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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

Jiang Xie<sup>a,b,\*</sup>, C. Anwar A. Chahal<sup>a,c</sup>, Naima Covassin<sup>a</sup>, Phillip J. Schulte<sup>d</sup>, Prachi Singh<sup>a</sup>, Narat Srivali<sup>e</sup>, Virend K. Somers<sup>a</sup>, Sean M. Caples<sup>e</sup>

<sup>a</sup> Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

<sup>b</sup> Pulmonary Department of Beijing An Zhen Hospital, Capital Medical University, Beijing, China

<sup>c</sup> Mayo Graduate School, Mayo Clinic, Rochester, MN, USA

<sup>d</sup> Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA

<sup>e</sup> Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

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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 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)  $\geq 5/h$ , and 15.3% with a diagnosis of AF. In univariate logistic modelling, individuals with periodic limb movement index (PLMI)  $\geq 30/h$  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  $\geq 30/h$  or periodic limb movement arousal index (PLMAI)  $\geq 5/h$  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.

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### 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  $\geq 76$  years [11].

\* Corresponding author at: Department of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55902, USA.

E-mail addresses: [Xie.Jiang@mayo.edu](mailto:Xie.Jiang@mayo.edu), [Frank782008@aliyun.com](mailto:Frank782008@aliyun.com) (J. Xie).

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.

### 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  $\geq 90\%$  decrease of airflow for at least 10 s (as viewed on the thermal airflow channel), and hypopneas were defined by a  $\geq 30\%$  decline in airflow for at least 10 s (as viewed on the nasal pressure channel) accompanied by an oxygen desaturation of  $\geq 4\%$ . 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  $\geq 5$ /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  $\geq 30$ /h, and PLMAI  $< 1$ /h, PLMAI 1 to  $< 5$ /h, and PLMAI  $\geq 5$ /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  $\geq 30$ /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  $\geq 30$ /h were older and had higher comorbidities 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  $\geq 30$ /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  $\geq 5$ /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 comorbidities (hypertension, diabetes, coronary artery disease, heart

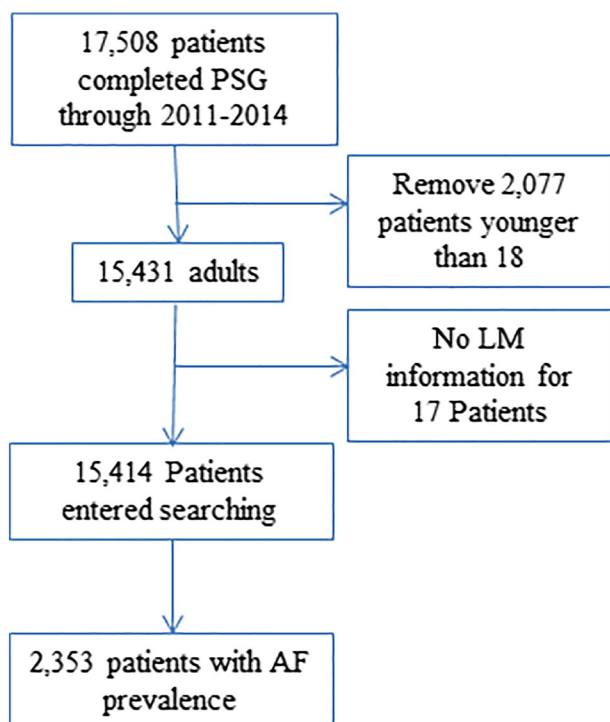


Fig. 1. Flow chart of sample selection. Abbreviations: AF = atrial fibrillation; LM = limb movement; PSG = polysomnography.

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