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Periodic limb movements of sleep are associated with an increased prevalence of atrial fibrillation in patients with mild sleep-disordered breathing

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ABSTRACT

Background: Growing evidence indicates that periodic limb movements of sleep (PLMS) may be related to increased risk of developing cardiovascular disease. However, the association of PLMS with atrial fibrillation (AF) is unclear, especially in patients with sleep-disordered breathing (SDB). This study sought to investigate whether PLMS were associated with increased AF prevalence, independent of established risk factors.
Methods: We performed a cross-sectional study of patients who underwent attended polysomnography at Mayo Clinic from 2011 to 2014. The association of PLMS with AF prevalence was estimated by using logistic regression models.
Results: 15,414 patients were studied, 76.3% of individuals with SDB defined by apnea-hypopnea index (AHI) ≥5/h, and 15.3% with a diagnosis of AF. In univariate logistic modelling, individuals with periodic limb movement index (PLMI) ≥30/h had higher odds of AF (odds ratio [OR] 1.96, 95% confidence interval [CI]1.79–2.16, $p < 0.001$) when compared to patients with PLMI <15/h. After multivariate adjustment (for age, race, sex, history of smoking, hypertension, diabetes, coronary artery disease, heart failure, cerebrovascular disease, renal disease, iron deficiency anemia, chronic obstructive pulmonary disease, AHI, arousal index), in mild SDB patients, a PLMI ≥30/h or periodic limb movement arousal index (PLMAI) ≥5/h had significantly higher odds of AF than those with PLMI <15/h (OR 1.21, 95% CI 1.00–1.47, $p = 0.048$) or PLMAI <1/h (OR 1.27, 95% CI 1.03–1.56, $p = 0.024$).
Conclusions: Frequent PLMS are independently associated with AF prevalence in patients with mild SDB. Further studies are needed to better understand the relationship with incident AF.

1. Introduction

Periodic limb movements of sleep (PLMS), triggered subcortically, are described as rhythmic extensions of the big toe and dorsiflexion of the ankle, with occasional flexions of the hip and knee. Several factors, including genetic diathesis [1], dopaminergic impairment [2] and iron status [3], may be etiologically implicated in PLMS occurrence. Whilst PLMS can be seen during normal sleep, they can also be associated with arousals and sleep-related complaints such as insomnia and unrefreshing sleep [4]. The clinical importance of PLMS, particularly in the absence of restless leg syndrome, is not known, but recent studies have independently associated PLMS with the development of cardiovascular diseases (CVD) and have shown them to predict mortality in patients with CVD [5–8]. However, studies specifically examining the relationship between PLMS and atrial fibrillation (AF) are scarce. In a retrospective study including 373 patients with diagnosed AF, frequent PLMS were shown to increase the risk of progression from paroxysmal/persistent AF to permanent AF [9]. Also, the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study which included 2793 community-dwelling elderly men, reported a modest association between PLMS and AF prevalence in patients with chronic heart failure and myocardial infarction [10]. Over a long follow-up of MrOS participants, PLMS induced arousals were associated with incident AF in men aged ≥76 years [11].

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While the association of sleep-disordered breathing (SDB) with increased AF risk is well established [12–14], the potential pathogenic contribution of comorbid PLMS in patients with SDB has not been previously investigated. In this study, we sought to examine the association between PLMS and AF prevalence among a large group of patients who were referred for clinical evaluation mainly for suspected SDB. The aim of this study was to test whether PLMS are associated with AF prevalence in SDB patients, independent of established risk factors, including SDB.

2. Materials and methods

2.1. Study population

The study included all individuals referred to the Mayo Clinic Center for Sleep Medicine in Rochester, MN who underwent polysomnography (PSG) from January 1st 2011 to December 31st 2014, and consented to using their information in medical research (Fig. 1). 2077 patients younger than 18 years at the date of PSG were excluded from the analysis. PLMS data were not available in 17 patients due to technical failures. The final cohort of study participants included 15,414 patients whose clinical information was collected. This study was approved by the Mayo Clinic Institutional Review Board.

2.2. Confirmation of AF and comorbidities

The Mayo Clinic uses a unified medical record in which all diagnoses made during office visits, clinic consultations, nursing home care, emergency department visits, surgical procedures, hospitalizations, and autopsy examinations are listed and assigned a searchable modified hospital International Classification of Disease (ICD) adaptation code [15]. Patients' diagnosis of AF and comorbidities were identified using the Advanced Cohort Explorer (ACE), an advanced query tool that allows access to clinical and administrative data from multiple clinical and hospital source systems within Mayo Clinic Rochester [16,17]. The search strategy included using ICD-9 codes in combination with key words. The criteria for prevalent AF included any clinical diagnosis prior to PSG or AF detected during PSG (a minimum single-channel electrocardiography recording is obtained as standard with PSG). To avoid misclassifying prevalent AF with incident AF, AF detected within one month after PSG was included in the pre-defined prevalence period. To avoid missing diagnoses, patients without a diagnosis of AF before PSG were censored again in the part of the clinical note in the ACE system by searching any recorded information of AF and atrial flutter, with results being manually read by investigators. Fourteen (0.113‰) out of 12,405 patients with no AF diagnosis were verified to have AF recorded before PSG. Demographic data including age, race, sex and body mass index, smoking history, previous medical history of heart failure, diabetes, coronary artery disease, hypertension, cerebrovascular disease, renal disease, iron deficiency anemia, pulmonary embolism, and chronic obstructive pulmonary disease (COPD) were also extracted.

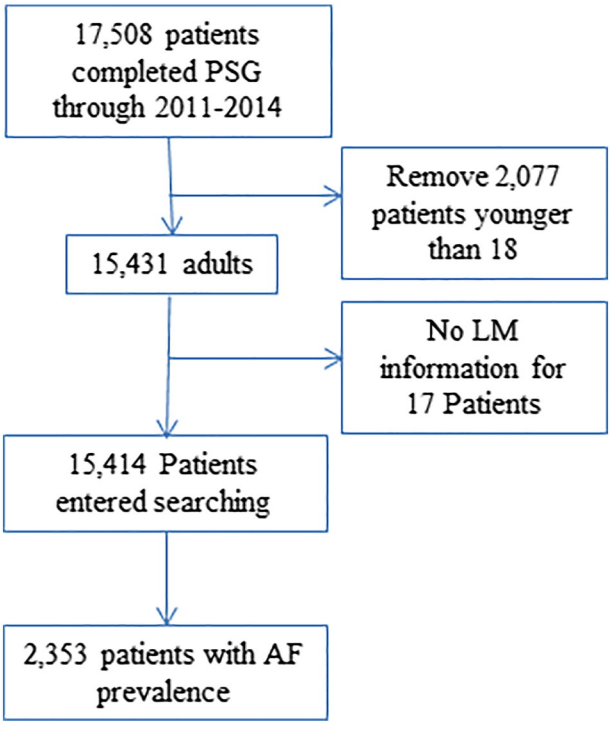

Fig. 1. Flow chart of sample selection. Abbreviations: AF = atrial fibrillation; LM = limb movement; PSG = polysomnography.

2.3. Polysomnography

All subjects' sleep evaluations were performed at the Mayo Clinic Center for Sleep Medicine, an American Academy of Sleep Medicine (AASM)-accredited sleep center. During all PSG studies, airflow was monitored by nasal pressure transducer and oronasal thermocouple; the electroencephalogram, electrooculogram, and submental electromyogram were recorded with surface electrodes. PSGs were scored by experienced registered PSG technologists and verified by board-certified sleep specialists. Apneas were defined as a ≥90% decrease of airflow for at least 10 s (as viewed on the thermal airflow channel), and hypopneas were defined by a ≥30% decline in airflow for at least 10 s (as viewed on the nasal pressure channel) accompanied by an oxygen desaturation of ≥4%. Apneas without evidence of respiratory effort were scored as central, while those with respiratory effort were categorized as obstructive. For patients with multiple studies, baseline parameters from the first PSG were utilized. A total of 11,446 (74.3%) PSGs were split-night studies (the first procedure diagnostic followed by a trial of continuous positive airway pressure [CPAP] and/or oxygenation). To prevent confounding, only the baseline data were used in these cases. Variables derived from the PSG included sleep efficiency, arousal index (AI), apnea-hypopnea index (AHI), periodic limb movement index (PLMI), and periodic limb movement arousal index (PLMAI). AHI was calculated as the average number of apneas and hypopneas per hour of sleep, and SDB was diagnosed based on an AHI ≥5/h. A limb movement (LM) was scored in accordance with AASM [18,19], where the duration of LM was between 0.5 and 10 s and there was a >8 uV amplitude increase from baseline in a leg electromyogram channel. An LM would not be scored if it occurred during a period from 0.5 s preceding an apnea, hypopnea, or respiratory effort-related arousal to 0.5 s following. An arousal and an LM were considered associated with each other when there was <0.5 s between the end of one event and the onset of the other event regardless of which was first. To be considered periodic, at least 4 LMs were needed to occur in succession no <5 s and no more than 90 s apart. PLMI was the total number of periodic LMs per hour of sleep. PLMAI was the total number of periodic LMs per hour of sleep in which an arousal was associated with LM.

For the purpose of our study, using PLMS variables, patients were grouped into subjects with PLMI <15/h, PLMI 15 to <30/h, and PLMI ≥30/h, and PLMAI <1/h, PLMAI 1 to <5/h, and PLMAI ≥5/h [5,10]. Similarly, patients were stratified by AHI into non-SDB (AHI <5/h), mild SDB (AHI 5 to <15/h), moderate SDB (AHI 15 to <30/h), and severe SDB (AHI ≥30/h).

2.4. Statistical analysis

Continuous variables were described as medians and 25th and 75th percentiles, whereas categorical variables were described as frequency and percentage. Statistical interaction between PLMS with severity of SDB was examined. Logistic regression analysis was used to investigate associations between PLMS variables and AF prevalence. Multivariable logistic regression was used to explore the independent odds associated with AF prevalence. Adjustment factors were determined based on univariate associations with AF prevalence, except for medication of anti-arrhythmia drugs, which was not included because it may be taken mostly to maintain sinus rhythm after incidence of arrhythmias rather than primary preventative therapy. Linearity assumptions for continuous variables were assessed and restricted cubic splines used (when appropriate) to satisfy the assumption. Analyses were performed using SAS 9.4 and JMP, version 10 (SAS Institute; Cary, North Carolina), and a p-value <0.05 was considered statistically significant.

3. Results

3.1. Study population

The study population consisted of 15,414 subjects, 14,208 (92.2%) Caucasian and 9087 (59.0%) male with a median age of 59 years. Baseline characteristics of patients grouped by PLMI strata are described in Table 1. Patients with PLMI ≥30/h were older and had higher commodities as demonstrated. SDB was present in 11,754 (76.3%) subjects, 5126 (33.3%) mild, 2933 (19.0%) moderate and 3695(24.0%) severe. As shown in Supplemental Fig. 1, patients with PLMI ≥30/h accounted for 30.3%, 40.7%, 40.9%, and 31.6% of subjects with non-SDB, mild SDB, moderate SDB and severe SDB respectively. A PLMAI ≥5/h accounted for 37.2%, 42.1%, 40.0% and 25.0% of subjects with non-SDB, mild SDB, moderate SDB and severe SDB respectively. Patients diagnosed with AF were significantly older than non-AF subjects (supplemental Table 1) with higher rates of smoking, of Caucasian race and had a higher prevalence of commodities (hypertension, diabetes, coronary artery disease, heart

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Table 1
Clinical characteristics of study patients by PLMI group ($n = 15{,}414$).

Characteristics	PLMI <15/h ($n = 7835$)	PLMI 15 to 30/h ($n = 2016$)	PLMI ≥30/h ($n = 5563$)	p
Age, median (25th, 75th centile), years	55 (44,65)	57 (46,67)	64 (55,73)	$P < 0.001$
Male sex, n (%)	4253 (54.3)	1113 (55.2)	3721 (66.9)	0.001
Caucasian race, n (%)	7083 (90.4)	1880 (93.3)	5245 (94.3)	0.001
Body mass index, median (25th, 75th centile), kg/m^2	32.9 (28.5,38.1)	32.4 (28.2,37.5)	32.4 (28.8,37.4)	0.117
History of smoking, n (%)	3650 (49.1)	977 (51.0)	2903 (54.2)	$P < 0.001$
Dopamine antagonist, n (%)	295 (3.8)	67 (3.3)	215 (3.9)	0.542
Anti-arrhythmic medications, n (%)	691 (8.8)	174 (8.6)	580 (10.4)	0.003
Heart failure, n (%)	369 (4.7)	108 (5.4)	469 (8.4)	$P < 0.001$
Diabetes, n (%)	1436 (18.3)	399 (19.8)	1335 (24.0)	$P < 0.001$
Coronary artery disease, n (%)	1373 (17.5)	396 (19.6)	1632 (29.3)	$P < 0.001$
Hypertension, n (%)	3298 (42.1)	881 (43.7)	3027 (54.4)	$P < 0.001$
Cerebrovascular disease, n (%)	217 (2.8)	54 (2.7)	221 (4.0)	0.0002
Renal disease, n (%)	120 (1.5)	45 (2.2)	154 (2.8)	$P < 0.001$
Iron deficiency anemia, n (%)	459 (5.9)	127 (6.3)	412 (7.4)	0.002
Pulmonary embolism, n (%)	150 (1.9)	25 (1.2)	133 (2.4)	0.0051
COPD, n (%)	377 (4.8)	113 (5.6)	449 (8.1)	$P < 0.001$
AHI, median (25th, 75th centile),/h	11 (4,32)	10 (3,24)	12 (5,26)	$P < 0.001$
Arousal index, median (25th, 75th centile),/h	27 (17,45)	31 (20,46)	39 (26,57)	$P < 0.001$

Abbreviations: AHI = apnea hypopnea index; COPD = chronic obstructive pulmonary disease; PLMI = periodic limb movement index.

failure, cerebrovascular disease, renal disease, COPD and iron deficiency anemia).

3.2. Association of PLMS with AF prevalence

Using univariate logistic modelling, individuals with PLMI ≥30/h had two times higher odds of AF (odds ratio [OR] 1.96, 95% confidence interval [CI] 1.79–2.16, $p < 0.001$) when compared to patients with PLMI <15/h. Patients with PLMAI ≥5/h were at higher odds of AF than those with PLMAI <1/h (OR 1.67, 95% CI 1.51–1.85, $p < 0.001$). Compared with non-SDB patients, subjects with mild (OR 1.97, 95% CI 1.71–2.27, $p < 0.001$), moderate (OR 2.50, 95% CI 2.15–2.92, $p < 0.001$), and severe SDB (OR 2.96, 95% CI 2.57–3.42, $p < 0.001$) all had higher odds of AF.

After adjusting for variables including age, race, sex, history of smoking, hypertension, diabetes, coronary artery disease, heart failure, cerebrovascular disease, renal disease, COPD, iron deficiency anemia, AHI and AI (exclude LM associated arousal) the significance of higher odds of AF in patients with PLMI ≥30/h compared to those with PLMI <15/h did not persist (OR 1.09, 95% CI 0.97–1.22, $p = 0.134$). Similarly, patients with PLMAI ≥5/h had insignificantly higher odds of AF than subjects with PLMAI <1/h in multivariate analysis (OR 1.12, 95% CI 0.99–1.26, $p = 0.076$). In subgroup analyses among subjects ≥59 years, both PLMI ≥30/h and PLMAI ≥5/h showed significantly higher odds of AF than those with PLMI <15/h and PLMAI <1/h (OR 1.23, 95% CI 1.08–1.39, $p = 0.0012$ and OR 1.27, 95% CI 1.11–1.45, $p = 0.0005$, respectively) (Table 2). Severe SDB was associated with higher odds of AF than non-SDB (OR 1.32, 95% CI 1.12–1.56, $p = 0.0009$) in multivariate analysis (AHI was not adjusted for).

3.3. Association of AF in patients with SDB and PLMS

No significant interaction was observed between PLMI and PLMAI (as continuous variables) with severity of SDB for the prevalence of AF ($p = 0.927$ and $p = 0.666$). Similarly, there was no significant interaction between PLMI and PLMAI stratification (as categorical variables) and severity of SDB for AF prevalence ($p = 0.429$ and $p = 0.363$). As shown in Supplemental Fig. 2, in patients with non-SDB, mild SDB, moderate SDB and severe SDB, subjects with PLMI ≥30/h compared with those with PLMI <15/h had significantly higher crude odds of AF (OR 2.4, 95% CI 1.84–3.08, $p < 0.001$, OR 2.02, 95% CI 1.71–2.39, $P < 0.001$, OR1.9, 95% CI 1.54–2.32, $p < 0.001$ and OR1.83, 95% CI 1.54–2.18, $p < 0.001$, respectively). Similarly, patients with PLMAI ≥5/h vs. those with PLMAI <1/h had significantly higher crude odds of AF in all stratified SDB categories (OR 2.1, 95% CI 1.58–2.84, $p < 0.001$, OR 2.0, 95% CI 1.70–2.46, $p < 0.001$, OR 1.9, 95% CI 1.52–2.37, $p < 0.001$ and OR 1.6, 95% CI 1.30–1.89, $p < 0.001$, respectively).

However, in the multivariate adjustment model, the significant association of PLMS with AF prevalence did not persist in non-SDB, moderate SDB and severe SDB subjects. In the mild SDB group (Fig. 2), patients with PLMI ≥30/h had 1.21 times higher odds of AF when compared with patients with PLMI <15/h (OR 1.21, 95% CI 1.00–1.47, $p = 0.048$). Similarly, only in mild SDB patients did subjects with PLMAI ≥ 5/h have significantly higher odds of AF than those with PLMAI <1/h (OR 1.27, 95% CI 1.03–1.56, $p = 0.024$).

4. Discussion

Our study confirmed that frequent PLMS with arousals are independently associated with AF prevalence among patients referred for PSG,

Table 2
PLMS and AF odds by age in Multivariable Logistic Regression.

	Age < 59 years ($n = 7538$)		Age ≥ 59 years ($n = 7876$)	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
PLMI <15/h	–	–	–	–
PLMI 15 to <30/h	1.14	0.82–1.55	0.98	0.81–1.18
PLMI ≥30/h	1.14	0.89–1.45	1.23	1.08–1.39
PLMAI <1/h	–	–	–	–
PLMAI 1 to <5/h	1.30	1.00–1.68	1.09	0.93–1.27
PLMAI ≥5/h	1.01	0.77–1.32	1.27	1.11–1.45

Abbreviations: AF = atrial fibrillation; PLMAI = periodic limb movement arousal index; PLMI = periodic limb movement index; PLMS = periodic limb movements of sleep.

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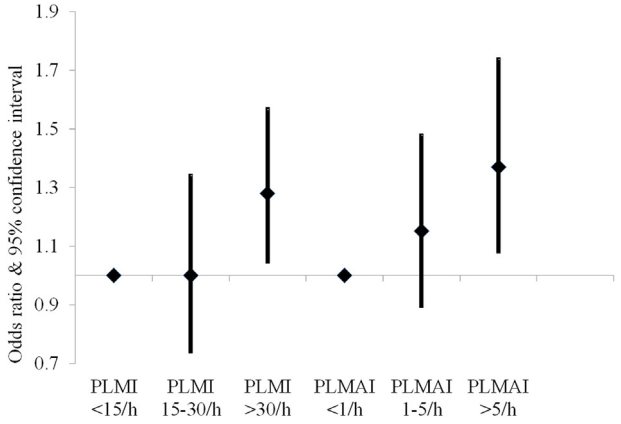

Fig. 2. Odds of AF prevalence in mild SDB patients in Multivariable Logistic Regression. Patients with PLMI >30/h vs. PLMI <15/h, and PLMAI >5/h vs. PLMAI <1/h had significantly higher odds of AF prevalence. Abbreviations: AF = atrial fibrillation; PLMAI = periodic limb movement arousal index; PLMI = periodic limb movement index; SDB = sleep-disordered breathing.

most often for suspicion of SDB. This finding is consistent with previous studies demonstrating the contribution of PLMS to progression from paroxysmal to permanent AF [9], AF prevalence [10] and incidence [11] with additional information about relationship with mild SDB. Evaluation of SDB together with PLMS, despite PMLS not being a recognized risk factor, may provide additional information useful for prediction and prevention of AF, ultimately facilitating personalized treatment.

The etiological mechanisms linking PLMS and AF are not completely understood, but several theories have been proposed. First, compared with SDB, in which hypoxemia and left atrial stretch are thought to be the dominant pathological mechanisms for AF [15,20], pro-arrhythmogenicity in patients with PLMS may be more closely related to the autonomic oscillation and disturbance associated with LM [21,22], and cardiac autonomic dysfunction has been proved to be associated with higher AF incidence [23]. Recurrent heart rate increments during sleep reflect sympatho-vagal imbalance associated with PLMS [22,24]. Analysis of the low frequency to high frequency spectral power ratio of heart rate variability suggests cardiac sympathetic dominance and vagal withdrawal with PLMS [22,24]. Further, arousal may be associated with significant sympathetic overdrive [25] and PLMS-related cardiac disturbance may be more prominent if EEG arousals are present [26]. Further studies are needed to confirm this trend initially reported in the MrOS Sleep study [11] showing PLMS with arousal are more proarrhythmogenic than isolated PLMS. Importantly, several reports described heart rate increases preceding the onset of LM and peak during or after an LM [27–29], suggesting that increased sympathetic activation and arousal facilitates PLMS rather than the PLMS being responsible for an increased sympathetic activation [21]. Bi-directional effects, i.e. autonomic changes and arousal contributing to LM occurrence and vice versa, are also plausible. Second, PLMS may also lead to BP surges in sleep, a nocturnal non-dipping BP profile [26, 30,31] and this is potentially associated with left atrial and ventricular enlargement [32]. This is pertinent as left atrial size is the single most important determinant for the development of AF. Older subjects who have a higher prevalence of structural and electrical remodeling of the heart, are more susceptible to AF; the increased odds of AF with PLMS as shown by our data and the MrOS Sleep study [11] may be the variable which initiates and maintains AF in this group. Third, patients with PLMS (such as restless leg syndrome) may not only have sleep fragmentation induced by LM associated arousal, but also have difficulties in sleep initiation which are not common in SDB. Poor sleep quality may affect the decline of sympathetic activity and cardiac recovery. Noticeably, although PLMS and SDB may lead to arrhythmia by partially similar mechanisms, their relative contributions may be sleep stage specific: PLMS occur in NREM sleep, while SDB is more frequent and severe in REM, which may explain the combined pathophysiological effects.

Although severe SDB may independently increase the likelihood of AF, the association between PLMS and AF prevalence was only found to be independently significant in patients with mild SDB in this study. This result suggests that PLMS may contribute additional risk in patients with mild SDB, who do not usually warrant intervention. Identifying PLMS in mild SDB patients may help stratify patients at risk of incident AF, who may benefit from the early introduction of CPAP therapy which was showed to reduce PLMS in mild SDB subjects [33], although it should be noted that PLMS reduction after CPAP in mild SDB may be partly due to the removal of few unscored breathing concerns, i.e. upper airway resistance. In patients with severe SDB, frequent breathing events may suppress PLMS [33] and manifestation of its dysrhythmogenic effects. *Vis-à-vis*, there may be a dominant maximal threshold effect associated with severe SDB with high levels of hypoxemia and arousals, beyond which the effects of PLMS are reduced. However, we cannot deduce that the effects of PLMS in severe SDB are negligible, as severe SDB suppresses PLMS. Equally, based on current data, we cannot conclude that PLMS is synergistic with severe SDB for arrhythmia. Interestingly, PLMS rebound is seen after CPAP use in severe OSA [33], which reveals that PLMS are suppressed by severe apnea and therefore potential effects on CV profile are difficult to discern before CPAP treatment. It will also be interesting to evaluate whether post-CPAP PLMS may undermine the beneficial effect of AHI elimination by CPAP and became an important pathological risk factor in subjects with severe OSA.

4.1. Strengths and limitations

One of the strengths is that we included a large population of consecutive patients who underwent attended PSG scored by technicians who were not part of the study team. The Center for Sleep Medicine internal validation measures ensure consistency between different technicians and sleep physicians, with dual reporting of every case. Second, prior to 2007, scoring of LM during breathing events was technically at the scorers' discretion with some practitioners including and others excluding this measure. The standardized approach reduces bias and improves generalizability. There are limitations inherent to the study design. First, the patients without SDB were not healthy controls, since they were referred for PSG for suspected sleep disorders (referral bias). Second, given the high percentage of Caucasian patients, generalizability of the results in this study may be limited, particularly as the prevalence of PLMS may differ among races. Third, a cross-sectional study design precludes determining a temporal relationship between PLMS, SDB, and AF. Recently published data in MrOS study suggested PLMS increases incident AF in community-dwelling men older than 76 [11]. Further studies may test whether PLMS adds additional risk to SDB subjects. Finally, accurate classification of AF category was not achievable during the data extraction, so all types of AFs were included and grouped together, including AF diagnosed incidentally. This may include asymptomatic AF as AF is notorious for being associated with non-specific and insidious symptoms, only becoming apparent once sinus rhythm is restored. Further, it is possible that the prevalence of AF is higher as those not diagnosed, especially those without symptoms are not going to present.

5. Conclusion

Frequent PLMS with arousals are independently associated with AF prevalence in patients with mild SDB. It would be informative for clinicians to assess PLMS together with SDB when evaluating risk for the development of AF. Whether CPAP treatment of SDB influences the dysrhythmogenic effect of PLMS is to be determined. Further studies

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are needed to better understand the relationship between PLMS and AF, both in treated and untreated SDB.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.04.060.

Disclosures

None.

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