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Clinical characteristics of Asian patients with sleep apnea with low arousal threshold and sleep structure change with continuous positive airway pressure

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Abstract

Purpose Low respiratory arousal threshold (ArTH) has been observed to be prevalent in patients with obstructive sleep apnea (OSA), and is associated with poor adherence to continuous positive airway pressure (CPAP) treatment. This study aimed to examine the associations between low ArTH and clinical characteristics. The second aim was to examine sleep structure changes between diagnostic polysomnography (PSG) and CPAP titration studies.

Methods PSG data for 3718 adults who had an apnea-hypopnea index (AHI) ≥ 5 were reviewed retrospectively, as well as 206 CPAP titration studies among these participants. Participants were dichotomized into low- and high-ArTH groups according to their PSG parameters. The associations between low ArTH and clinical characteristics were examined by multivariate logistic regressions. The sleep structure changes between PSG and CPAP titration studies were examined by repeated measures ANOVA.

Results Fifty percent of patients with OSA had low ArTH. Compared with high-ArTH patients, low-ArTH patients were less obese and composed of a higher percentage of women. In logistic regression models, low ArTH was associated with bruxism and nocturia, but not with illnesses after adjusting for AHI and body mass index. Compared with diagnostic PSG studies, low-ArTH patients had significantly decreased stage changes and increased percentage of rapid eye movement sleep during CPAP titration studies.

Conclusion Low ArTH was prevalent in this large sample of patients with OSA. Arousal threshold was not associated with an increased risk of physical illnesses but was with certain clinical complaints. Low-ArTH patients benefited from CPAP titration study for improved sleep structure.

Keywords Arousal · Obstructive sleep apnea · Continuous positive airway pressure · Asia

Introduction

Obstructive sleep apnea (OSA) is a disease with complex pathological etiologies, and low respiratory arousal threshold (ArTH) has been suggested to be an exacerbating factor [1]. The increase of negative intrathoracic pressure leads to cortical arousal during an obstructive apnea event [2]. Arousals may occur before or after upper airway opening [3], depending on the levels of both arousal threshold and effective upper airway recruitment threshold which vary between individual [2]. Premature arousal increases respiratory instability as well as subsequent respiratory events [4], and it also prevents deep sleep. Except for obese patients with OSA who depend on cortical arousal to open upper airways, arousal is considered to have negative effects on OSA severity [3].

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Low ArTH is prevalent among non-obese patients with OSA [5], and non-obese patients with OSA are common in Asia [6, 7]. Low-ArTH OSA patients had been observed to be non-obese and had worse compliance with continuous positive airway pressure (CPAP) use compared with high-ArTH patients in Western populations [5, 8]. Despite that low-ArTH OSA may be common in the Asian population, the clinical characteristics have not been examined. The symptom profiles of OSA patients are different between ethnicity groups in international studies [9, 10]. In addition to typical OSA symptoms included in screening tools such as snoring, witnessed apneas, and excessive sleepiness, numerous clinical symptoms were complained by OSA patients, for example, morning headache, nocturia, bruxism, and gastrointestinal reflux. Antidepressant use has been observed to be associated with low ArTH, but physical illnesses were not [8]. Whether low-ArTH patients present a different clinical profile from high-ArTH patients was unclear.

Furthermore, treatment recommendations for OSA may differ between low- and high-ArTH patients. CPAP reduced ArTH in severe OSA patients [11, 12], and is often intolerable to less severe OSA patients [13]. Hypnotics help improve sleep quality such that individuals who are prone to repeated awakenings on CPAP treatment may tolerate better [14, 15]. Some but not all studies showed that hypnotics increased ArTH and decreased AHI [16], while the effect was most prominent among low-ArTH patients [17]. Although CPAP is a powerful treatment choice for OSA, it could be underused among low-ArTH patients. It also has not been examined how CPAP treatment changes sleep structures among low-ArTH patients.

In this study, we aimed to examine the prevalence of low ArTH in an Asian population, and the clinical characteristics associated with low ArTH. The second aim was to examine sleep structure changes between PSG study and CPAP titration studies among low- and high-ArTH patients. We hypothesized that high-ArTH patients had more improvement in arousal frequency and deep sleep fraction with CPAP titration compared with low-ArTH patients.

Methods

Study participants

We retrospectively retrieved 6695 PSG and CPAP titration study data from a sleep center in central Taiwan between February 2008 and December 2015. Patients were referred to a sleep center by physicians for diagnostic PSG studies (Fig. 1), and indications included snoring, and assessment of obstructive sleep apnea, hypersomnia, insomnia, parasomnias, and periodic limb movement disorders. The patients' body weight and height were measured by technicians before the studies. Clinical characteristics were evaluated with a self-administered questionnaire before PSG study, including 10 sleep-related symptoms and 10 physical illnesses. The symptoms and physical illnesses were chosen based on guidelines for indications for polysomnography, and symptoms surveyed in previous studies [18]. Symptoms included in the questionnaire were snoring, morning headache, drooling at night, nocturia, unrefreshing sleep, memory problems, reflux, dry mouth, and bruxism. Epworth Sleepiness Scale (ESS) was used to evaluate daytime sleepiness, and a total score ≥ 11 was defined as having excessive daytime sleepiness. Physical illnesses included are hyperlipidemia, cerebrovascular accidents, myocardial infarction, allergic rhinitis, asthma, cor pulmonale, angina, hyperuricemia, diabetes mellitus, and hypertension. The patients were asked whether they have been diagnosed with these illnesses by a physician. This study was approved by the Institutional Review Board of China Medical University Hospital (CMUH103-REC2-082).

Polysomnography and CPAP titration study

Patients arrived at the sleep center before 2300 h, and the following parameters were measured: 6-channel electroencephalography; electrooculography; electrocardiography; nasal air pressure transducer; oronasal thermistor; thoracic and abdominal movements; electromyography with submental and shin leads; finger oxygen saturation (SpO_2); sound recordings; piezoelectric sensor for snore detection; and videotaping. Only patients who aged ≥ 18 years and had a total time in bed ≥ 6 h and a total sleep time ≥ 3.5 h in the PSG study were included (Fig. 1). Sleep staging and respiratory events coding were accomplished by certificated sleep technicians according to the 2007 AASM recommended criteria [19]. Obstructive apnea was defined as cessation of airflow through the nose with paradoxical chest and abdominal movements, and hypopnea was defined as a ≥ 30% reduction in nasal pressure with paradoxical chest and abdominal movements resulting in desaturation of at least 4% of SpO_2. AHI was calculated as the average number of apneas and hypopneas per hour. A total of 5209 patients completed diagnostic polysomnography and those who had OSA (AHI ≥ 5, $N = 3718$) were included in the following analysis.

Epiglottic and esophageal manometry with polysomnography (PSG) have been considered to be the standard way to quantify ArTH. However, only a few sleep laboratories have accessibility to these invasive procedures for clinical and research use. Edwards et al. have demonstrated that an index derived from PSG parameters, i.e., AHI, nadir oxygen saturation, and fraction of hypopnea, had a sensitivity of 80.4% and a specificity of 88.0% for predicting low ArTH [20]. Low ArTH can be identified through laboratory PSG or even portable PSG studies. The participants were categorized into low-ArTH groups if they had a score of ≥ 2 on the following 3-point scale: (1)

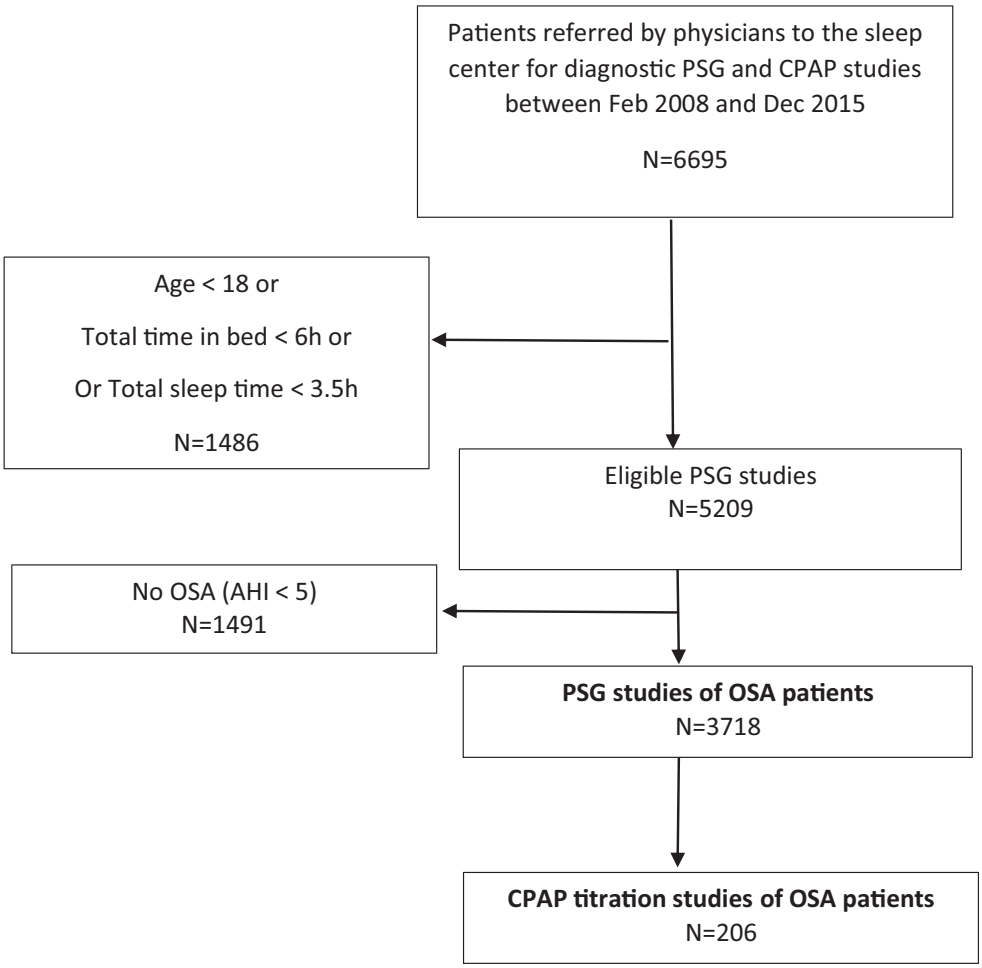

Fig. 1 Flowchart of diagnostic PSG and CPAP titration study selection (PSG, polysomnography; CPAP, continuous positive airway pressure)

AHI < 30 events/h sleep, (2) nadir SpO_2 > 82.5%, and (3) fraction of hypopneas > 58.3% [20]. Otherwise, they were categorized as having high ArTH.

Among the 3718 patients who had PSG studies, we identified 206 patients who also had CPAP titration study during the study period. CPAP pressures were titrated by sleep technicians until the AHI was less than 5 during the rapid eye movement (REM) stage or the patient was sleeping in a supine position. All sleep parameters were measured the same as in PSG studies.

Statistical analysis

We compared the demographic characteristics, sleep structure parameters from PSG studies, and clinical characteristics between low- and high-ArTH groups. The differences were tested by Student *t* tests for continuous variables and chi-square tests for categorical variables. The significance level was set at Bonferroni-adjusted *p* values (0.05/36 = 0.0014). Logistic regression models were used to examine the odds ratio (OR) of low ArTH (reference as high ArTH) for physical illnesses and clinical symptoms, adjusted for age, gender, body mass index, and AHI. In fully adjusted models, we further included all 10 clinical symptoms and all 10 physical illnesses in the models, respectively. To examine the sleep structure changes between PSG and CPAP titration study and between low- and high-ArTH patients, repeated measures analysis of variance (ANOVA) as a 2 × 2 mixed model was used. ArTH was treated as the between-subject factor and CPAP titration was treated as the within-subject factor. *p* values for the ArTH group effect, CPAP titration effect, and interaction effect were reported. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for all of the analyses.

Results

Overall, the percentages of mild (5 ≤ AHI < 15), moderate (15 ≤ AHI < 30), and severe (AHI ≥ 30) OSA in our sample were 36.3%, 25.9%, and 37.9%, respectively. As shown in Table 1, 50.2% of the OSA patients were categorized as having a low ArTH. Compared with the high-ArTH group, the low-ArTH group were less obese and had a significantly higher percentage of women. Compared with high-ArTH

Table 1 Baseline demographic characteristics, polysomnographic parameters, and clinical symptoms and history of illness of low and high arousal threshold OSA patients (N = 3718)

	Low arousal threshold (N = 1868) Mean ± SD/N(%)	High arousal threshold (N = 1850) Mean ± SD/N(%)	p	Standardized mean difference
Individual characteristics				
Age	44.79 ± 15.91	46.61 ± 13.92	0.143	0.134
Gender (female)	447 (23.93)	234 (12.65)	< 0.001	–
Body mass index (kg/m^2)	26.75 ± 4.66	28.40 ± 5.18	< 0.001	0.347
PSG sleep parameters				
Apnea-hypopnea index (h^{-1})	13.96 ± 7.82	46.02 ± 24.69	< 0.001	1.318
Nadir SpO_2 (%)	83.47 ± 6.50	72.25 ± 10.13	< 0.001	− 1.134
Time with SpO_2 < 90% (%)	4.14 ± 10.00	20.75 ± 21.57	< 0.001	0.886
Total arousal index (h^{-1})	25.08 ± 14.26	41.44 ± 21.82	< 0.001	0.812
Sleep onset latency (minutes)	11.64 ± 11.42	10.52 ± 10.93	0.003	− 0.101
Total sleep time (h)	5.40 ± 0.81	5.27 ± 0.78	< 0.001	− 0.073
Sleep efficiency (%)	81.53 ± 11.02	80.32 ± 10.99	0.006	− 0.110
Wake after sleep onset (minutes)	60.04 ± 40.33	65.73 ± 40.87	< 0.001	0.140
Stage changes	155.43 ± 56.85	198.43 ± 84.18	< 0.001	0.574
Stage 1 sleep (%)	24.13 ± 14.29	40.16 ± 21.43	< 0.001	0.808
Stage 2 sleep (%)	53.16 ± 14.09	40.03 ± 19.07	< 0.001	− 0.725
Slow-wave sleep (%)	2.67 ± 7.03	1.06 ± 4.27	< 0.001	− 0.491
Rapid eye movement sleep (%)	20.04 ± 7.04	18.75 ± 7.50	< 0.001	− 0.176
Clinical symptoms				
Excessive daytime sleepiness	701 (37.51)	801 (43.30)	< 0.001	
Snore	1743 (93.46)	1790 (96.86)	< 0.001	
Morning headache	592 (31.83)	476 (25.83)	< 0.001	
Drooling at night	969 (51.96)	1094 (59.26)	< 0.001	
Nocturia	840 (45.09)	864 (46.78)	0.302	
Unrefreshing sleep	1413 (75.76)	1390 (75.26)	0.720	
Memory problems	1058 (56.91)	1009 (54.75)	0.185	
Dry mouth	1403 (75.27)	1430 (77.51)	0.109	
Reflux	828 (44.42)	844 (45.84)	0.384	
Bruxism	428 (23.02)	316 (17.16)	< 0.001	
Physical illnesses				
Hyperlipidemia	525 (28.18)	581 (31.58)	0.024	
Cerebrovascular accidents	35 (1.88)	52 (2.82)	0.058	
Myocardial infarction	72 (3.87)	56 (3.04)	0.167	
Allergic rhinitis	805 (43.23)	757 (41.01)	0.170	
Asthma	211 (11.33)	177 (9.6)	0.087	
Cor pulmonale	26 (1.40)	32 (1.74)	0.410	
Angina	243 (13.04)	215 (11.69)	0.212	
Hyperuricemia	282 (15.15)	351 (19.05)	0.002	
Diabetes mellitus	192 (10.31)	216 (11.70)	0.175	
Hypertension	687 (36.90)	821 (44.74)	< 0.001	

patients, the baseline PSG study parameters in low ArTH patients were slightly lower in wake after sleep onset time, and higher in the percentage of slow-wave sleep and REM sleep ($p < 0.0014$). As to clinical symptoms, low-ArTH patients reported more morning headache and bruxism, while high-ArTH patients reported more excessive daytime sleepiness, snoring, and drooling at night ($p < 0.0014$). Hypertension was significantly more often reported by high-ArTH patients ($p < 0.0014$).

After adjusting for individual characteristics and AHI (Table 2), no physical illness was significantly associated with low ArTH. Compared with high ArTH, low ArTH was associated with morning headache (adjusted OR = 1.27, 95% CI = 1.04–1.55), nocturia (adjusted OR = 1.43, 95% CI = 1.19–1.72), and bruxism (adjusted OR = 1.29, 95% CI = 1.04–1.61). In fully adjusted models, only nocturia and bruxism were significantly associated with low ArTH. We further stratified the participants into mild/moderate OSA and severe OSA groups (supplementary Table S1). Nocturia and bruxism were significantly associated with low ArTH in mild/moderate OSA group but not in the severe OSA group. We also stratified the participants by sex, and we observed that nocturia and bruxism were associated with low ArTH only in women (supplementary Table S2). In addition, excessive daytime sleepiness and morning headache were associated with low ArTH in men and women, respectively. Gastrointestinal reflux and unrefreshing sleep were negatively associated with low ArTH in women. In terms of physical illnesses, asthma was associated with low ArTH, but cor pulmonale was negatively associated with low ArTH in women.

Table 2 Odds ratio and 95% confidence interval of low arousal threshold for physical illnesses and clinical symptoms, compared with high arousal threshold ($N = 3718$)

	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Physical illnesses		
Hyperlipidemia	1.01 (0.83, 1.23)	0.95 (0.75, 1.19)
Cerebrovascular accidents	0.70 (0.39, 1.24)	0.74 (0.39, 1.40)
Myocardial infarction	1.44 (0.87, 2.38)	1.52 (0.86, 2.71)
Allergic rhinitis	0.94 (0.79, 1.12)	0.88 (0.72, 1.07)
Asthma	1.30 (0.97, 1.74)	1.35 (0.95, 1.91)
Cor pulmonale	0.97 (0.47, 1.99)	0.77 (0.33, 1.77)
Angina	1.24 (0.94, 1.62)	1.21 (0.89, 1.65)
Hyperuricemia	1.02 (0.81, 1.30)	1.04 (0.78, 1.38)
Diabetes mellitus	1.09 (0.81, 1.47)	1.11 (0.78, 1.58)
Hypertension	1.04 (0.86, 1.26)	1.05 (0.84, 1.31)
Clinical symptoms		
Excessive daytime sleepiness	1.08 (0.93, 1.26)	1.21 (0.97, 1.49)
Snore	0.77 (0.51, 1.18)	0.72 (0.45, 1.13)
Morning headache	*1.27 (1.04, 1.55)*	1.19 (0.95, 1.50)
Drooling	1.00 (0.83, 1.20)	0.91 (0.74, 1.12)
Nocturia	*1.43 (1.19, 1.72)*	*1.34 (1.08, 1.65)*
Unrefreshing sleep	1.07 (0.87, 1.32)	0.92 (0.71, 1.18)
Memory problems	1.02 (0.86, 1.22)	0.90 (0.73, 1.11)
Dry mouth	1.10 (0.89, 1.34)	1.06 (0.84, 1.35)
Reflux	1.11 (0.93, 1.33)	0.99 (0.80, 1.21)
Bruxism	*1.29 (1.04, 1.61)*	*1.37 (1.07, 1.76)*

Model 1 was adjusted for age, sex, body mass index, and apnea-hypopnea index. Model 2 was further adjusted with all physical illnesses and all clinical symptoms in two respective models

Significant results ($p < 0.05$) were shown in italics

Among the 3718 patients, 2.9% patients with low ArTH and 8.2% patients with high ArTH received CPAP titration studies. Compared with those who had not received CPAP titration studies, those who had received CPAP titration studies were older and had a higher BMI and AHI, and a higher percentage of men and high ArTH (supplementary Table S3). Among the 206 patients who had CPAP titration studies, a significant effect of CPAP treatment on sleep structures was observed (Table 3). AHI, total arousal index, total sleep time, sleep efficiency, wake after sleep onset, and stage changes significantly improved, and the percentage of stage 1 sleep decreased and slow-wave sleep and REM sleep increased during CPAP titration studies compared with diagnostic PSG studies. Among these parameters, a significant interaction effect was observed for AHI, suggesting that the high-ArTH group had a larger extent of improvement with CPAP than the low-ArTH group. Otherwise, no significant interaction effects were observed for total sleep time, sleep efficiency, stage changes, and percentage of REM sleep, indicating that both groups had significant improvements in their sleep structure. We further stratified the 206 participants into obese (BMI ≥ 30) and non-obese (BMI < 30) groups (supplementary Table S4). The significance of CPAP effect was similar between the two groups.

Discussion

This study identified low-ArTH OSA patients in a large Asian clinical sample. Half of the patients with OSA had low ArTH in our sample. Patients with low ArTH were less obese and had better sleep structure and less history of hypertension. Low ArTH was associated with bruxism and nocturia after adjusting for age, sex, body mass index, and AHI, but not with physical illnesses. CPAP titration improved sleep structure in both low- and high-ArTH patients.

In several studies of non-Asian patients with OSA, 30 to 60% of patients had low ArTH [5, 8, 17, 20, 21]. In a study comparing Asian and Caucasian patients with OSA, 43.8% and 63.7% patients were classified as having low ArTH, respectively [22]. It is possible that our participants had less severe OSA than participants in previous studies [8, 21, 22], so our prevalence of low ArTH was higher. Given that low-

Table 3 Sleep structure of PSG studies and CPAP titration studies in low and high arousal threshold groups ($N = 206$). *PSG*, polysomnography; *CPAP*, continuous positive airway pressure

	Low arousal threshold ($N = 55$)		High arousal threshold ($N = 151$)		Group effect	CPAP effect	Interaction effect
	(Mean ± SD)		(Mean ± SD)				
	PSG	CPAP	PSG	CPAP	*p*	*p*	*p*
CPAP level (cmH_2O)	–	5.95 ± 1.37	–	7.86 ± 2.59			
AHI (h^{-1})	21.15 ± 9.29	5.33 ± 8.74	54.82 ± 22.32	11.06 ± 10.40	< 0.001	< 0.001	0.019
Nadir SpO_2 (%)	81.73 ± 6.81	86.80 ± 5.37	71.21 ± 8.73	82.56 ± 7.29	< 0.001	0.554	0.788
Total arousal index (h^{-1})	35.41 ± 17.98	29.91 ± 20.81	49.64 ± 22.39	28.52 ± 16.46	< 0.001	< 0.001	0.266
Sleep onset latency (mins)	9.75 ± 8.47	8.78 ± 10.93	11.18 ± 12.98	8.85 ± 12.54	0.702	0.019	0.111
Total sleep time (h)	5.31 ± 0.95	5.47 ± 1.24	5.27 ± 0.83	5.63 ± 1.11	0.569	< 0.001	0.851
Sleep efficiency (%)	78.75 ± 11.97	80.19 ± 12.83	78.91 ± 11.21	83.52 ± 11.71	0.584	< 0.001	0.675
Wake after sleep onset (mins)	75.57 ± 47.84	72.45 ± 49.08	73.24 ± 41.66	57.62 ± 43.70	0.501	< 0.001	0.852
Stage changes	173.35 ± 73.61	144.98 ± 61.72	205.58 ± 81.90	150.13 ± 64.50	< 0.001	< 0.001	0.968
Stage 1 sleep (%)	33.25 ± 22.42	28.21 ± 20.45	44.58 ± 21.88	24.66 ± 14.99	< 0.001	< 0.001	0.700
Stage 2 sleep (%)	50.06 ± 19.53	51.65 ± 18.22	37.73 ± 19.69	52.39 ± 14.78	< 0.001	0.193	0.520
Slow-wave sleep (%)	0.17 ± 0.56	0.25 ± 0.82	0.40 ± 1.95	0.54 ± 2.07	0.243	< 0.001	0.408
REM sleep (%)	16.62 ± 7.11	19.90 ± 7.85	17.54 ± 7.80	22.40 ± 8.06	0.724	< 0.001	0.489

p values for group effect (low and high arousal threshold), CPAP effect, and interaction between group and CPAP effect using repeated measures ANOVA were shown

ArTH patients were more prevalent among non-obese patients with OSA [5], this finding may also be explained by that non-obese patients with OSA are more common in Asia [5, 6]. Nevertheless, the cutoff points for obesity were inconsistent in these studies, and obesity definitions have been recommended to be different between ethnicity groups [23]. In addition, craniofacial compromise plays a greater role in OSA severity in Asian patients than in Caucasian patients [24], but a higher prevalence of low ArTH was observed in patients with mild compared to severe craniofacial compromise only in Caucasian but not Asian patients [22]. Therefore, whether the different prevalence of low ArTH in Asian and Caucasian patients with OSA is attributable to differences in craniofacial compromise is not clear. Furthermore, recent studies have shown that compared with other ethnicity groups, Asian patients with OSA had fewer symptoms of sleep disturbance or daytime sleepiness, but had more upper airway symptoms [9]. However, we did not find associations of low ArTH with sleep symptoms (unrefreshing sleep and excessive daytime sleepiness) or snoring, but low ArTH was associated with nocturia and bruxism, which have been less studied.

The association between nocturia and low ArTH is bidirectional. Low-ArTH patients may be easily wakened, and hence complained of nocturia or frequent nocturia leading to frequent arousal and loss of slow-wave sleep [25]. Nocturia has been found to be associated with oxygen desaturation during sleep and OSA severity [26]. The mechanism underlying the co-occurrence of sleep apnea and nocturia was suggested to be an elevated atrial natriuretic peptide secondary to negative intrathoracic pressure [27], and apnea-induced alpha sympathetic nervous activity [28]. In low-ArTH patients, the negative intrathoracic pressure before arousal reaches a lesser extent than that in high-ArTH patients [2]; therefore, the atrial natriuretic peptide should be lower among low-ArTH patients. Furthermore, it has been observed that the increase in sympathetic activation is more due to arousal than to hypoxia [29]. Therefore, the mechanism of elevated sympathetic tone among low-ArTH patients for nocturia is more plausible. Low ArTH has been observed to be associated with insomnia, post-traumatic stress disorder symptoms, and depression [30, 31]. The elevated sympathetic tone may explain the relationship between these clinical symptoms and cortical hyperarousal in OSA patients with low ArTH.

Bruxism occurred during or following arousal related with apnea events [32], and the frequency of sleep bruxism is associated with the severity of OSA. Bruxism increases before REM sleep [33], suggesting a mechanism related to stage changes. Another report showed that apnea events are more related to oromotor activities other than sleep bruxism [34]. Sleep bruxism has been suggested to be either a protective mechanism for apnea which is responsible for airway opening, or merely a result of arousal. OSA patients with low ArTH often arouse before adequate recruitment of upper airway muscles [2]; hence, in this case, the arousal probably occurs with bruxism rather than after bruxism. Based on our findings,

the plausible explanation is that frequent arousals in low-ArTH patients lead to more bruxism complaints, compared with high-ArTH patients with similar OSA severity. This observation is supported by the previous finding that low ArTH is associated with comorbid insomnia [30].

Women were more prevalent in the low-ArTH group in this study than in the high-ArTH group. Low ArTH was associated with comorbid insomnia in a recent study of Asian OSA patients [30], whereas female patients had a higher presentation of disturbed sleep symptoms than men [35]. Our findings were consistent with these observations and suggested that low ArTH may be a prevalent phenotype among female OSA patients in Asia. The clinical symptoms related with low ArTH were different between sexes in this study. A previous study observed that, among OSA patients, morning headache, reflux, and nocturia were more frequently reported by women than men [36]. Morning headache was more commonly found in patients with insomnia and psychological distress, and women were observed to have these symptoms more frequently. In contrast, excessive daytime sleepiness was associated with low ArTH only in men in our study. One study suggested that male OSA patients had an increased risk of having daytime sleepiness compared to female patients, and the physiological mechanisms are probably different [37]. Our findings suggest that low ArTH may be a mechanism causing daytime sleepiness in men but not women. However, our findings were inconsistent with those from previous studies in the associations between reflux and unrefreshing sleep and low ArTH [36]. More studies are needed to confirm the associations. Furthermore, asthma was significantly associated with low ArTH only in women in this study. One study has reported that asthma was twice as prevalent in female OSA patients compared to male patients [38]. Our findings further suggest that, in asthmatic female patients, low ArTH may contribute to their OSA pathophysiology. In addition, there was a higher percentage of women in patients who did not receive subsequent CPAP titration in our study. Treatment choices designed for the low-ArTH phenotype in women OSA patients need to be further studied and developed.

The finding that arousal threshold was not associated with physical illnesses after adjusting for OSA severity is consistent with findings from a Caucasian population study [8]. AHI has been observed to be a predictor for cardiovascular-related disease among Asian OSA patients [6]. Our results suggest that low ArTH may be associated with physical illnesses only when it significantly increases AHI. Nevertheless, longitudinal studies to examine the effect of elevating ArTH on long-term physical illnesses are scarce but are needed to support such intervention [16, 17]. Furthermore, bruxism and nocturia were not associated with low ArTH in severe OSA patients in this study. Given that the prevalence of low ArTH is low among Asian severe OSA patients [22], we suggest that low ArTH plays a minor role in the pathology and related clinical symptoms than other factors such as craniofacial compromise among Asian severe OSA patients.

Although CPAP adherence was worse among low-ArTH patients [5, 8], we observed that CPAP titration did not deteriorate but instead improved sleep structures among low-ArTH patients. A rebound of 40% slow-wave sleep and 20% REM during first CPAP use among OSA patients was expected [39]. In our study, REM increased by 19.7% and 27.7% while slow-wave sleep increased by 47.1% and 35.0% in low- and high-ArTH groups, respectively. These results suggest that even in low-ArTH patients, CPAP therapy should not be avoided due to the fear of worsened sleep. The lower percentage of low ArTH patients who received CPAP titration than high ArTH patients may reflect a lower severity of OSA, or a lower motivation for CPAP therapy. Nevertheless, CPAP study results in this study should be interpreted with caution because of the small number of subsequent CPAP titration studies. Patients who were younger, with a lower severity of OSA and low ArTH, were less likely to receive CPAP therapy in our study. Therefore, the long-term effect of CPAP therapy on sleep quality, especially in less severe OSA patients, needs further study.

This study has several limitations. First, the ArTH scoring has only been validated in a Caucasian population, although it has been applied to a study among Asian OSA patients [22]. Furthermore, hypopnea was defined by the American Association of Sleep Medicine (AASM) recommended criteria but by the Chicago criteria in previous studies [20]. Because the hypopnea index derived from the AASM criteria is lower than that derived from the Chicago criteria, the hypopnea fraction and AHI are probably underestimated in this study compared to previous studies. Nonetheless, compared with invasive procedures, the estimation with PSG parameter enabled us to study large clinical samples. Second, a large proportion of OSA patients in our sample did not receive CPAP titration study. In our sleep center, some patients directly look for CPAP producers without titration study, and some patients sought other treatments. CPAP therapy acceptance rate was low in Taiwan, especially in those with low severity [22]. Therefore, those who had received CPAP titration study may represent patients who had higher motivations and preparedness for CPAP therapy and thus their sleep was less disturbed during titration. Future studies are needed to examine the long-term effect of CPAP treatment on sleep quality among low-ArTH patients. Third, a previous study observed that use of antidepressants and antihypertensive medications was significantly associated with low ArTH [8]. However, we did not gather the information of medication use which may interfere with ArTH. Since headache, nocturia, and bruxism are common side effects of these medications, the confounding effect of medication use cannot be ruled out. Moreover, the physical illnesses were self-reported and therefore were

subject to bias. Finally, the study results are generalizable to the Taiwanese population referred by clinicians to a sleep center for evaluation.

In conclusion, low ArTH was prevalent in this large OSA patient sample. Adjusting for obesity and OSA severity, low ArTH was not associated with physical illnesses but was associated with nocturia and bruxism. The causal relationship between these clinical symptoms and ArTH needs to be studied in the future. Low-ArTH patients had better sleep structure than high-ArTH patients, and they had improved sleep structure during CPAP titration studies compared with diagnostic PSG studies. Both high- and low-ArTH patients benefited from a CPAP titration study for improved sleep structure. To develop individualized therapies for OSA patients with different phenotypes, the effect of CPAP therapy on arousal thresholds in OSA patients, specifically respiratory event related and spontaneous arousals, needs to be examined in future studies.

Authors' contributions Wan-Ju Cheng and Liang-Wen Hang contributed to the conception and design of the study, the analysis of data, and interpretation of results. Shun-Sen Huang and Liang-Wen Hang contributed to data collection and management. Wan-Ju Cheng drafted the paper and Liang-Wen Hang did major revisions. All authors read and approved the final manuscript.

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Data availability The de-identified data is available on request from the correspondence author.

Compliance with ethical standards

Disclaimer The funder had no role in the study design, the collection, analysis and interpretation of the data, the writing of the report, or the decision to submit the paper for publication.

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

Ethics approval This study involved human subjects and was approved by the Institutional Review Board of China Medical University Hospital (CMUH103-REC2-082).

Consent to participate Clinical data were reviewed retrospectively and informed consent was waived.

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