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Polysomnographic features of low arousal threshold in overlap syndrome involving obstructive sleep apnea and chronic obstructive pulmonary disease

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Abstract

Purpose In patients with overlap syndrome (OVS), the pathophysiologies of obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease can interact with one another. Focusing on low arousal threshold, the authors evaluated polysomnographic features of OVS patients.

Methods This retrospective, multicenter study was conducted at three hospitals in Japan. Patients aged ≥ 60 years who underwent polysomnography and pulmonary function testing were reviewed. Severity of airflow limitation (AFL) was classified according to the Global Initiative for Chronic Obstructive Lung Disease criteria. Low arousal threshold was predicted based on the following polysomnography features: lower apnea-hypopnea index (AHI); higher nadir oxygen saturation, and larger hypopnea fraction of total respiratory events. These features were compared among patients with only OSA ($n = 126$), OVS with mild AFL ($n = 16$), and OVS with moderate/severe AFL ($n = 22$).

Results A low arousal threshold was more frequently exhibited by OVS patients with moderate/severe AFL than by those with OSA only ($p = 0.016$) and OVS with mild AFL ($p = 0.026$). As forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) decreased in OVS patients, the mean length of apnea decreased ($r = 0.388$, $p = 0.016$), hypopnea fractions increased ($r = -0.337$, $p = 0.039$), and AHI decreased ($r = 0.424$, $p = 0.008$). FEV_1/FVC contributed to low arousal threshold independent of age, sex, smoking history, hospital, or body mass index in all subjects (OR 0.946 [95% CI 0.909–0.984]) and in OVS patients (OR 0.799 [95% CI 0.679–0.940]).

Conclusions This study first described peculiar polysomnographic features in OVS patients with moderate/severe AFL, suggesting a high prevalence of low arousal threshold.

Keywords Arousal · Chronic obstructive pulmonary disease · Obstructive sleep apnea · Polysomnography · Spirometry

Introduction

Both chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) are common diseases in adults. The prevalence of COPD is estimated to be nearly 20% of all adults ≥ 60 years of age in Japan [1]. Meanwhile, the prevalence of OSA, with apnea-hypopnea index (AHI) > 15 events/h, was 23.9% of commercial motor vehicle drivers in Japan [2].

It remains to be clarified whether OSA occurs more frequently in COPD patients than in the general population [3, 4]. However, some reports have indicated that the prognosis of overlap syndrome (OVS) of COPD and OSA is poorer than that of COPD alone [5]. Moreover, these diseases can interact with one another in pathophysiology, even if co-existence is incidental [6, 7].

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The pathophysiology of OSA cannot be explained solely by the anatomical collapsibility of the upper airways [8, 9]. Multiple factors contribute to the pathogenesis of OSA, including low arousal threshold, low dilator muscle activity, and respiratory control dysregulation [10]. The features of polysomnography (PSG) findings can aid in elucidating the mechanism underlying the association between COPD and OSA. In particular, Edwards et al. [11] reported that low arousal threshold can be predicted by three PSG features, namely, low AHI, high nadir oxygen saturation (SpO_2), and large hypopnea fraction of total respiratory events. In the patients with low arousal threshold, brief awakening easily occurs following relatively mild airway obstruction during sleep, resulting in persistent breathing instability [12]. Since low sleep efficiency is a common feature of COPD [13], we hypothesized that low arousal threshold would be frequently associated with breathing disorders during sleep in OVS patients.

In the present study, we evaluated PSG findings, focusing on low arousal threshold, in OVS patients from three hospitals in Japan.

Methods

Study design

This multicenter retrospective study was conducted at three hospitals in Tokyo, Japan. Patients ≥ 60 years of age, who underwent PSG up to July 2015 and also underwent pulmonary function testing within 5 years from the date of their PSG evaluation, were reviewed.

Among the patients reviewed, only those with AHI ≥ 5 events/h were enrolled as OSA patients with or without any symptoms due to sleep breathing disorders.

The study design was approved by the institutional review board of each institute (permission number 2630 in the University of Tokyo Hospital, 14-093 in Juntendo University Hospital, and 26-01-416 in Respiratory Care Clinic of Nippon Medical School). Given the retrospective nature of the study and the use of anonymized patient data, requirements for informed consent were waived.

Diagnosis of COPD and OVS

Forced expiratory volume in 1 s (FEV_1) predicted and vital capacity (VC) predicted were calculated using reference equations from the Japanese Respiratory Society [14]. COPD was defined in patients who exhibited FEV_1/forced vital capacity (FVC) < 70% and had a smoking history of > 10 pack-years. Severity of airflow limitation (AFL) was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria as follows: GOLD1, mild ($FEV_1 \geq 80\%$ predicted); GOLD2, moderate ($50\% \leq FEV_1 < 80\%$ predicted); and GOLD3, severe ($30\% \leq FEV_1 < 50\%$ predicted). There were no patients with $FEV_1 < 30\%$ predicted.

The term "OVS" was used for patients with both OSA and COPD, and "OSA only" for OSA patients with an FEV_1/FVC ≥ 70% and VC ≥ 80% predicted.

PSG

All patients underwent overnight PSG studies under room air conditions. The recordings included electroencephalogram, electro-oculogram, and submental electromyogram. Oronasal thermistor channel, pressure sensor channel, and arterial oxygen saturation were also monitored. All recordings were scored visually by an experienced rater.

In all three hospitals, apnea was defined as cessation of airflow lasting ≥ 10 s. As for hypopnea, the University of Tokyo Hospital (hospital A) used the criteria of a ≥ 50% reduction in airflow lasting ≥ 10 s, accompanied by a ≥ 3% decrease in SpO_2 or arousal, while Juntendo University Hospital (hospital B) and Respiratory Care Clinic (hospital C) used the criteria of a ≥ 30% reduction in airflow lasting ≥ 10 s, accompanied by ≥ 3% decrease in SpO_2 or arousal.

Prediction of low arousal threshold

The clinical scoring system described by Edwards et al. [11] was used to predict the presence of low arousal threshold. First, scoring (0 to 3) was based on the following three criteria: AHI < 30 events/h, a nadir $SpO_2 > 82.5\%$, and hypopnea fraction of total respiratory events > 58.3%. Subsequently, a total score ≥ 2 was defined as a low arousal threshold.

Statistical analysis

Comparisons among the groups ware performed using the Mann-Whitney *U* test for continuous variables, and the χ^2 test or Fisher's exact test for categorical variables. Correlation analyses were performed using Spearman's rank correlation. A logistic regression model was used to determine the factors associated with low arousal threshold in a stepwise method. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS version 25 (IBM Corporation, Armonk, NY, USA).

Results

Due to the availability of previous PSG records, hospital A enrolled 67 patients (51 OSA only and 16 OVS) who underwent PSG between April 2011 and July 2015, hospital

B enrolled 82 patients (64 OSA only and 18 OVS) who underwent PSG between January 2010 and July 2015, and hospital C enrolled 15 patients (11 OSA only and 4 OVS) who underwent PSG between April 2013 and July 2015.

The background characteristics and PSG data of the subjects are summarized in Table 1. Due to slight differences in the criteria for hypopnea, the data are also shown separately for hospital A and hospitals B/C (see Table S1 and Table S2 in the supplemental material). Males were predominant in the OVS group. In hospitals B/C, the OVS patients with moderate/severe AFL were more elderly than patients with OSA only.

AHI, oxygen desaturation index (ODI), nadir SpO_2, sleep structure, and arousal index were not significantly different between the groups. However, low arousal threshold was significantly more frequently exhibited in OVS patients with moderate/severe AFL than in those with OSA only and in OVS patients with mild AFL in the combined data ($p = 0.016$, $p = 0.026$, respectively) (Table 1). Separate data from hospital A and hospitals B/C also demonstrated the same features, although the difference did not reach statistical significance (see Table S1 and Table S2 in the supplemental material).

To evaluate the association between the arousal threshold and pulmonary function in the OVS group, the correlations between each component of low arousal threshold prediction and %VC, $\%FEV_1$, or FEV_1/FVC were analyzed (Table 2). In addition, the mean length of apnea and hypopnea was evaluated because these parameters can be related to low arousal threshold. As pulmonary function deteriorated, the mean length of apnea and hypopnea decreased, AHI decreased, nadir SpO_2 increased, and hypopnea fraction increased. In particular, FEV_1/FVC demonstrated a statistically significant correlation with mean length of apnea, AHI, and hypopnea fraction (Table 2). Although some correlations did not reach statistical significance in each hospital, the trend was almost completely preserved.

Table 1 Background characteristics and polysomnography data for the entire patient cohort

	OSA only ($n = 126$)	Overlap AFL GOLD1 ($n = 16$)	Overlap AFL GOLD2–3 ($n = 22$)	*p* value vs OSA only	*p* value vs AFL GOLD1
Age, years	68.7 ± 6.4	69.4 ± 7.1	71.4 ± 5.8	0.043*	0.201
BMI	26.1 ± 4.5	24.8 ± 2.9	25.0 ± 5.1	0.125	0.872
Male (*n*, %)	91 (72.2%)	16 (100%)	21 (95.5%)	0.019*	0.579
Smoking (*n*, %)	54 (42.9%)	16 (100%)	22 (100%)	< 0.001*	–
VC, %predicted	103.0 ± 13.0	113.3 ± 12.1	84.4 ± 9.9	< 0.001*	< 0.001*
FEV_1, %predicted	100.1 ± 15.0	92.0 ± 11.0	59.8 ± 12.8	< 0.001*	< 0.001*
FEV_1/FVC	77.8 ± 4.6	66.4 ± 3.6	58.4 ± 9.3	< 0.001*	0.001*
AHI, /h	39.6 ± 20.7	36.8 ± 15.6	38.1 ± 25.3	0.592	0.759
3% ODI, /h	32.3 ± 21.2	29.7 ± 15.4	30.6 ± 22.6	0.696	0.672
Duration of $SpO_2 < 90\%$ / TST, %	11.5 ± 20.1	8.5 ± 8.9	12.6 ± 24.3	0.752	0.693
Nadir SpO_2	67.4 ± 22.3	72.1 ± 18.2	73.6 ± 19.7	0.135	0.589
Duration of REM/TST, %	14.2 ± 7.1	15.2 ± 5.0	14.0 ± 6.8	0.998	0.827
Duration of N3/TST, %	4.3 ± 5.5	3.4 ± 4.9	3.3 ± 3.6	0.695	0.715
Arousal index, /h	38.5 ± 19.2	37.3 ± 13.2	40.2 ± 22.0	0.796	0.630
Mean length of apnea, s	37.3 ± 21.4	35.2 ± 13.2	30.7 ± 20.5	0.056	0.073
Mean length of hypopnea, s	27.5 ± 7.4	33.5 ± 7.7	25.9 ± 6.7	0.256	0.003*
Hypopnea fraction of respiratory events, %	48.9 ± 27.1	39.5 ± 28.3	60.0 ± 29.6	0.088	0.036*
AHI < 30 (*n*, %)	44 (34.9%)	5 (31.3%)	10 (45.5%)	0.344	0.376
Nadir $SpO_2 > 82.5\%$ (*n*, %)	37 (29.4%)	5 (31.3%)	9 (40.9%)	0.280	0.542
Hypopnea fraction > 58.3% (*n*, %)	50 (39.7%)	4 (25.0%)	13 (59.1%)	0.089	0.037*
Low arousal threshold (*n*, %)	36 (28.6%)	3 (18.8%)	12 (54.5%)	0.016*	0.026*

The age and BMI are from the data of polysomnography. Mean ± SD is shown, if not mentioned otherwise. *P* values show the comparison between the overlap syndrome patients with GOLD2–3 AFL and patients with OSA only or the overlap syndrome patients with GOLD1 AFL

OSA obstructive sleep apnea, *AFL* airflow limitation, *BMI* body mass index, *VC* vital capacity, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *AHI* apnea-hypopnea index, *ODI* oxygen desaturation index, *SpO_2* oxygen saturation, *TST* total sleep time

*Statistically significant difference

Table 2 The correlations between pulmonary function and the polysomnography data with regard to low arousal threshold in overlap syndrome patients

		Hospital A		Hospital B and C		Combined	
		$n = 16$		$n = 22$		$n = 38$	
		r	p	r	p	r	p
Mean length of apnea	VC, %predicted	0.671	0.004*	0.168	0.456	0.259	0.117
	FEV_1, %predicted	0.638	0.008*	0.345	0.116	0.278	0.092
	FEV_1/FVC	0.479	0.06	0.476	0.025*	0.388	0.016*
Mean length of hypopnea	VC, %predicted	0.632	0.009*	0.566	0.007*	0.53	0.001*
	FEV_1, %predicted	0.588	0.017*	0.575	0.006*	0.486	0.002*
	FEV_1/FVC	0.37	0.159	0.362	0.107	0.323	0.051
AHI	VC, %predicted	0.43	0.096	− 0.029	0.899	0.068	0.687
	FEV_1, %predicted	0.467	0.068	0.251	0.259	0.234	0.157
	FEV_1/FVC	0.427	0.099	0.49	0.021*	0.424	0.008*
Nadir SpO_2	VC, %predicted	− 0.312	0.24	0.012	0.956	− 0.015	0.927
	FEV_1, %predicted	− 0.117	0.667	− 0.137	0.544	− 0.009	0.959
	FEV1/FVC	− 0.084	0.757	− 0.5	0.018*	− 0.28	0.088
Hypopnea fraction of respiratory events	VC, %predicted	− 0.435	0.092	− 0.547	0.008*	− 0.442	0.005*
	FEV_1, %predicted	− 0.441	0.087	− 0.551	0.008*	− 0.382	0.018*
	FEV_1/FVC	− 0.309	0.244	− 0.417	0.054	− 0.337	0.039*

*Statistically significant correlation

Finally, factors potentially determining low arousal threshold in all patients and OVS patients was evaluated using multiple logistic regression analysis. Using age, smoking history, BMI, hospital, and FEV_1/FVC as independent variables, the multiple logistic regression analysis revealed that BMI and FEV_1/FVC were associated with low arousal threshold in the entire patient cohort. In OVS patients, only FEV_1/FVC was associated with low arousal threshold (Table 3). Considering the effect of OSA severity, the multiple logistic regression analysis was also performed by adding AHI as an independent variable. This analysis revealed that AHI and FEV_1/FVC were associated with low arousal threshold in the entire patient cohort and in OVS patients (Table 3).

Discussion

In the present study, we demonstrated that OVS patients with moderate/severe AFL often exhibited PSG features of low arousal threshold.

Theoretically, COPD can affect sleep apnea and hypopnea through various mechanisms. However, few findings had been reported to demonstrate the linkage between OSA and COPD. Zhao et al. [4] reported that individuals with obstructive airway diseases exhibited shorter mean apnea and hypopnea lengths than those without obstructive airway diseases. This finding is consistent with our results, although some correlations did not reach statistical significance in our analyses (Tables 1 and 2). Meanwhile, apnea length was relatively longer than hypopnea length in our study, contrasting with the report of Zhao et al. [4]. This difference may be due in part to the presence of many severe OSA patients in our study. Biselli et al. [15] reported that increases in lung volumes augment upper airway patency, resulting in decreased incidence of sleep apnea [4, 16]. These findings are also compatible with our results because our findings indicated the significant correlation between AHI and FEV_1/FVC and supported importance of low arousal threshold in the etiology of breathing disorders during sleep in OVS.

At the same time, COPD patients can desaturate more quickly with a small degree of upper airway obstruction, which can also increase the number of hypopnea events compared with apnea. However, 3% ODI and duration of $SpO_2 <$ 90% were not different among the groups in our study, suggesting that frequent oxygen desaturation would not be a major cause of increase in hypopnea fraction in our study. Although arousal indexes were not different among the groups in our study, previous studies have reported lower arousal index in patients with lower arousal threshold, possibly due to lower AHI [11, 17]. Considering these previous reports, arousal indexes would not be useful in predicting arousal threshold.

To date, the factors that contribute to low arousal threshold in OSA patients have not been clarified well. The correlation

Table 3 Independent predictors of low arousal threshold

	Odds ratio	95% confidence interval	*p* value
In the entire patient cohort ($n = 164$)			
Method A			
BMI	0.897	0.818–0.983	0.020
FEV_1/FVC	0.946	0.909–0.984	0.006
Method B			
AHI	0.850	0.805–0.898	0.000
FEV_1/FVC	0.924	0.864–0.988	0.021
In overlap syndrome patients ($n = 38$)			
Method A			
FEV_1/FVC	0.799	0.679–0.940	0.007
Method B			
AHI	0.898	0.826–0.977	0.012
FEV_1/FVC	0.778	0.615–0.984	0.036

Multiple logistic regression analysis using age, cigarette smoking, BMI, hospital, and FEV_1/FVC as independent variables in method A. Multiple logistic regression analysis using age, cigarette smoking, BMI, hospital, FEV_1/FVC, and AHI as independent variables in method B. Dependent variables: 0 = not low arousal threshold, 1 = low arousal threshold

between BMI and low arousal threshold in our entire cohort is consistent with the previous findings by Edwards et al. [11]. Eckert et al. [18] reported that eszopiclone reduced AHI in OSA patients with low arousal threshold by preventing arousal. However, the findings by Smith et al. [19] did not support these effects of non-benzodiazepine sedative hypnotics. Our findings are, to the best of our knowledge, the first report of comorbidities that contribute to low arousal threshold in OSA patients, which can inform future investigations on the pathogenesis of low arousal threshold in some OSA patients. Additionally, a recent investigation indicated poor adherence to continuous positive airway pressure (CPAP) therapy in non-obese OSA patients with low arousal threshold [17]. Therefore, the high prevalence of low arousal threshold in OVS patients in our study may suggest that CPAP adherence should be checked carefully in these patients.

Although FEV_1/FVC was associated with the polysomnographic features of low arousal threshold in our study, the pulmonary function parameter that most strongly affects arousal threshold was not identified. Since previous findings of OSA in idiopathic pulmonary fibrosis also indicated a high number of hypopnea events compared with apnea [20], any type of pulmonary dysfunction would contribute to low arousal threshold. Regrettably, only a small number of our patients with OSA only and those with mild airflow limitation performed the measurements of lung volume or diffusing capacity of the lungs. This is an important concern that warrants further investigation in future studies.

Our investigations had several limitations. First, we differentiated patients with low arousal threshold by using the scoring system described by Edwards et al. [11], not by directly measuring intrathoracic pressure. Especially, it remained to be ascertained whether this scoring system is applicable to patients with pulmonary diseases. However, the direct measurement of intrathoracic pressure during sleep is burdensome for the patients with moderate/severe AFL. As several other investigations have used this scoring system [17, 19, 21], our findings can be an important clue to clarify the pathogenesis of breathing disorder during sleep in COPD patients. Second, our investigation was a retrospective study involving patients who underwent both PSG and pulmonary function testing. Therefore, there may have been some bias from general OVS patients. However, the multicenter design of our study would have mitigated some bias. In addition, some of our findings are consistent with a previous cross-sectional study involving community-dwelling individuals [4], which also support the generalizability of our findings. Third, the number of OVS patients was low. Because the percentage of OVS patients is low among OSA patients, much larger-scale studies are crucial to confirm our findings. In addition, precise characterization of COPD was also difficult in our study. COPD was defined purely based on spirometry results and smoking history because sufficient clinical symptom data had not been obtained. A future large-scale prospective study would indicate more clearly what factors of COPD are associated with low arousal threshold in OVS patients. Finally, due to differences in scoring criteria for hypopnea among the participating hospitals, the interpretation of results may have introduced some confusion. However, our data demonstrated consistent trends between hospital A and hospitals B/C, which strengthen the certainty of our findings.

In conclusion, the present study was the first to describe the peculiar features of PSG in OVS patients with moderate/severe AFL, suggesting a high prevalence of low arousal threshold.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Given the retrospective nature of the study and the use of anonymized patient data, formal consent is not required.

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References

1. Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, Takahashi K, Nishimura K, Ishioka S, Aizawa H, Zaher C (2004) COPD in Japan: the Nippon COPD epidemiology study. Respirology 9(4):458–465
2. Ueyama M, Kokuto H, Sugihara H, Oikawa S, Suzuki F, Goto H, Kudoh S (2018) Investigation of obstructive sleep apnea using portable monitors and health check data in Japanese drivers. J Atheroscler Thromb 25:1118–1127. https://doi.org/10.5551/jat.41806
3. Shawon MS, Perret JL, Senaratna CV, Lodge C, Hamilton GS, Dharmage SC (2017) Current evidence on prevalence and clinical outcomes of co-morbid obstructive sleep apnea and chronic obstructive pulmonary disease: a systematic review. Sleep Med Rev 32:58–68. https://doi.org/10.1016/j.smrv.2016.02.007
4. Zhao YY, Blackwell T, Ensrud KE, Stone KL, Omachi TA, Redline S, Osteoporotic Fractures in Men (MrOS) Study Group (2016) Sleep apnea and obstructive airway disease in older men: outcomes of sleep disorders in older men study. Sleep 39(7):1343–1351. https://doi.org/10.5665/sleep.5960
5. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR (2010) Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med 182(3):325–331. https://doi.org/10.1164/rccm.200912-1869OC
6. Owens RL, Macrea MM, Teodorescu M (2017) The overlaps of asthma or COPD with OSA: a focused review. Respirology 22(6):1073–1083. https://doi.org/10.1111/resp.13107
7. Malhotra A, Schwartz AR, Schneider H, Owens RL, DeYoung P, Han MK, Wedzicha JA, Hansel NN, Zeidler MR, Wilson KC, Badr MS, ATS Assembly on Sleep and Respiratory Neurobiology (2018) Research Priorities in Pathophysiology for Sleep-disordered Breathing in Patients with Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Research Statement. Am J Respir Crit Care Med 197(3):289–299. https://doi.org/10.1164/rccm.201712-2510ST
8. Bosi M, De Vito A, Kotecha B, Viglietta L, Braghiroli A, Steier J, Pengo M, Sorrenti G, Gobbi R, Vicini C, Poletti V (2018) Phenotyping the pathophysiology of obstructive sleep apnea using polygraphy/polysomnography: a review of the literature. Sleep Breath 22(3):579–592. https://doi.org/10.1007/s11325-017-1613-3
9. Edwards BA, Eckert DJ, Jordan AS (2017) Obstructive sleep apnoea pathogenesis from mild to severe: is it all the same? Respirology 22(1):33–42. https://doi.org/10.1111/resp.12913
10. White DP (2005) Pathogenesis of obstructive and central sleep apnea. Am J Respir Crit Care Med 172(11):1363–1370
11. Edwards BA, Eckert DJ, McSharry DG, Sands SA, Desai A, Kehlmann G, Bakker JP, Genta PR, Owens RL, White DP, Wellman A, Malhotra A (2014) Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea. Am J Respir Crit Care Med 190(11):1293–1300. https://doi.org/10.1164/rccm.201404-0718OC
12. Eckert DJ, Younes MK (2014) Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. J Appl Physiol (1985) 116(3):302–313. https://doi.org/10.1152/japplphysiol.00649.2013
13. Budhiraja R, Siddiqi TA, Quan SF (2015) Sleep disorders in chronic obstructive pulmonary disease: etiology, impact, and management. J Clin Sleep Med 11(3):259–270. https://doi.org/10.5664/jcsm.4540
14. Tamura G, Aizawa H, Nagai A, Inoue H (2007) Common prediction equations of respiratory function tests from children to adults in Japan. Nihon Kokyuki Gakkai Zasshi 45(7):526–542
15. Biselli P, Grossman PR, Kirkness JP, Patil SP, Smith PL, Schwartz AR, Schneider H (2015) The effect of increased lung volume in chronic obstructive pulmonary disease on upper airway obstruction during sleep. J Appl Physiol (1985) 119(3):266–271. https://doi.org/10.1152/japplphysiol.00455.2014
16. Krachman SL, Tiwari R, Vega ME, Yu D, Soler X, Jaffe F, Kim V, Swift I, D'Alonzo GE, Criner GJ, Investigators COPDG (2016) Effect of emphysema severity on the apnea-hypopnea index in smokers with obstructive sleep apnea. Ann Am Thorac Soc 13(7):1129–1135. https://doi.org/10.1513/AnnalsATS.201511-765OC
17. Zinchuk A, Edwards BA, Jeon S, Koo BB, Concato J, Sands S, Wellman A, Yaggi HK (2018) Prevalence, associated clinical features, and impact on continuous positive airway pressure use of a low respiratory arousal threshold among male United States veterans with obstructive sleep apnea. J Clin Sleep Med 14(5):809–817. https://doi.org/10.5664/jcsm.7112
18. Eckert DJ, Owens RL, Kehlmann GB, Wellman A, Rahangdale S, Yim-Yeh S, White DP, Malhotra A (2011) Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. Clin Sci (Lond) 120(12):505–514. https://doi.org/10.1042/CS20100588
19. Smith PR, Sheikh KL, Costan-Toth C, Forsthoefel D, Bridges E, Andrada TF, Holley AB (2017) Eszopiclone and zolpidem do not affect the prevalence of the low arousal threshold phenotype. J Clin Sleep Med 13(1):115–119. https://doi.org/10.5664/jcsm.6402
20. Lancaster LH, Mason WR, Parnell JA, Rice TW, Loyd JE, Milstone AP, Collard HR, Malow BA (2009) Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. Chest 136(3):772–778. https://doi.org/10.1378/chest.08-2776
21. Lee RWW, Sutherland K, Sands SA, Edwards BA, Chan TO, S S Ng S, Hui DS, Cistulli PA (2017) Differences in respiratory arousal threshold in Caucasian and Chinese patients with obstructive sleep apnoea. Respirology 22(5):1015–1021. https://doi.org/10.1111/resp.13022