Low Arousal Threshold: A potential bridge between OSA and Periodic Limb Movements of Sleep

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Abstract

Objective: Periodic Limb Movements of Sleep (PLMS) is a poorly understood comorbidity with close association to Obstructive Sleep Apnea (OSA). The mechanistic link between the two is unclear. Recent studies on the latter have uncovered low respiratory arousal threshold as an important non-anatomical cause of the disorder. This study sought to investigate whether periodic limb movements are associated with the low respiratory arousal threshold (ArTH) in OSA.

Methods: Retrospective data on 720 OSA patients (mean age = 47.0) who underwent Polysomnography (PSG) were collected. Patients were divided into the OSA-PLMS group (n=116) and the OSA-only group (n=604). Multiple logistic regression analysis was used to examine the correlation between PLMS and its potential risk factors including clinical variables, polysomnographic parameters as well as low ArTH. The resulting model was validated in the external MrOS database.

Results: The patients in the OSA-PLMS group tend to be older, with a higher prevalence of hypertension, diabetes, and stroke. Significant predictors of PLMS included age, diabetes, proportion of Stage N1 Sleep, average SaO□, and low respiratory arousal threshold (OR=5.51 (3.35-9.05), p<0.001). When validated against the MrOS database, low ArTH remained a significant predictor of PLMS with an odds ratio of 1.46 (1.18-1.81, p < 0.001).

Interpretation: This is the first study that demonstrated a strong correlation between PLMS and low respiratory arousal threshold. This suggests a possible mechanistic link between the physical manifestations of PLMS and the non-anatomical low arousal threshold phenotype in OSA.

Statement Of Significance

This study examined the hitherto poorly understood association between OSA and PLMS and demonstrated for the first time a strong correlation between PLMS and a low respiratory threshold (a non-anatomical cause of OSA). This potentially poses the respiratory arousal threshold as the missing link between the respiratory phenomenon of OSA and the neurologically driven disorder of PLMS.

Clinically, this provides insights into why OSA patients may be more susceptible to PLMS and identified the low respiratory arousal threshold as a possible new therapeutic target in this group of patients, who are especially vulnerable to an elevated risk of cardiovascular diseases. As such, we call for more attention to this group of OSA patients with PLMS.

Introduction

Periodic limb movement in sleep (PLMS) is characterized as periodic episodes of stereotyped limb movements that occur involuntarily and repetitively during nocturnal rest[1], though patients are usually unaware of such movements and the arousals induced[2]. Standard criteria define periodic limb movements as ≥ 15 leg movements per hour during sleep[1]. The incidence of PLMS increases with age and is associated with several predisposing medical conditions, including narcolepsy, Parkinson's disease, idiopathic REM sleep behavior disorder, and diabetes mellitus[3]. Though there appears to be no clear link between PLMS and excessive daytime sleepiness[4,5], PLMS has been reported to be associated with poorer sleep quality[6], arousals[7,8] and possibly sleep fragmentation[4] and increased risks of cardiovascular diseases[9]. PLM is also observed in 80% of patients with restless legs syndrome (RLS)[10] and 24–48% of patients with Obstructive Sleep Apnea (OSA) [11].

A large body of literature has demonstrated the close clinical association between Obstructive Sleep Apnea (OSA) and Periodic Limb Movements (PLM)[4–6,12]. Yet, up till now, the pathogenesis and etiology of PLM and the mechanism of its close association with OSA remain unclear. In many cases, PLMS is noted only as an accompanying incidental finding in PSG conducted for OSA[5,11]. One study has nevertheless shown that periodic limb movements in moderate to severe OSA patients worsens after CPAP treatment[13], and another demonstrated a reduced long-term adherence to CPAP treatment in OSA patients with PLMS[14]. This can be explained by the fact that CPAP only tackles the anatomical causes of OSA, i.e. the upper airway obstruction, while failing to address the other non-anatomical factors. Indeed, these non-anatomical factors of OSA have recently become another focus of much academic interest[15–18], identifying patients with distinct phenotypes including (1) ineffective upper-airway dilator muscles; (2) unstable ventilatory control, i.e. high loop gain; (3) low respiratory arousal. Given the PLM's propensity to lead to arousals[7,8], we hypothesized that such periodic limb movements may be associated with the low respiratory arousal phenotype seen in OSA. As such, we set out to examine retrospective data as a first step to explore the contributory factors leading to PLMS in OSA patients and the role of low arousal threshold.

Method

Participants

A retrospective cohort study was carried out with data from 793 OSA patients diagnosed at the Department of the Second Affiliated Hospital of Soochow University from January 2013 to July 2019. All patients were over 18 years old. Individuals taking medications or suffering from diseases that affect PLM such as restless legs, narcolepsy, multisystem atrophy, spinal cord injury, Parkinson's disease were also excluded. Individuals with insomnia were also excluded. Only PSG readings with effective monitoring time ≥ 8 hours were included for analysis. The participants in the study gave informed consent and the study protocol has been approved by the Research Ethics Committee of the Second Affiliated Hospital of Soochow University, Suzhou, China.

Polysomnography and sleep analysis

The participants underwent overnight, supervised, laboratory-based video polysomnography. The PSG recorded from 22:00 to 07:00 the next morning. Compumedics Grael multifunctional PSG monitoring system was used for all signal acquisition (Compumedics Company, Australia). All polysomnographic

recordings included six electroencephalogram (EEG) channels (F3/A2, F4/A1, C3/A2, C4/A1, O1/A2, O2/A1), bilateral electrooculograms (EOGs), submental and bilateral anterior tibialis electromyograms (EMGs), electrocardiograms (ECGs), the nasal and oronasal airflow (by using nasal pressure monitor and thermistor), arterial oxygen saturation (via finger pulse oximetry), chest and abdominal movements (via inductance plethysmography).

Sleep Stage Analysis and Scoring

Sleep stages and sleep-related respiratory analysis were scored manually by a registered technician according to the AASM scoring criteria[19]. The apnea-hypopnea index (AHI) was calculated as the mean number of apneas and hypopneas (with ≥ 3% desaturation or an arousal) per hour of sleep. The oxygen desaturation index was defined as the mean number of ≥ 3% desaturation events per hour of sleep[20]. Based on the scoring of sleep stages and respiratory analyses, limb movements were scored manually by a registered technician blind to the study. Limb Movements (LM) was defined as an 8-μV increase in the EMG voltage at the right and left anterior tibialis above the resting EMG voltage. Each LM event lasts 0.5 to 10 seconds. LM events during wakefulness or within 0.5 s before or after respiratory events were manually excluded. PLM was defined as a minimum of four consecutive LM events within a 5 to 90 seconds interval. The PLM Index (PLMI) was scored as the number of PLM per hour of sleep[19]. In the scoring of arousals, during non-rapid eye movement sleep (NREM), an EEG arousal was defined as "an abrupt shift in EEG frequency, which may include theta waves, alpha waves, and/or frequencies greater than 16 Hz, but not 'spindles' of 3 s or greater in duration". An arousal was scored during rapid eye movement (REM) sleep when the required EEG changes were accompanied by a concurrent increase in electromyography amplitude. Other measures include total sleep time (TST), proportions of each sleep stage, minimum arterial oxygen saturation (minSaO₂), average arterial oxygen saturation (avgSaO₂), percentage of total time at SaO₂ < 90% (TS90), sleep efficiency, sleep latency, REM latency and Arousal index.

Definitions of PLMS and Low Arousal Threshold

The newer 2005 AASM criteria for Periodic Limb Movement Disorder (PLMD) adopted a cut-off of ≥ 15 leg movements per hour during sleep, using which the OSA patients were grouped into the OSA-only group and OSA-PLMS group. As the older pre-2005 cut-off of ≥ 5 PLM per hour is still used in some studies, we have included a parallel set of results in the supplement materials using ≥ 5 as cut-off (with very similar results, see supplemental material 1). For the evaluation of the arousal threshold, we adopted a clinical screening tool developed by Edwards et al.[21]. In their study, epiglottic catheter data were collected from 146 participants who underwent overnight polysomnography to physically measure their ArTH (nadir epiglottic pressure before arousal). Comparing against this gold standard of epiglottic ArTH measurement, a clinical screening tool was developed to include three criteria: (1) AHI < 30 / h; (2) minSaO₂ > 82.5% and (3) Fraction of hypopneas ($F_{Hypopnea}$) > 58.3% of the total number of respiratory events, allocating a score of one to each criterion. A total score of two or more categorizes the patient as having a low respiratory arousal threshold (defined as an epiglottic pressure on the breath before arousal greater than − 15 cmH_2O in the paper by Edwards et al.). This tool achieved a sensitivity and a specificity of 80.4% and 88.0%, respectively.

Statistical analysis

Statistical analyses were conducted using SPSS 22.0 statistical software[22]. Firstly, we tested the Gaussian distribution of values using the Kolmogorov–Smirnov test. Non-normally distributed data are represented by the median interquartile range (IQR). The categorical variables were compared using the chi-square test, continuous correction chi-square test, or Fisher exact test. Mann-Whitney rank sum test was used for data with non-normal distribution or variable variances. A probability value of $p < 0.05$ was considered statistically significant. A binary logistic regression analysis was used to identify potential predictors of PLMS from a matrix of clinical data and PSG parameters. All independent variables with $p < 0.2$ in the univariate analysis were included in a final multivariate analysis to obtain a list of independent predictors of PLMS risks.

Validation of the relationship between PLMS and ArTH using the MrOS database

The relationship between low arousal thresholds and PLMS found in the sample was then validated in the MrOS database. The details of the MrOS study have been published elsewhere[23–26]. Among the study population, 3135 community-dwelling men aged 65 years or older were chosen to undergo complete sleep monitoring. We used the same inclusion criteria as in our study and finally included 2232 subjects with complete PSG data in the validation analysis, where the average age was 76.4 years. Four stepwise binary logistic models with increasing numbers of predictors were created, with the final model being the most comprehensive which included all the predictors used in the data analyses in our cohort.

Results

Among the data of 793 OSA patients initially sampled, we excluded 43 patients with conditions and/or drug therapies known or suspected to influence limb movements, 20 patients with effective PSG study time < 8 hours, and 10 further patients with significant artifacts in PSG recordings. The final study population consisted of 720 patients (see Fig. 1), in which there were 107 females, 613 males, with a mean age of 47.0 years.

Using PLMI ≥ 15 as criteria, 604 patients were classified as OSA-only and 116 as OSA with PLMS. Patients in the OSA-PLMS group tend to be older (60.5 vs 42 years in OSA-only, $p < 0.001$). In terms of complications, the patients in the OSA-PLMS group exhibited higher prevalence of hypertension (62/116 vs 195/604 in OSA-only, $p < 0.001$), diabetes (21/116 vs 27/604, $p < 0.001$), and stroke (22/116 vs 44/604, $p < 0.001$). (See Table 1)

Table 1
Subject characteristics in OSA-PLMS and OSA-only group

	OSA-PLMS	OSA-only	Z/χ^2	*p*
	(n = 116)	(n = 604)		
Age	60.5 (48.5–69)	42 (35–53)	-8.842	< 0.001**
Sex	98/116	515/604	0.0478	0.828
BMI	26.4 (24.2–28.7)	26.1 (24.2–28.1)	-1.013	0.311
ESS	9 (5–13)	8 (4–12)	-1.632	0.103
Hypertension	62/116	195/604	18.988	< 0.001**
Diabetes	21/116	27/604	29.068	< 0.001**
Arrhythmia	11/116	44/604	0.666	0.414
Stroke	22/116	44/604	15.946	< 0.001**
CAD	2/116	8/604	0.112	1.00
Asthma	1/116	8/604	0.170	1.00
COPD	1/116	5/604	0.001	1.00
GERD	1/116	4/604	0.056	1.00

Abbreviation: BMI, body mass index; ESS, Epworth Sleepiness Scale; CAD: coronary artery disease; COPD, chronic obstructive pulmonary disease; GERD, Gastroesophageal reflux disease; Values were expressed as median (interquartile range in brackets); *p ≤ 0.05 **p ≤ 0.01

Sleep parameters

Patients in the OSA-PLMS group exhibited lower sleep efficiency (81.3% vs 86.4% in OSA-only, $p < 0.001$), higher proportion of Stage N1 sleep (20.2% vs 13.1%, $p < 0.001$), lower proportion of Stage N2 sleep (44.8% vs 51.6%, $p < 0.001$), higher minimum pulse oxygen (83.5% vs 81%, $p = 0.045$), and lower mean pulse oxygen (95% (94%-96%) vs 95% (95%-96%), $p = 0.004$). There were no significant cross-group differences in TST, sleep latency, latency to REM, proportion of Stage N3 sleep, proportion of REM sleep, ODI, AHI between the two groups. (See Table 2) The proportion of patients with a low arousal threshold was significantly higher in the OSA-PLMS group than in the OSA-only group (46.6% vs 19.7%, $p < 0.001$). Among the three variables used to determine arousal threshold, the OSA-PLMS group contained a significant higher proportion of patients meeting the criteria of MinSaO$_2$ > 82.5% (53.4% vs 34.9%, $p < 0.001$) and the criteria of $F_{Hypopnea}$ > 58.3% (25% vs 11.3%, $p < 0.001$) than that of the OSA-only group. (See Table 3)

Table 2
Polysomnography parameters in the OSA-PLMS and OSA-only group

	OSA-PLMS	OSA-only	Z	*p*
	(n = 116)	(n = 604)		
TST, min	416.5 (333.4–470.4)	428 (369.6–471)	-1.437	0.151
Sleep Efficiency %	81.3 (69.63–88.33)	86.4 (76.5–92.7)	-4.398	< 0.001**
Sleep Latency, min	4.5 (1–15.1)	4.5 (1.5–11)	-0.350	0.727
REM Latency, min	97.5 (60.6–160.6)	92.5 (69–138)	-0.527	0.598
NREM I sleep %	20.2 (12.7–32.8)	13.1 (8.3–19.4)	-6.143	< 0.001**
NREM II sleep %	44.8 (35.7–53.4)	51.6(45.2–58.1)	-5.081	< 0.001**
NREM III sleep %	14.0 (6.8–20.3)	14.7 (10.0–19.5)	-1.545	0.122
REM sleep %	18.0 (12.7–23.0)	18.8 (14.6–22.7)	-1.1	0.271
ODI	17.4 (6.6–35.7)	19.4 (12.7–26.6)	-0.869	0.385
AHI	24.1 (10.8–42.9)	24.5 (14.5–33.1)	-0.726	0.468
minSaO₂	83.5% (74% – 87%)	81% (77% – 84%)	-2.004	0.045*
avgSaO₂	95% (94% – 96%)	95% (95% – 96%)	-2.912	0.004**
TS90	2.3% (0.2% – 12.0%)	2.8% (1.2% – 5.1%)	-0.438	0.661
Arousal Index	17.8 (9.3–30.4)	15.7 (9.8–24.0)	-1.898	0.058

Abbreviations: TST, total sleep time; REM, rapid eye movement; NREM, non-rapid eye movement; ODI, oxygen desaturation index; AHI, apnea-hypopnea index; avgSaO₂, mean arterial oxygen saturation; minSaO₂, lowest arterial oxygen saturation; TS90, percentage of total time at oxygen saturation level < 90%. Values were expressed as median (interquartile range in brackets). *p ≤ 0.05 **p ≤ 0.01

Table 3
Arousal Threshold and its predictors in OSA patients in the OSA-PLMS and OSA-only groups.

	OSA-PLMS	OSA-only	χ^2	*p*
	(N = 116)	(N = 604)		
Low ArTH	54 (46.6%)	119 (19.7%)	58.89	< 0.001**
AHI < 30	69 (59.5%)	364 (60.3%)	0.025	0.875
minSaO₂ > 82.5%	62 (53.4%)	211 (34.9%)	14.17	< 0.001**
$F_{Hypopnea}$ > 58.3%	29 (25%)	68 (11.3%)	15.763	< 0.001**

Abbreviations: OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; minSaO₂, lowest arterial oxygen saturation; ArTH, arousal threshold; $F_{Hypopnea}$, Fraction of hypopnea in all respiratory events; *p ≤ 0.05 **p ≤ 0.01

Multivariate Logistic Regression

In the initial univariate analysis of 720 patients, we found that low arousal thresholds were associated with PLMS (p < 0.001). Since the lowest pulse oxygen and $F_{Hypopnea}$ were implicitly included in the calculation of low ArTH, these two items were excluded in the multivariate regression analysis. The results of the multivariate regression showed that age, diabetes, proportion of Stage N1 sleep, mean pulse oxygen, and low arousal threshold (OR = 5.51, 3.35–9.05) were independent predictors of PLMS. (See Table 4)

Table 4
Regression analyses of factors associated with PLMS among OSA participants

	Univariate analysis			Multivariate analysis		
	β	p	OR (95% CI)	β	p	OR (95% CI)
Age	0.071	< 0.001	1.073 (1.056–1.091)	0.051	< 0.001	1.052 (1.032–1.072)
Hypertension	0.879	< 0.001	2.408 (1.610–3.602)	0.092	0.721	1.096 (0.661–1.818)
Diabetes	1.553	< 0.001	4.724 (2.566–8.696)	0.944	0.016*	2.570 (1.189–5.554)
Stroke	1.091	< 0.001	2.979 (1.708–5.196)	0.070	0.844	1.073 (0.534–2.156)
SleepEff	-0.028	< 0.001	0.972 (0.961–0.985)	0.012	0.164	1.012 (0.995–1.030)
N1P	0.053	< 0.001	1.054 (1.038–1.071)	0.036	0.002**	1.037 (1.014–1.061)
N2P	-0.039	< 0.001	0.962 (0.946–0.978)	-0.001	0.956	0.999 (0.979–1.020)
AvgSaO₂	-0.731	< 0.001	0.690 (0.598–0.796	-0.374	< 0.001	0.688 (0.587–0.806)
MinSaO₂	-0.009	0.451	0.991 (0.969–1.014)	Not included		
Low ArTH	1.543	< 0.001	4.679 (3.086–7.096)	1.706	< 0.001	5.509 (3.352–9.053)

Abbreviations: SleepEff, sleep efficiency; N1P, proportion of NREM-1 sleep; N2P, proportion of NREM-2 sleep; avgSaO₂, mean arterial oxygen saturation; minSaO₂, lowest arterial oxygen saturation; ArTH, arousal threshold. *p ≤ 0.05 **p ≤ 0.01

Validation using MrOS Dataset

To validate the relationship between low arousal threshold (ArTH) and PLMS found in this study, we applied the multivariate logistic model to the MrOS dataset. Four logistic regression models were used with each adding a set of independent variables. Adjusting for age and BMI, Model 1 showed that men with low ArTH had an increased risk of PLMS, with OR = 1.27 (1.05–1.54). Model 2 showed an increased OR of 1.52 (1.24–1.87), after correcting for the proportion of Stage N1, N2, and N3 sleep and sleep efficiency based on Model 1. Model 3 corrected for AvgSaO₂ and TS90 on the basis of Model 2, and the Odds Ratio of low ArTH remained at 1.45 (1.17–1.80). Model 4 corrected for concurrent hypertension, diabetes mellitus, atrial fibrillation, stroke based on Model 3. This final model showed that PLMS was predicted by older age, higher arousal index (both $p < 0.001$), lower proportion of Stage N3 Sleep ($p = 0.033$), history of asthma (OR = 1.42, $p = 0.037$) and low ArTH (OR = 1.46 (1.18–1.81), $p < 0.001$) (See Table 5).

Table 5
Risk of PLMS by arousal threshold in the MrOS Dataset

	High ArTH	Low ArTH	*p*
Model 1: Age + BMI	Ref	1.27 (1.05–1.54)	0.016*
Model 2: Model 1 + SleepEff + N1P + N2P + N3P + Arousal Index	Ref	1.52 (1.24–1.87)	0.001**
Model 3: Model 2 + avgSaO₂ + TS90	Ref	1.45 (1.17–1.80)	0.001**
Model 4: Model 3 + HTN + Diabetes + Arrhythmia + Asthma + Stroke	Ref	1.46 (1.18–1.81)	0.001**

Abbreviations: Ref, reference; ArTH, arousal threshold; SleepEff, sleep efficiency; N1P, proportion of NREM-1 sleep; N2P, proportion of NREM-2 sleep; N3P, proportion of NREM-3 sleep; avgSaO₂, average arterial oxygen saturation; *p ≤ 0.05 **p ≤ 0.01

Discussion

PLMS has thus far been regarded as mostly an incidental concomitant phenomenon found in PSG monitoring in OSA patients since patients rarely present with isolated complaints of PLMS due to the lack of attendant leg discomfort as in RLS. However, this is no coincidence: current literature supports the view that PLMS is more common in OSA patients than in the general population. Taking PLMI ≥ 5 as the standard, Canada and the United States reported that the prevalence of PLMS in OSA patients is 48%[11] and 33%[27], respectively, compared to a prevalence of 4–11% in all adults[28]. Our study included only the Chinese population, where the prevalence was found to be 22.1% using the same PLMI ≥ 5 standard, or 16.1% using the newer PLMI ≥ 15 standard. Along with another study that recorded a prevalence of 20.1% in Taiwan[29], this suggests that the occurrence of PLMS in the Chinese OSA population may be lower than that in the North American population.

In the OSA-PLMS group, the sleep efficiency of the patients appeared to be lower than that in the OSA-only group. In terms of the sleep structure, patients in the OSA-PLMS group displayed a higher proportion of stage N1 sleep and lower proportion of stage N2 sleep stage (Table 2). As is consistent with the literature[6,7], this points to the disruption of sleep structure due to the periodic limb motor movements in OSA patients combined with PLMS. The potential mechanisms of such disruption can be manifold. Some studies have found that PLM is often accompanied by frequent EEG arousals[30], which regardless of their causes, prevent deeper, more stable stages of sleep. Furthermore, among OSA patients, about one-third are clinically characterized by a low respiratory arousal

threshold[31], which is a key factor associated with increased ventilatory instability and more severe OSA [32]. As shown by both our data and the MrOS external dataset, OSA-PLMS patients demonstrate an elevated tendency to have a low arousal threshold. Low arousal threshold leads to premature airflow recovery and limits the accumulation of respiratory stimuli required to activate pharyngeal dilators [33]. Transient hyperventilation response after awakening causes blood CO₂ levels to continue to decline after the end of apnea events, aggravating ventilatory instability and perpetuates the cycle of repetitive arousals, leading to sleep disruption[17,32]. Indeed, this mechanism of low arousal threshold could offer an explanation for the increased arousals and reduced sleep efficiency in OSA-PLMS patients seen in some studies[6,7], bridging the gap between the ostensibly unrelated symptoms of PLMS and OSA. Crucially, this negative effect is further compounded by the more recent finding that put into doubt the traditional belief that arousals are necessary for re-opening of the obstructed airway[18,33], that is, arousals are not a "protective" mechanism as traditionally suggested and low ArTH contributes to the pathogenesis of severe OSA[34].

In our study, the methodology adopted to identify patients with low ArTH was a prediction tool developed by Edwards et al. [21], whose study validated this prediction tool against the gold standard epiglottic ArTH measurement in 146 patients. The tool achieved a reasonably high sensitivity (80.4%) and specificity (88.0%), and its robustness is further affirmed through its adoption by many recent studies [35–39]. This made possible the retrospective data collection and external dataset validation on a much larger sample of patients than the arguably more accurate invasive epiglottic measurement could. In our sample, 46.6% of patients in the OSA-PLMS group were of the low arousal threshold phenotype, compared to 19.7% in the OSA-only group ($p < 0.001$, Table 3). Using multivariate logistic regression, this difference is estimated to represent an odds ratio of 5.51 (3.35–9.05, $p < 0.001$) for patients with low ArTH. This relationship between low ArTH and PLMS is further validated using the MrOS database (N = 2232) where the odds ratio was calculated at 1.46 (1.18–1.81, $p < 0.001$). The MrOS cohort had a median age of 76.3 years, while the median age in our study was 45 years. This suggests that low arousal threshold is not only a risk factor for OSA but also and plays an important role in predisposing OSA patients to PLMS in *all age groups*.

Clinical significance

Despite its muted significance in patient complaints, PLMS combined with OSA represents notable cardiovascular and cerebrovascular risks. One multisite, longitudinal study by A. Zinchuk et al. of 1247 US veterans assessed the relationship between OSA phenotype and cardiovascular outcomes. Based on the polysomnographic features, seven phenotypes were identified among the OSA patients using cluster analysis, namely, "mild", "periodic limb movements of sleep (PLMS)", "NREM and arousal", "REM and hypoxia", "hypopnea and hypoxia", "arousal and poor sleep" and "combined severe". Astonishingly, membership to the "PLMS (N = 119)" cluster was shown to be an even better predictor than AHI categories (AHI ≥ 30 vs AHI < 15) in predicting cardiovascular outcomes, and the PLMS cluster carries the highest risks of negative cardiovascular outcomes (OR = 2.02, 1.32–3.08) among the six clusters[12]. In our study, we found that the prevalence of hypertension, arrhythmia, diabetes mellitus, and stroke in the OSA-PLMS group was higher than that in the OSA-only group. Similarly, a study by Koo BB et al demonstrated the relationship between PLMS and CVD in the MrOS sleep study cohort[40]. Besides cardiovascular risks, recent research has observed associations between PLMS and attention-deficit/hyperactivity disorder (ADHD)[41], as well as depression[42].

Such strong links between PLMS and heightened risks of cardiovascular and psychological disorders point to either the direct effect of this motor disorder or, more likely, the presence of a more sinister mechanism underlying both PLMS and cardiovascular risks. Currently, several hypotheses exist to explain this relationship. One hypothesis implicated the repetitive abnormal autonomic response to PLMS[30]. In a study by W. Cassel et al., increased lability in blood pressure was recorded during leg movements compared to controls. The study also observed a temporal relationship between the onset of PLM and blood pressure elevations[43]. Another study by Carolina Lombardi et al. also demonstrated an increment of blood pressure equal to 2.64 mm Hg in patients with significant PLMS when compared to patients without significant PLMS ($p = 0.044$)[44]. Yet, from the OSA perspective, a correlation has been repeatedly shown between hypertension and sleep disruption. Thus, in light of the relationship we have shown between low ArTH and PLMS, we postulate that a central mechanism underlying the low arousal threshold could bridge the missing link between PLMS and hypertension, through the transient moderation of the autonomic nervous system (as in the former study by W. Cassel et al.,) and the process of sleep disruption in the longer term (as in the latter study by Carolina Lombardi et al., also see[12]). Regardless of the cause of such risks, current evidence highlights the importance of early intervention in patients with OSA complicated by PLMS to reduce their risks of cardiovascular events and psychological disorders.

Inadequacy of current approaches to the management of OSA-PLMS patients

There has been a lack of research attention to the specific treatment of PLMS. On the one hand, the clinical symptoms of this group of patients are not obvious or bothersome to patients, due to the absence of strong discomfort as in RLS; on the other hand, the currently used treatments and medications lack robust research trials of effectiveness. Evidently, the underlying link between PLMS and a whole host of comorbidities warrant further investigation into this clinical disorder, despite its lack of frank clinical symptoms. In PLMS patients who are often treated by CPAP for their concomitant OSA, studies have shown that CPAP treatment has no clear impact on the severity of PLMS[6,13]. The current treatment approaches of PLMS mainly "borrow" from the pharmacological treatments of RLS, where the current guideline presents a "standard" level of recommendation for pramipexole and ropinirole and a "guideline" level of recommendation for levodopa with dopa decarboxylase inhibitor, opioids, gabapentin enacarbil in the treatment of RLS[45]. These drugs reduce PLMS but usually do not eliminate them, which may continue to be directly or indirectly a risk for cardiovascular diseases[46].

From the OSA perspective, the mainstay of the current management approach is the use of Continuous Positive Airway Pressure (CPAP) therapy. However, the treatment efficacy of CPAP in the subgroup of combined OSA-PLM patients leaves much to be desired. A study has shown that patients with combined PLMS demonstrate poorer adherence to CPAP treatment[14]. Interestingly, A. Zinchuk et al. found a markedly poorer adherence to long-term CPAP therapy in the nonobese (BMI < 30) OSA patients with low ArTH when compared to patients with high ArTH[47]. In our study, we demonstrated a strong correlation between low arousal threshold and PLMS. This might suggest that these two subgroups of CPAP non-complying patients with low ArTH and PLMS are highly

overlapping or even mechanistically linked by a common etiology. Given its accompanying cardiovascular risks in these patients, we call for more attention to this low ArTH – PLMS subgroup of OSA.

Pharmacological approaches that raise the arousal threshold may simultaneously improve PLMS, OSA, and CPAP adherence in this cohort. Indeed, one of the foci of research has been the drug therapy for OSA targeting low arousal thresholds. A pilot experiment shows that the application of 3 mg of eszopiclone improved AHI (25 times/h vs 14 times/h) and sleep quality in patients with low arousal thresholds, without worsening hypoxemia[48]. In our study, the OSA-PLMS group has a high proportion of low arousal thresholds, and it can be envisaged that the use of this class of drugs in the treatment of OSA may be effective in this population.

Limitations

This retrospective study is purely observational, and the findings could only establish a correlation between PLMS and low arousal threshold, while further research is needed to establish the direction of causality. Admittedly, to enable the collection of a large dataset to make possible the analysis of such subtle clinical correlations, the gold standard epiglottic ArTH measurement would be extremely difficult, if not impossible. As such, the classification of low arousal threshold in this study was based on a validated clinical prediction tool, which in turn, brings the additional utility in terms of potential applications in community screening of OSA patients and their phenotypes. This also enables the validation of our findings in the widely analysed and validated MrOS cohort. It should also be noted that most patients had only one session of PSG, which could be susceptible to the influence of the “first night effect”.

Conclusion

Our study presents, to our knowledge, the first piece of evidence that identifies low arousal threshold as an independent predictor for PLMS in OSA patients in both locally collected primary data and the MrOS cohort dataset. This poses low arousal threshold as a potential link between OSA and PLM, where low ArTH serves as a non-anatomical etiology to the former and as a risk factor for the latter. In light of the elevated risks of cardiovascular and cerebrovascular diseases in PLM patients both in our study and the current literature, we recommend more investigations should be done to gain further understanding into the role of low arousal threshold in treating this group of OSA-PLMS patients, as well as the accompanying cardiovascular comorbidities.

Declarations

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Ethics approval: Approved by the Research Ethics Committee of the Second Affiliated Hospital of Soochow University, Suzhou, China

Consent to participate & publication: Informed consent was sought from all patients involved, with the understanding that anonymized data could be used for research and publications

Author Contribution

Chen Rui supervised the study, inspired the experimental design and reviewed the manuscript; Qiaojun Wang and Yezhou Li collected and analyzed data and drafted the manuscript; Jie Li, Jing Wang and Jiucheng Shen conducted the medical assessment of the patients; Fei Han and Hao Gui analyzed the PSG data for the study; Kaida Guo was involved in the statistical analysis; Huaman Wu and Delu Wang provided guidance on experimental design; All authors reviewed and approved the final manuscript.

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Figures

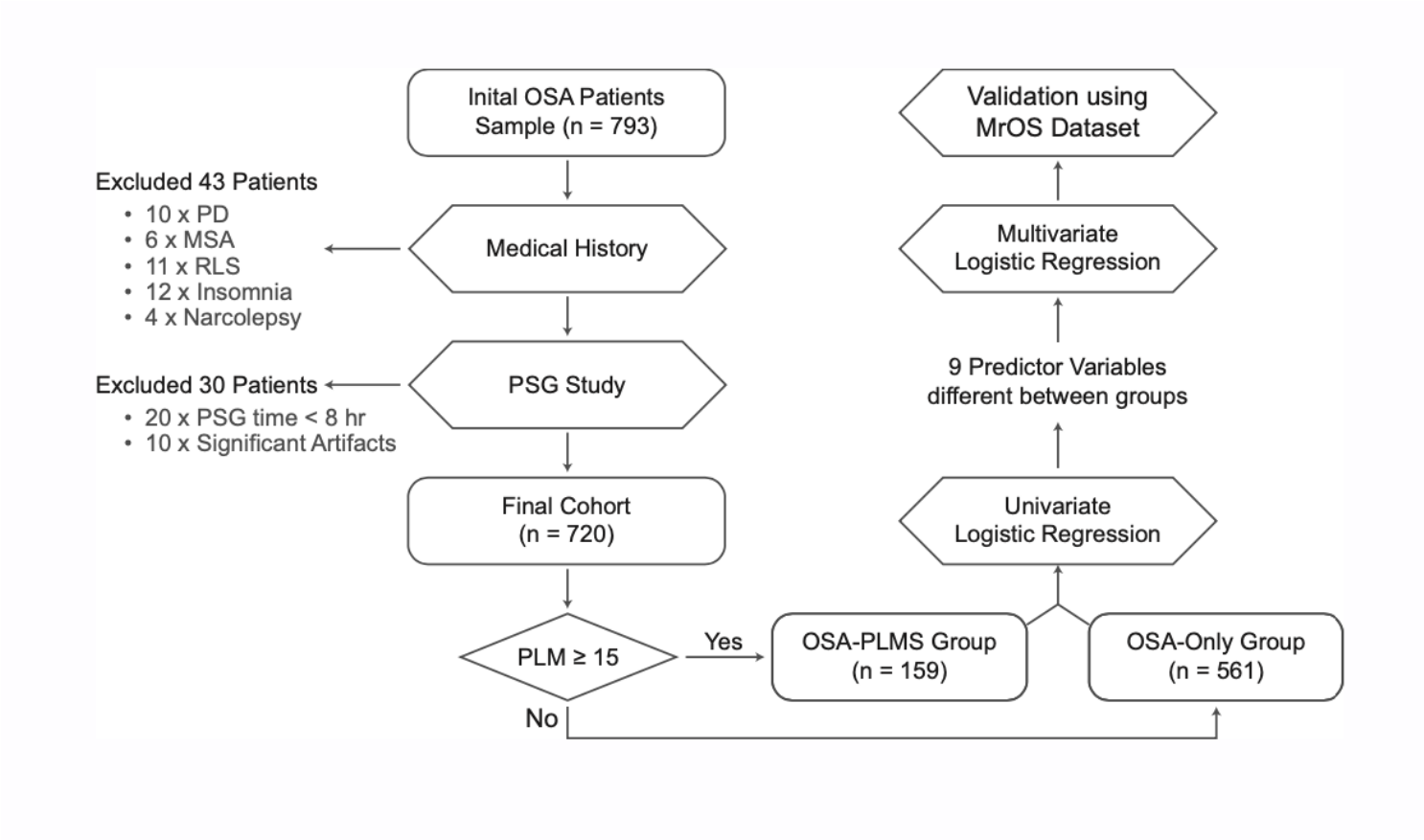

Figure 1

Study flow diagram. In this study, 793 OSA patients with an AHI of ≥5 were enrolled. Among the 793 patients, 720 participants were eventually included in the study. Abbreviations: PD, Parkinson's disease; MSA, multiple system atrophy; RLS, restless leg syndrome; PLMI, periodic leg movement index; PLMS, periodic leg movement in sleep; ArTH, arousal threshold.

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