predict SWS, a multiple regression (Table 3) was performed using the predictor variables of minimum oxygen saturation.

The regression and ANOVA outputs indicated that the regression models were statistically significant and suggested that minimum oxygen saturation (standardized coefficients = 0.23, $t = 5.11$, $p = 0.001$) significantly predicted variance in SWS.

DISCUSSION

This study aimed to evaluate the relationship between SWS and blood oxygen saturation in 589 patients with OSA based on the PSG scores. The study findings supported the hypotheses.

In this study, it was hypothesized that there would be a significant difference in SWS scores among groups of mild, moderate, and severe apnea. Results indicated that SWS was significantly lower in the severe AHI cohort than in the moderate AHI group. These data are consistent with previous findings about SWS in patients with apnea [21,22,29].

SWS plays an important role in memory and cognitive function, and reduction in fatigue [9]. In other words, SWS plays an important role in homeostasis, cerebral restoration, and recovery [30,31]. In patients with severe apnea, the amount of SWS is reduced, as shown in our results (Table 2). Therefore, it is reasonable to propose that increasing oxygen saturation may be beneficial to those with apnea. There are several ways to increase blood oxygen saturation such as continuous positive airway pressure [32]. There also appears to be a strong relationship between SWS and reduced arousal from sleep. Arousal from sleep is dependent on sleep–respiration interactions in different stages of sleep. Notably, autonomic activation and higher cortical arousal

Table 1. Demographic characteristics and polysomnographic findings for the apnea cohorts

Variables	Mild apnea (n = 291)	Moderate apnea (n = 155)	Severe apnea (n = 143)	F	p-value
	M (SD)	M (SD)	M (SD)		
Age (yr)	45.32 (13.87)	48.17 (14.21)	49.15 (12.77)	11.99	0.030
Height (cm)	170.51 (12.20)	170.38 (10.76)	169.90 (9.82)	0.14	0.860
Weight (kg)	81.29 (16.30)	87.99 (17.05)	90.51 (19.03)	16.35	0.001
BMI (kg/m ²)	28.22 (6.10)	30.46 (5.41)	31.56 (8.39)	14.03	0.001
Global PSQI score	10.00 (5.75)	7.89 (4.92)	7.92 (4.87)	10.95	0.001
Total time of sleep (h)	8.30 (3.08)	6.16 (1.26)	6.28 (3.86)	0.44	0.640
Wake index (/h)	5.35 (5.18)	5.54 (7.74)	6.10 (4.12)	0.79	0.450
Apnea-hypopnea index (/h)	9.04 (2.86)	21.56 (4.17)	42.86 (8.54)	208.43	0.001
Respiratory disturbance index (/h)	12.19 (5.56)	24.64 (5.90)	47.02 (11.23)	1056.41	0.001
Arousal index (/h)	26.09 (11.99)	26.82 (13.52)	32.30 (15.17)	11.13	0.001
PLM arousal	1.28 (2.58)	1.20 (2.34)	1.42 (3.06)	0.26	0.760
Minimum oxygen saturation, SpO ₂ (%)	84.57 (7.00)	78.59 (10.35)	72.80 (12.88)	74.44	0.001
Average oxygen saturation, SpO ₂ (%)	92.62 (3.13)	90.19 (6.09)	88.56 (6.66)	33.85	0.001
Average heart rate (bpm)	65.74 (11.57)	70.86 (11.53)	70.28 (13.00)	11.11	0.001
Periodic leg movements (/h)	8.27 (12.23)	9.16 (16.17)	8.16 (12.12)	0.28	0.750

Between group degree of freedom = 2, within group degree of freedom = 286.

BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; PLM, periodic leg movements.

Table 2. Differences in SWS according to AHI severity

Groups based on AHI score*	Number	Mean SWS	Std. deviation	df	F	p-value
Mild apnea	291	13.59	12.86	2 (586)	2.97	0.05
Moderate apnea	155	15.70	15.26			
Severe apnea	143	11.75	14.78			
Total	589	13.70	14.05			

*AHI score 5–15, mild apnea; 16–30 moderate apnea; and > 30 for severe apnea.

AHI, apnea-hypopnea index.

Table 3. Regression model summary for slow wave sleep

Model	R	R ²	Adjusted R	F	df	p-value
Linear	0.239	0.057	0.055	26.14	1	0.001

Dependent variable: slow wave sleep.

have been reported in patients with apnea [33]. SWS helps to reduce arousal events [34]. Clinical data have shown that respiratory events, as well as RAs, are most prevalent in lighter stages of NREM sleep [35]. Arousal microarchitecture could be a key to understanding respiratory events. Furthermore, there is evidence that duration and intensity of RAs correlate with PSG-related disease severity in patients with apnea [36]. Therefore, it may be helpful in clinical practice and research to consider SWS as a target for methods to counteract arousal events in patients with apnea.

Regarding the second hypothesis, we expected a positive association between SWS and minimum oxygen saturation scores, and the data supported this assumption. Moreover, the findings were aligned with those of the previous studies that demonstrat-

ed a similar connection [21,22,37]. In the present study, results indicated that as the oxygen saturation decreases, the amount of SWS decreases. For instance, the lower minimum oxygen saturation (mean score = 72.80%) was observed in the severe apnea cohort. Indeed, prior research has found that when people with sleep apnea enter SWS, the amount of apneic events increases due to the decrease in oxygen desaturation during sleep [38]. Therefore, this could be a reason for the reduction in SWS in people with apnea.

Based on recent imaging studies, in people with apnea, some brain regions such as the anterior cingulate, frontal cortical, and brainstem areas are subject to structural changes [39]. Previous studies suggested that the arousal stimulus in NREM is related to the level of inspiratory effort. Therefore, mechanisms of arousal in sleep apnea might also play a role in the relationship between SWS and oxygen saturation [40,41].

Finally, our third hypothesis was supported by the findings. The present results showed that lower oxygen saturation is associated with lower SWS. It appears that different factors that

increase the breathing effort, (e.g., hypercapnia and hypoxia), as well as mechanical respiratory events during sleep, trigger an RA which could explain this connection [8,42]. In particular, oxygen desaturation seems to play an important role in levels of SWS. A previous study [43] indicated that the maximum oxygen desaturations (SaO₂) during respiratory events with arousals are larger than the desaturations in events without arousals. Moreover, the sleep stages seem to play an important role in oxygen desaturation.

Limitations

The present study had several limitations. First, confounding variables such as depression, insomnia, and medical conditions may have influenced the study outcomes. While inclusion and exclusion criteria were used to mitigate the potential for these confounds, such conditions often co-occur and might have impacted the results. Second, in the present study, we did not provide specific details regarding the duration of reduced oxygen saturation. This information is important for a comprehensive understanding of the effects being investigated. Future research should include detailed information on the duration of reduced oxygen saturation, to provide a more complete picture. Lastly, AHI is a widely used metric, but it primarily focuses on the number of apneas and hypopneas per hour of sleep and may not fully capture the complex nature of sleep apnea. Therefore, it is important to consider other measures and clinical assessments to provide a more comprehensive evaluation of sleep apnea severity.

Conclusion

There was a significant positive correlation between SWS and oxygen saturation in people with sleep apnea. Lower SWS scores were associated with lower oxygen saturation. Furthermore, oxygen saturation significantly predicted SWS. Given the role that SWS plays in cognitive function and reduction in fatigue and arousal events, the clinical ramifications of these findings are worthy of consideration. Our findings imply that oxygen saturation interventions could help enhancing SWS duration.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Author Contributions

Conceptualization: Ebrahim Norouzi, Habibolah Khazaie. Data analysis: Ebrahim Norouzi, Ali Zakei, Alexandra J. Bratty. Methodology: Habibolah Khazaie, Ebrahim Norouzi. Project administration: Habibolah Khazaie, Ebrahim Norouzi. Supervision: Habibolah Khazaie, Ebrahim Norouzi. Writing—original draft: Habibolah Khazaie, Ebrahim Norouzi. Writing—review & editing: all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

Kermanshah University of Medical Sciences provided financial support in

the form of research assistance funding. The sponsor had no role in the design or conduct of this research.

Acknowledgements

The authors would like to express their gratitude and appreciation for data collection and supporting work performed by Saeid Salimi (Kermanshah University of Medical Sciences, Kermanshah, Iran).

REFERENCES

- Walsh JK. Enhancement of slow wave sleep: implications for insomnia. *J Clin Sleep Med* 2009;5(2 Suppl):S27-32.
- Léger D, Debellemanniere E, Rabat A, Bayon V, Benchenane K, Chennaoui M. Slow-wave sleep: from the cell to the clinic. *Sleep Med Rev* 2018;41:113-32.
- Benson KL. Schizophrenia and its associated sleep disorders. In: Barkoukis TJ, Matheson JK, Ferber R, Doghramji K. Therapy in sleep medicine. Philadelphia, PA: Elsevier Saunders 2012;705-13.
- Ju YS, Ooms SJ, Sutphen C, Macauley SL, Zangrilli MA, Jerome G, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid- β levels. *Brain* 2017;140:2104-11.
- Fultz NE, Bonmassar G, Setsompop K, Stickgold RA, Rosen BR, Polimeni JR, et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science* 2019;366:628-31.
- Brooks LJ, Olsen MN, Bacevice AM, Beebe A, Constantinopoulou S, Taylor HG. Relationship between sleep, sleep apnea, and neuropsychological function in children with Down syndrome. *Sleep Breath* 2015;19:197-204.
- Esser SK, Hill SL, Tononi G. Sleep homeostasis and cortical synchronization: I. Modeling the effects of synaptic strength on sleep slow waves. *Sleep* 2007;30:1617-30.
- Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev* 2006;10:49-62.
- Roth T. Slow wave sleep: does it matter? *J Clin Sleep Med* 2009;5(2 Suppl):S4-5.
- Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull* 2003;62:143-50.
- Assimakopoulos K, Karaivazoglou K, Skokou M, Kalogeropoulou M, Kolios P, Gourzis P, et al. Genetic variations associated with sleep disorders in patients with schizophrenia: a systematic review. *Medicine (Basel)* 2018;5:27.
- Castelnovo A, Lopez R, Proserpio P, Nobili L, Dauvilliers Y. NREM sleep parasomnias as disorders of sleep-state dissociation. *Nat Rev Neurol* 2018;14:470-81.
- Sarkar S, Katshu MZ, Nizamie SH, Praharaj SK. Slow wave sleep deficits as a trait marker in patients with schizophrenia. *Schizophr Res* 2010;124:127-33.
- Landsness EC, Goldstein MR, Peterson MJ, Tononi G, Benca RM. Antidepressant effects of selective slow wave sleep deprivation in major depression: a high-density EEG investigation. *J Psychiatr Res* 2011;45:1019-26.
- Roizenblatt S, Neto NS, Tufik S. Sleep disorders and fibromyalgia. *Curr Pain Headache Rep* 2011;15:347-57.
- Lipinska G, Thomas KGF. Rapid eye movement fragmentation, not slow-wave sleep, predicts neutral declarative memory consolidation in posttraumatic stress disorder. *J Sleep Res* 2019;28:e12846.
- Fuller KH, Waters WF, Binks PG, Anderson T. Generalized anxiety and sleep architecture: a polysomnographic investigation. *Sleep* 1997;20:370-6.
- Varga AW, Ducca EL, Kishi A, Fischer E, Parekh A, Koushyk V, et al. Effects of aging on slow-wave sleep dynamics and human spatial navigational memory consolidation. *Neurobiol Aging* 2016;42:142-9.
- Dijk DJ. Slow-wave sleep deficiency and enhancement: implications for insomnia and its management. *World J Biol Psychiatry* 2010;11(Suppl 1):22-8.

20. Afifi L, Guilleminault C, Colrain IM. Sleep and respiratory stimulus specific dampening of cortical responsiveness in OSAS. *Respir Physiol Neurobiol* 2003;136:221-34.
21. Catcheside PG, Jordan AS. Reflex tachycardia with airway opening in obstructive sleep apnea. *Sleep* 2013;36:819-21.
22. Ren R, Covassin N, Zhang Y, Lei F, Yang L, Zhou J, et al. Interaction between slow wave sleep and obstructive sleep apnea in prevalent hypertension. *Hypertension* 2020;75:516-23.
23. Naismith S, Winter V, Gotsopoulos H, Hickie I, Cistulli P. Neurobehavioral functioning in obstructive sleep apnea: differential effects of sleep quality, hypoxemia and subjective sleepiness. *J Clin Exp Neuropsychol* 2004;26:43-54.
24. Liu S, Shen J, Li Y, Wang J, Wang J, Xu J, et al. EEG power spectral analysis of abnormal cortical activations during REM/NREM sleep in obstructive sleep apnea. *Front Neurol* 2021;12:643855.
25. Mullins AE, Kam K, Parekh A, Bubu OM, Osorio RS, Varga AW. Obstructive sleep apnea and its treatment in aging: effects on Alzheimer's disease biomarkers, cognition, brain structure and neurophysiology. *Neurobiol Dis* 2020;145:105054.
26. Mullins AE, Kim JW, Wong KKH, Bartlett DJ, Vakulin A, Dijk DJ, et al. Sleep EEG microstructure is associated with neurobehavioural impairment after extended wakefulness in obstructive sleep apnea. *Sleep Breath* 2021;25:347-54.
27. Holm S. Declaration of Helsinki. In: LaFollette H. The international encyclopedia of ethics. 1st ed. Chichester: John Wiley & Sons, Inc. 2013; 1232.
28. Jung SY, Rhee EH, Al-Dilajjan KF, Kim SW, Min JY. Impact of AASM 2012 recommended hypopnea criteria on surgical outcomes for obstructive sleep apnea. *Laryngoscope* 2020;130:825-31.
29. Weber K, Penzel T, Peter JH, Becker H, Schwarzenberger F, Schäfer K, et al. [Disordered sleep structure in apnea patients--methods of the objective assessment of sleep fragmentation using the EEG]. *Prax Klin Pneumol* 1987;41:390-3. German
30. Benington JH, Heller HC. Restoration of brain energy metabolism as the function of sleep. *Prog Neurobiol* 1995;45:347-60.
31. Murphy MJ, Peterson MJ. Sleep disturbances in depression. *Sleep Med Clin* 2015;10:17-23.
32. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016;375:919-31.
33. Jordan AS, Eckert DJ, Wellman A, Trinder JA, Malhotra A, White DP. Termination of respiratory events with and without cortical arousal in obstructive sleep apnea. *Am J Respir Crit Care Med* 2011;184:1183-91.
34. Gilmartin GS, Thomas RJ. Mechanisms of arousal from sleep and their consequences. *Curr Opin Pulm Med* 2004;10:468-74.
35. Ratnavadivel R, Chau N, Stadler D, Yeo A, McEvoy RD, Catcheside PG. Marked reduction in obstructive sleep apnea severity in slow wave sleep. *J Clin Sleep Med* 2009;5:519-24.
36. Bahr K, Geisler V, Huppertz T, Groppa S, Matthias C, Gouveris H, et al. Intensity of respiratory cortical arousals is a distinct pathophysiologic feature and is associated with disease severity in obstructive sleep apnea patients. *Brain Sci* 2021;11:282.
37. Ko CY, Fan JM, Hu AK, Su HZ, Yang JH, Huang LM, et al. Disruption of sleep architecture in Prevoletta enterotype of patients with obstructive sleep apnea-hypopnea syndrome. *Brain Behav* 2019;9:e01287.
38. Sahib A, Roy B, Kang D, Aysola RS, Wen E, Kumar R. Relationships between brain tissue damage, oxygen desaturation, and disease severity in obstructive sleep apnea evaluated by diffusion tensor imaging. *J Clin Sleep Med* 2022;18:2713-21.
39. Torabi-Nami M, Mehrabi S, Borhani-Haghighi A, Derman S. Withstanding the obstructive sleep apnea syndrome at the expense of arousal instability, altered cerebral autoregulation and neurocognitive decline. *J Integr Neurosci* 2015;14:169-93.
40. Berry RB, Gleeson K. Respiratory arousal from sleep: mechanisms and significance. *Sleep* 1997;20:654-75.
41. Zhou GL, Pan Y, Liao YY, Liang JX, Zhang XM, Luo YX. Short-term impact of sleep apnea/hypopnea on the interaction between various cortical areas. *Clin EEG Neurosci* 2021;52:296-306.
42. Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. *Am J Respir Crit Care Med* 2004;169:623-33.
43. Fleetham J, West P, Mezon B, Conway W, Roth T, Kryger M. Sleep, arousals, and oxygen desaturation in chronic obstructive pulmonary disease. The effect of oxygen therapy. *Am Rev Respir Dis* 1982;126:429-33.