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Periodic Limb Movements during Sleep and Cardiac Arrhythmia in Older Men (MrOS Sleep)

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SCIENTIFIC INVESTIGATIONS

Study Objectives: To determine if periodic limb movements during sleep (PLMS) are associated with nocturnal cardiac arrhythmia.

Methods: 2,793 community-dwelling older men underwent polysomnography with measurement of limb movements and EKG. Logistic regression assessed association of periodic limb movement index and periodic limb movement arousal index with arrhythmia including atrial fibrillation and non-sustained ventricular tachycardia detected by polysomnography. Models were adjusted for age, race, cardiovascular risk factors, and clinic site. Secondary analyses were subset to men without calcium channel/β-adrenergic medication usage, and stratified by congestive heart failure or myocardial infarction history.

Results: In the overall cohort, periodic limb movement index, and periodic limb movement arousal index were not associated with ventricular or atrial arrhythmia after considering potential confounders. In men not taking calcium channel/β-blocking medication, increased adjusted odds of non-sustained ventricular tachycardia were observed for periodic limb movement index (OR = 1.30 per SD increase; 95% CI 1.00, 1.68) and periodic limb movement arousal index (OR = 1.29 per SD increase; 95% CI 1.03, 1.62). In men with CHF or MI, there was a suggested association of atrial fibrillation with periodic limb movement index (OR = 1.29, 95% CI 0.96, 1.73 per SD increase; p = 0.09) or periodic limb movement arousal index (OR = 1.21, 95% CI 0.94, 1.57 per SD increase; p = 0.14), although results were not statistically significant.

Conclusions: There is not an association between PLMS and cardiac arrhythmia in all older men but in subsets of men, particularly those with structural heart disease and not on calcium channel or β-adrenergic medication, cardiac arrhythmia does associate with PLMS.

Keywords: PLMS, arrhythmia, periodic, leg, cardiac

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Periodic limb movements during sleep (PLMS) consist of recurring muscular activations in the legs which occur in sleep. Individual movements involve contractions of foot and leg muscles lasting seconds and in severe cases can number into the hundreds each night.[1] The clinical significance of these repetitive movements is unclear, but when they occur with arousal, sleep fragmentation and daytime somnolence can result.[2] We recently demonstrated that PLMS in elderly men are also associated with incident myocardial infarction and peripheral vascular disease.[3] PLMS have also been associated with increased mortality in a cohort of patients with congestive heart failure (CHF).[4] Mechanisms underlying this increased mortality and cardiovascular risk are not firmly established, but autonomic nervous system hyperactivity is an intriguing possibility. This is supported by the observation that PLMS, occurring both with and without cortical arousal, are associated with stereotypic autonomic responses consisting of increases in both blood pressure and heart rate followed by a heart rate decline below the pre-movement rate.[5-7]

The repetitive occurrence of this sympathovagal response throughout the night may contribute to cardiovascular risk through altering vascular tone, endothelial integrity, and/or by triggering cardiac arrhythmias. Specifically, sympathetic nerve hyperactivity may induce electrical irritability in cardiac ventricles, triggering ventricular arrhythmia, while dysfunctional vagal modulation may inhibit atrioventricular nodal function, leading to atrially mediated arrhythmia.[8-10] Alternatively, PLMS may be a marker for poor cardiovascular health. It may be that

BRIEF SUMMARY

Current Knowledge/Study Rationale: Periodic limb movements during sleep (PLMS) are associated with increased sympathetic nervous activity which may increase individual susceptibility to cardiac arrhythmia. The purpose of this study was to determine if cardiac arrhythmia was more common in individuals with PLMS.

Study Impact: The current finding that PLMS is associated with cardiac arrhythmia in subsets of older men with structural heart disease and those not taking certain anti-arrhythmic medications suggests that men with PLMS may have increased susceptibility to cardiac arrhythmia. Clinicians should be aware of this potential association between PLMS and cardiac arrhythmia, but at the present time additional investigation is needed in this area to make more concrete clinical inferences.

PLMS do not provoke arrhythmia but rather both of these entities arise from autonomic abnormalities.

To address whether PLMS are associated with cardiac arrhythmias, we analyzed data from the Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep Study). The MrOS Sleep cohort is a large population-based sample of older men designed to examine multiple sleep related exposures and their potential association with cardiovascular outcomes. We hypothesized that the frequency of PLMS with and without arousal would be associated with increased rates of nocturnal ventricular and atrial arrhythmias and conduction delays. In addition, we explored whether the use of medications with anti-arrhythmic properties modified any relationship between PLMS and arrhythmias and examined data from men with prior myocardial infarction (MI) or CHF to determine if they, in particular, had increased associations of PLMS to cardiac rhythm disturbances.

METHODS

Participants

The MrOS Sleep Study was conducted between December 2003 and March 2005 and included a comprehensive sleep assessment in 3,135 elderly male participants of the parent Osteoporotic Fractures in Men (MrOS) Study cohort. The study involved 6 clinical centers (Birmingham, AL Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA), a coordinating center (San Francisco Coordinating Center) and a Sleep Reading Center (Case Western Reserve University, Cleveland, OH). Study design and methods of recruitment have been previously published.[11,12] Of the 3,135 men from the MrOS Sleep Study cohort, 179 refused polysomnography and an additional 45 had unusable data, resulting in 2,911 subjects who underwent home polysomnography. Men with missing polysomnographic data were more likely to be of minority race ($p < 0.001$), but were similar for all other characteristics examined. In addition, 118 men with pacemaker implantation were excluded from the analysis, leaving 2,793 men in the analytic sample. Protocols were approved by the institutional review board at each site, and all participants provided written informed consent.

Polysomnography

Unattended in-home polysomnography (PSG; Safiro, Compumedics, Inc., Melborne, Australia) was conducted, with a recording montage that included: C_3/A_2 and C_4/A_1 electroencephalography, bilateral electrooculography, submental electromyography, thoracic and abdominal respiratory inductance plethysmography, naso-oral thermistry, nasal pressure transduction, finger pulse oximetry, lead I EKG (sampled at 250 Hz) and bilateral anterior tibialis piezoelectric movement sensors. Home visits were performed by centrally-trained staff using procedures previously described.[13] Data were scored by certified research polysomnologists at the central Sleep Reading Center using standardized criteria modified for use in large cohort studies, with established high levels of reliability.[13,14] Apneas were identified by the near absence of airflow lasting ≥ 10 sec, while hypopneas were identified by ≥ 30% reduction of breathing amplitude lasting ≥ 10 sec as assessed by the summed abdominal and thoracic respiratory inductance signal or, when unclear, by the other respiratory signals. For this analysis, only apneas and hypopneas linked to ≥ 3% oxygen desaturation were included in the apnea-hypopnea index (AHI; i.e., total number of apneas and hypopneas per hour of sleep).[13] Arousals were scored according to published guidelines and summarized as the total number of arousals per hour of sleep (arousal index).[15]

Periodic limb movements were scored to be consistent with the AASM guidelines active at the time sleep studies in this cohort began. Individual leg movements were scored if there was a clear amplitude increase from baseline and the duration of movement was ≥ 0.5 sec and ≤ 5.0 seconds. To be considered periodic and for a final determination of PLMS, ≥ 4 movements needed to occur in succession no less and no more than 5 and 90 sec apart, respectively, according to the AASM criteria at the time of scoring.[16] Leg movements following respiratory events were excluded unless they were part of a 4 (or more) movement cluster with ≥ 2 movements occurring independently of respiratory events. The periodic limb movement index (PLMI) was computed as the total number of periodic leg movements per hour of sleep and the periodic limb movement arousal index (PLMAI) was calculated as the total number of periodic leg movements per hour of sleep in which EEG arousal occurred within 3 sec of movement termination.[17] An in-laboratory validation study conducted in 51 subjects in whom the PLMI was assessed concurrently in a blinded fashion using piezoelectric leg sensors scored using the original AASM criteria and using leg electromyography scored using the 2007 AASM criteria showed a correlation of $r = 0.81$.[16,18] PLMI and PLMAI were examined as continuous variables in models.

Outcome Data

As part of the polysomnographic montage, single lead (Lead I) electrocardiography (EKG) was used to monitor heart rate and rhythm. EKG-specific software (Somte; CompuMedics Ltd., Abbotsford, Victoria, Australia) was used by a trained scorer to manually annotate the EKG signals while blinded to leg movement and all other signals. Arrhythmia of uncertain category was arbitrated by a medical physician (RM). A physician also confirmed atrial fibrillation/flutter (AF) and complex ventricular ectopy (CVE) when identified by the polysomnologist. Arrhythmia outcomes identified by polysomnography were defined as described previously.[19]

Ventricular arrhythmias annotated and summarized were: premature ventricular contractions (PVCs) ≥ 5/h, non-sustained ventricular tachycardia (NSVT: ≥ 3 consecutive ventricular ectopic beats with a mean rate of ≥ 100 beats/min) and complex ventricular ectopy defined as the occurrence of bigeminy, trigeminy, or quadrimeny or NSVT (CVE). Atrial arrhythmias were: premature atrial contractions (PACs) occurring ≥ 5 times per hour, AF (paroxysmal or continuous); supraventricular tachycardia (SVT). Conduction delay arrhythmias were: sinus pause with a duration ≥ 3 sec; first-degree atrioventricular (AV) block; second-degree AV block; and intraventricular conduction delay. For AV block identification, the PR interval was manually determined with the use of software-based calipers

based upon a 20-sec random sampling of artifact-free EKG from the beginning of each sleep study. AV block was defined by an average PR interval ≥ 200 milliseconds.

Covariate Data

Other information was collected at a clinic visit generally conducted within 1 month of the PSG recording (mean 6.9 ± 15.8 days before the recording). Questionnaires included information about demographic characteristics, medical history, physical activity, smoking, and alcohol use. History of coronary heart disease (CHD) was defined as self-report of prior diagnosis of myocardial infarction (MI), angina, bypass surgery, or angioplasty. Medications, both prescription and nonprescription, were inventoried, verified by examining pill bottles, and matched to ingredient(s) using the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).[20] Physical Activity Scale for the Elderly (PASE) measured physical activity level.[21] Height, weight, body mass index (BMI), and resting blood pressure were also measured. Prevalent hypertension was defined when ≥ 1 of the following criteria were present: antihypertensive medications usage (ACE inhibitors, calcium channel blockers, β-adrenergic blockers, diuretics, and angiotensin II receptor antagonists), hypertension self-report, or systolic or diastolic pressure ≥ 140 or 90 mm Hg, respectively.

Statistical Analysis

Participants were categorized across categories of PLMI (< 5, 5 to < 30, ≥ 30) and PLMAI (< 1, 1 to < 5 and ≥ 5); these categories were chosen based upon their close approximation of tertiles. Participant characteristics were compared across categories using χ^2 tests for categorical variables, ANOVA for normally distributed continuous variables, and Kruskal-Wallis tests for continuous variables with skewed distributions. Proportions of all outcomes by PLMI and PLMAI category were calculated, and a Chochran-Armitage test for trend was performed to examine an unadjusted linear trend across the categories.

Logistic regression was used to assess the association between PLMI or PLMAI and arrhythmia binary outcomes defined as occurrences (yes; no) of: NSVT, CVE, AF, supraventricular tachycardia, sinus pause, and first-degree AV block or of PVC ≥ 5/h and PAC ≥ 5/h. Model results are presented as odds ratios (OR) with 95% confidence intervals (CI). Models were minimally adjusted for clinic, age, race, and BMI. These models were then further adjusted for smoking, alcohol use, physical activity, and AHI. The full multivariable model was further adjusted by covariates that could be on the intermediate pathway (prevalent hypertension, history of CHD, history of congestive heart failure [CHF], history of diabetes and use of β-blockers or calcium channel blockers).

Interactions were explored between PLMI or PLMAI and exposures that may modify arrhythmia susceptibility: (1) Use of β-adrenergic or calcium channel blocker medications due to a reduction in cardiac ectopy associated with these medications, and (2) Presence of structural heart disease as suggested by CHF or MI because of underlying increased susceptibility to sympathoexcitation.[22,23] Stratifications by these parameters were performed when interactions were $p < 0.10$.

All significance levels reported were two-sided. Analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Overall Characteristics

The sample of 2,793 men was predominantly Caucasian, with a mean age of 76.2 ± 5.5 years. **Table 1** shows other baseline demographic characteristics of the overall cohort and the cohort stratified by PLMI and PLMAI categories. Almost one half of the sample had a PLMI ≥ 30 (44.7%; n = 1,248). Having higher levels of PLMI was associated with older age, Caucasian race, coronary heart disease, as well as with a higher arousal index and lower AHI. Having higher levels of PLMAI was observed in almost 27% (n = 750) of the sample. Increasing PLMAI category was associated with older age, Caucasian race, coronary heart disease, higher AHI and arousal index and the use of β-blocker medications. Neither PLMI nor PLMAI were associated with diabetes, prevalent hypertension, BMI, smoking status, alcohol intake, or CHF.

Unadjusted Associations of Arrhythmia with PLMI and PLMA

Table 2 shows the distributions of the different arrhythmia types in the overall cohort and according to PLMI and PLMAI category. Of the ventricular arrhythmias, ventricular ectopy identified as PVCs at a rate ≥ 5/h, was most common, observed in almost 42% of men. Complex ventricular arrhythmia was observed in 37.3% of men, while 3.2% were observed to have non-sustained ventricular tachycardia. Of the atrial arrhythmias, 60.0% had ≥ 5 PACs/h, while 23.0% had supraventricular tachycardia and 4.8% had paroxysms or sustained periods of AF. Of the conduction delay arrhythmias, sinus pauses were observed in 13.3% of men, with periods of first and second degree AV block observed in 40.1% and 2.2% of men, respectively. Modest but significant increases in the frequencies of PVCs (≥ 5/h), NSVT, CVE, PACs (≥ 5/h), and AF were observed with increasing PLMI category. In contrast, no association between PLMI category and conduction delays was observed. For increasing PLMAI category, significant increases were seen for frequencies of NSVT, CVE, PACs (≥ 5/h), sinus pause, and first degree AV block.

Adjusted Associations: Ventricular Arrhythmias

For ventricular arrhythmias including premature ventricular contractions, non-sustained ventricular tachycardia and complex ventricular ectopy, no significant associations were seen with PLMI or PLMAI after adjustment for multiple covariates (**Table 3**). For the outcome of NSVT, there were interactions between use of calcium channel/β-adrenergic blocking medication and both PLMI ($p = 0.08$) and PLMAI ($p < 0.01$). When considering the subset of men without β-adrenergic/calcium channel blocking medication usage (n = 1,763), after adjusting for clinic site, age, race, BMI, smoking, alcohol use, physical activity, AHI, prevalent hypertension, history of coronary heart disease, congestive heart failure, and diabetes, NSVT was associated with both PLMI (odds ratio of 1.30 per SD increase; 95% CI 1.00, 1.68) and PLMAI (odds ratio of 1.29 per SD increase; 95% CI 1.03, 1.62) (**Figure 1**).

Table 1—Distributions of participant characteristics by PLMI

Participant Characteristics	Overall Cohort (n = 2,793)	PLMI < 5 (n = 821)	5 ≤ PLMI < 30 (n = 724)	PLMI ≥ 30 (n = 1,248)	PLMAI < 1 (n = 1,122)	1 ≤ PLMAI < 5 (n = 921)	PLMAI ≥ 5 (n = 750)
Age	76.2 ± 5.5	75.4 ± 5.1	75.9 ± 5.4	76.9 ± 5.6‡	75.6 ± 5.2	76.1 ± 5.4	77.4 ± 5.7‡
Caucasian race, n (%)	2,529 (90.6)	707 (86.1)	642 (88.7)	1,180 (94.6)‡	968 (86.3)	842 (91.4)	719 (95.9)‡
BMI, kg/m^2	27.2 ± 3.8	27.2 ± 3.9	27.2 ± 4.0	27.3 ± 3.7	27.2 ± 3.9	27.2 ± 3.7	27.3 ± 3.8
Apnea-hypopnea index	17.0 ± 15.1	18.0 ± 15.3	16.8 ± 15.0	16.5 ± 15.1*	16.7 ± 15.2	15.6 ± 13.6	19.3 ± 16.5‡
PASE score	146.6 ± 71.5	151.8 ± 74.5	142.7 ± 71.8	145.5 ± 69.1*	148.4 ± 74.2	145.1 ± 70.8	145.8 ± 68.0
Current Smoking							
Never	1,094 (39.2)	302 (36.8)	290 (40.1)	502 (40.2)	433 (38.6)	361 (39.2)	300 (40.0)
Past	1,642 (58.8)	502 (61.1)	420 (58.0)	720 (57.7)	668 (59.5)	541 (58.7)	433 (57.7)
Current	57 (2.0)	17 (2.0)	14 (1.9)	26 (2.1)	21 (1.9)	19 (2.1)	17 (2.3)
Alcohol intake (drinks/week)							
0-2	1,659 (59.7)	479 (58.8)	428 (59.2)	752 (60.6)	674 (60.5)	551 (60.2)	434 (58.0)
3-13	970 (34.9)	295 (36.2)	253 (35.0)	422 (34.0)	385 (34.5)	313 (34.2)	272 (36.4)
≥ 14	150 (5.4)	41 (5.0)	42 (5.8)	67 (5.4)	56 (5.0)	52 (5.7)	42 (5.6)
Use of calcium ChBlk, n (%)	418 (15.0)	121 (14.7)	108 (14.9)	189 (15.1)	182 (16.2)	120 (13.0)	116 (15.5)
Use of β-blocker, n (%)	749 (26.8)	201 (24.5)	194 (26.8)	354 (28.4)	278 (24.8)	246 (26.7)	225 (30.0)*
Diabetes mellitus, n (%)	367 (13.1)	98 (12.0)	88 (12.2)	181 (14.5)	139 (12.4)	123 (13.4)	105 (14.0)
Coronary heart disease, n (%)**	793 (28.5)	201 (24.6)	196 (27.2)	396 (31.8)†	289 (25.9)	269 (29.3)	235 (31.4)*
Myocardial infarction, n (%)	450 (16.1)	112 (13.7)	112 (15.5)	226 (18.1)*	161 (14.4)	150 (16.3)	139 (18.5)
Congestive heart failure, n (%)	145 (5.2)	41 (5.0)	41 (5.7)	63 (5.1)	58 (5.2)	45 (4.9)	42 (5.6)
Prevalent hypertension, n (%)	1,881 (67.4)	531 (64.8)	484 (66.9)	866 (69.5)	734 (65.5)	627 (68.1)	520 (69.4)
Arousal index	23.6 ± 11.7	21.7 ± 10.4	23.2 ± 10.8	25.0 ± 12.7‡	20.3 ± 10.4	21.3 ± 9.3	31.2 ± 12.6‡

Data shown as mean ± SD unless specified. P-values for continuous variables are from an ANOVA for normally distributed variables, a Kruskal-Wallis test for skewed data. p-values for categorical data are from a χ^2 test for homogeneity. *p-value < 0.05, †p-value < 0.01, ‡p-value < 0.001. **Coronary heart disease includes self report of a prior diagnosis of myocardial infarction, angina, bypass surgery, or angioplasty. BMI, body mass index; ChBlk, channel blocker; PASE, Physical Activity Scale for the Elderly; PLMAI, periodic limb movement arousal index; PLMI, periodic limb movement index.

Table 2—Distributions of cardiac arrhythmias by categories of periodic limb movements

Type of Arrhythmia	Overall (N = 2,793)	PLMI < 5 (N = 821)	5 ≤ PLMI < 30 (N = 724)	PLMI ≥ 30 (N = 1,248)	PLMAI < 1 (N = 1,122)	1 ≤ PLMAI < 5 (N = 921)	PLMAI ≥ 5 (N = 750)
Ventricular arrhythmias							
≥ 5 premature ventricular contractions/h	1,153 (41.6)	323 (39.5)	279 (39.1)	551 (44.3)*	445 (40.1)	375 (41.1)	333 (44.4)
Non-sustained ventricular tachycardia	88 (3.2)	21 (2.6)	16 (2.2)	51 (4.1)*	28 (2.5)	29 (3.2)	31 (4.1)*
Complex ventricular ectopy	1,043 (37.3)	283 (34.5)	265 (36.6)	495 (39.7)*	388 (34.6)	359 (39.0)	296 (39.5)*
Atrial arrhythmias							
≥ 5 premature atrial contractions/h	1,664 (60.0)	473 (57.9)	397 (55.7)	794 (63.8)*	649 (58.4)	526 (57.6)	489 (65.2)*
Atrial fibrillation	134 (4.8)	31 (3.8)	30 (4.1)	73 (5.9)*	45 (4.0)	47 (5.1)	42 (5.6)
Supraventricular tachycardia	645 (23.1)	201 (24.5)	156 (21.6)	288 (23.1)	268 (23.9)	205 (22.3)	172 (22.9)
Conduction delay arrhythmias							
Sinus pause (≥ 3 sec)	372 (13.3)	99 (12.1)	89 (12.3)	184 (14.7)	124 (11.1)	137 (14.9)	111 (14.8)*
First degree atrioventricular block	1,120 (40.1)	320 (39.0)	285 (39.4)	515 (41.3)	434 (38.7)	348 (37.8)	338 (45.1)*
Second degree atrioventricular block Type 1	55 (2.0)	12 (1.5)	12 (1.7)	31 (2.5)	19 (1.7)	17 (1.9)	19 (2.5)
Second degree atrioventricular block Type 2	6 (0.2)	2 (0.2)	2 (0.3)	2 (0.2)	4 (0.4)	1 (0.1)	1 (0.1)
Intraventricular conduction delay	134 (4.8)	42 (5.1)	32 (4.4)	60 (4.8)	60 (5.4)	39 (4.2)	35 (4.7)

Data shown as n (%). *p-value for trend across categories < 0.05. PLMAI, periodic limb movement arousal index; PLMI, periodic limb movement index.

Adjusted Associations: Atrial Arrhythmias

Among the atrial arrhythmias including premature atrial contractions, atrial fibrillation and supraventricular tachycardia, no significant associations were seen with PLMI or PLMAI after adjustment for multiple covariates (**Table 3**). For the outcome of AF, there were significant interactions between history of CHF or MI and both PLMI (p = 0.03) and PLMAI (p = 0.01); consequently stratification of the cohort by cardiac history was conducted. Among 532 men with CHF or myocardial infarction, after full adjustment there was a suggestion of association with AF and PLMI (OR = 1.29, 95% CI 0.96, 1.73 per SD increase; p = 0.09) and PLMAI (OR = 1.21, 95%

Table 3—Associations of PLMI and PLMAI to prevalent nocturnal ventricular arrhythmia

	Model 1*	Model 2**	Fully Adjusted***
Ventricular			
PLMI (per SD increase = 37.2)			
≥ 5 premature ventricular contractions/h	1.05 (0.97, 1.14)	1.06 (0.98, 1.14)	1.05 (0.97, 1.14)
Non-sustained ventricular tachycardia	1.20 (0.99, 1.45)	1.20 (0.99, 1.45)	1.19 (0.98, 1.45)
Complex ventricular ectopy	1.05 (0.97, 1.14)	1.06 (0.98, 1.15)	1.06 (0.98, 1.15)
PLMAI (per SD increase = 5.7)			
≥ 5 premature ventricular contractions/h	1.00 (0.92, 1.08)	0.99 (0.91, 1.07)	0.98 (0.91, 1.07)
Non-sustained ventricular tachycardia	1.17 (0.99, 1.39)	1.17 (0.99, 1.39)	1.18 (1.00, 1.41)
Complex ventricular ectopy	0.98 (0.90, 1.06)	0.97 (0.89, 1.05)	0.97 (0.89, 1.05)
Atrial			
PLMI (per SD increase = 37.2)			
≥ 5 premature atrial contractions/h	1.07 (0.98, 1.16)	1.07 (0.99, 1.16)	1.07 (0.99, 1.16)
Atrial fibrillation	1.04 (0.88, 1.23)	1.05 (0.88, 1.24)	1.06 (0.89, 1.26)
Supraventricular tachycardia	0.97 (0.89, 1.06)	0.97 (0.89, 1.06)	0.98 (0.89, 1.07)
PLMAI (per SD increase = 5.7)			
≥ 5 premature atrial contractions/h	1.02 (0.94, 1.11)	1.01 (0.93, 1.10)	1.01 (0.93, 1.10)
Atrial fibrillation	1.01 (0.85, 1.19)	0.99 (0.84, 1.17)	1.00 (0.84, 1.18)
Supraventricular tachycardia	0.95 (0.87, 1.04)	0.94 (0.85, 1.03)	0.94 (0.86, 1.03)
Conduction Delay			
PLMI (per SD increase = 37.2)			
Sinus pause (≥ 3 sec)	1.08 (0.97, 1.20)	1.08 (0.97, 1.20)	1.07 (0.96, 1.20)
First degree atrioventricular block	1.07 (0.99, 1.15)	1.06 (0.98, 1.15)	1.06 (0.98, 1.14)
PLMAI (per SD increase = 5.7)			
Sinus pause (≥ 3 sec)	1.09 (0.98, 1.20)	1.09 (0.99, 1.21)	1.09 (0.99, 1.21)
First degree atrioventricular block	1.11 (1.02, 1.19)	1.12 (1.04, 1.21)	1.12 (1.03, 1.21)

Data shown as odds ratio (95% confidence interval). *Adjusted for clinic site, age, race, and BMI. **Adjusted for clinic site, age, race, BMI, smoking, alcohol use, physical activity, and AHI. ***Adjusted for clinic site, age, race, BMI, smoking, alcohol use, physical activity, AHI, prevalent hypertension, history of coronary heart disease, history of diabetes, history of congestive heart failure, and β-blocker or calcium channel blocker use. PLMAI, periodic limb movement arousal index; PLMI, periodic limb movement index.

CI 0.94, 1.57 per SD increase; p = 0.14), although results did not reach statistical significance (**Figure 2**).

Adjusted Analyses: Conduction Delay Arrhythmias

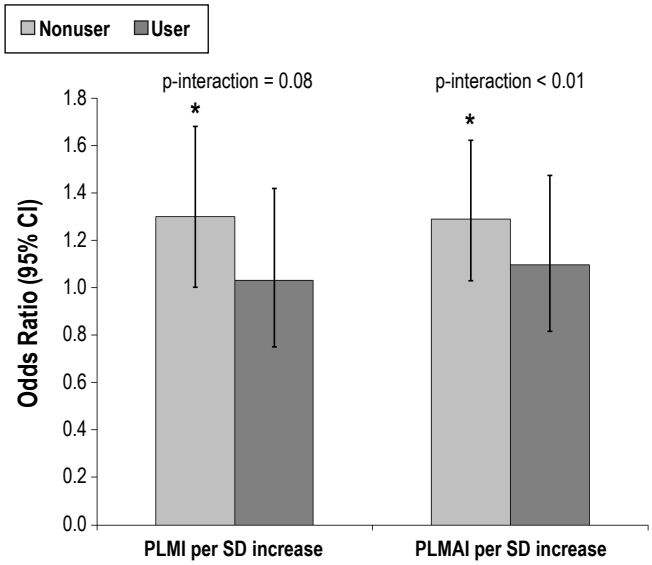
Among the conduction delay arrhythmias, first degree AV block was associated with PLMAI in minimally and fully adjusted models such that for every SD increase in PLMAI, the odds of having first-degree AV block increased by 12% (OR 1.12, 95% CI 1.03, 1.21 per SD increase; **Table 3**). This association became statistically nonsignificant when subjects taking calcium channel or β-adrenergic blocking medication were excluded. For sinus pause arrhythmia, neither PLMI nor PLMAI was significantly associated with increased risk after minimal or full multivariable adjustment. There was a significant interaction between history of CHF or MI and PLMAI (p = 0.02). In the subset of men with CHF or MI, increases in PLMAI were associated with increasing odds of having sinus pauses (OR = 1.27, 95% CI 1.03, 1.58 per SD increase) after full multivariable adjustment.

DISCUSSION

In this community sample of older men, PLMS frequency with and without arousal was not associated with ventricular, atrial or conduction delay cardiac arrhythmia after considering a broad set of potential confounders. Because of the potential role of sympathetic hyperactivity on arrhythmia propensity, we explored interactions between PLMS with markers of both structural heart disease and use of calcium channel or β-adrenergic blocking medication. Among men without calcium channel/β-adrenergic medication usage, incremental increases in the PLMI or PLMAI were associated with a significantly increased odds ratio for NSVT. Among men with a history of CHF or prior MI, incremental increases in PLMI or PLMAI also were associated with increases in the odds of having AF, although the results only approached statistical significance. These findings, although based on subgroup analyses, suggest that PLMS are associated with AF among men with underlying structural heart disease and NSVT among men not using calcium channel or β-blocker medications. Overall, these findings are not consistent with association between PLMS and cardiac arrhythmia in all older men but there may be subsets of men, particularly those with structural heart disease and not on calcium channel or β-adrenergic medication, in which cardiac arrhythmia does seem to associate with PLMS.

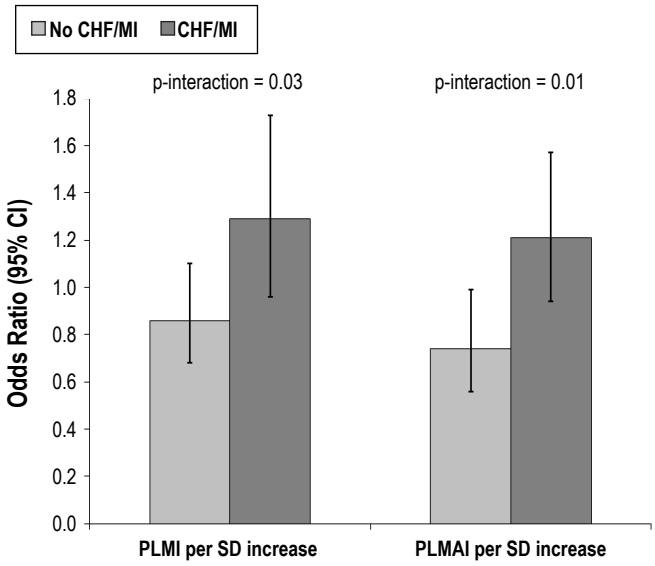
In general, a normal cardiac rhythm is maintained by a tightly regulated balance of sympathetic and vagal tone. Ventricular arrhythmia is associated with increased sympathetic activity.[24,25] Atrial arrhythmia and in particular atrial fibrillation may be triggered by vagal activation, although sympathetic

Figure 1—Non-sustained ventricular tachycardia outcome: interaction of PLMS and use of β-adrenergic or calcium channel blocking medication



In subjects not using β-adrenergic or calcium channel blocking medications, there was significantly increased odds of NSVT associated with PLMI (OR 1.30 per SD increase; 95% CI 1.00, 1.68) and PLMAI (OR 1.29 per SD increase; 95% CI 1.03, 1.62). Adjusted for clinic site, age, race, BMI, smoking, alcohol use, physical activity, AHI, prevalent hypertension, history of coronary heart disease, history of diabetes, history of congestive heart failure.*p-value < 0.05 NSVT, non-sustained ventricular tachycardia; OR, odds ratio; PLMAI, periodic limb movement arousal index; PLMI, periodic limb movement index; SD, standard deviation.

Figure 2—Atrial fibrillation outcome: interaction of PLMS and history of CHF or MI



For those subjects with structural heart disease, CHF or MI, there was a suggestion of an association with AF and PLMI (OR = 1.29, 95% CI 0.96, 1.73 per SD increase; p = 0.09) and PLMAI (OR = 1.21, 95% CI 0.94, 1.57 per SD increase; p = 0.14), although results did not reach statistical significance. Adjusted for clinic site, age, race, BMI, smoking, alcohol use, physical activity, AHI, prevalent hypertension, history of coronary heart disease, history of diabetes, and β-blocker or calcium channel blocker use. CHF, congestive heart failure; OR, odds ratio; MI, myocardial infarction; PLMAI, periodic limb movement arousal index; PLMI, periodic limb movement index.

hyperactivity may be involved when there is structural heart disease.[26] Both sympathetic and parasympathetic nervous activity are likely hyperactive in patients with PLMS. Typically, heart rate begins to accelerate 2-3 cardiac cycles before a PLM, peaks 4-5 cycles following a PLM, and falls below pre-movements rates 8-10 cycles after a PLM.[7] Consistent with this observation, measurement of heart rate variability in the setting of PLMS demonstrates both vagal and sympathetic activation with predominance of sympathetic activity.[27] These changes in autonomic tone as they pertain to cardiac arrhythmia may be most pertinent in men with PLMS when there is structural heart disease or in the absence of anti-arrhythmic medication.

In the primary analysis of the entire cohort, there was not an association between PLMS frequency and ventricular, atrial or conduction delay cardiac arrhythmia. In the cohort of men not taking calcium channel or β-adrenergic blocking medication, ventricular arrhythmia in the form of NSVT occurred at higher frequencies as both PLMI and PLMAI increased. In the cohort of men with CHF or MI, atrial arrhythmia in the form of AF was more likely and approached statistical significance with greater PLMI or PLMAI. It is important to interpret these findings cautiously, as they are produced from secondary analyses; however, the analyses were formulated based upon biological plausibility and were carried out a priori with these mechanisms in mind. These associations are consistent with the notion that when PLMS are either frequent or associated with arousal, sympathovagal responses may be sufficiently enhanced to contribute to atrial and ventricular arrhythmia in subsets of men at risk for having cardiac arrhythmia.

As the association of PLMS and arrhythmia was conducted on cross-sectional data, there is no information regarding directionality. It is tempting to assert that PLMS confers risk for arrhythmia and still certainly possible, but it is also conceivable that arrhythmia confers risk for PLMS or that both arrhythmia and PLMS arise from derangement in a similar system, like the autonomic nervous system. Justification for the first scenario is provided above. The middle scenario would likely make PLMS little more than a marker for cardiac disease. The last assumption that PLMS and arrhythmia arise from a similar abnormality is a very real possibility. It is clear that autonomic dysfunction in both sympathetic and parasympathetic arms of the nervous system increases risk for cardiac arrhythmia. The sympathetic nervous system extends from the thoracic to the lumbar spinal cord, while the parasympathetic system lies within the brainstem and sacral spinal cord. PLMS are also likely to arise from a spinal generator, and hyperexcitability within these spinal localizations could certainly result in abnormal limb movements as has been posited by previous investigators.[28,29]

Sleep disordered breathing is an important potential confounding factor to discuss as it relates to PLMS and is an independent risk factor for cardiac arrhythmia.[19,30] Although the relationship between PLMS and sleep disordered breathing is not clear, PLMS is common among patients with obstructive sleep apnea.[31] Furthermore, increased upper airway resistance

has been shown to coincide with PLMS.[32] In our study, the apnea-hypopnea index was included in models as a covariate to control for potential confounding related to sleep apnea. If, however, there are features related to sleep disordered breathing such as increased airway resistance not reflected in the AHI, then such a statistical adjustment may not completely account for potential confounding. Unfortunately, analyses of participants with low AHI to further explore potential confounding by sleep disordered breathing could not be carried out secondary to low arrhythmia event rates in this subset of men.

Strengths of the current study include analysis of a large community-dwelling sample of elderly men, not chosen according to predilection for PLMS or cardiac disease, allowing generalizability to other samples of older men. Data were collected and scored using highly standardized criteria with scorers blinded to PLMS status. Adjustment for multiple potential confounders including cardiovascular risk factors and sleep related variables allowed for careful consideration of potential confounders and interactions. Limitations of the study include the cross-sectional nature of the study and the absence of multiple-day Holter monitoring data to fully describe patterns of cardiac arrhythmias. Piezoelectric sensors and not the standard anterior tibialis electromyography were used to measure PLMS. Finally, the most significant findings were observed in secondary analyses of groups identified to be potentially subject to different levels of susceptibility to altered sympathovagal balance. Although such findings could be spurious, they represent analyses derived from a priori hypotheses that are well supported by the known clinical and physiological associations between sympathetic nervous system activity and cardiac electrical activity and are internally consistent.

In summary, PLMS are not associated with cardiac arrhythmia in a general cohort of older men. PLMS are associated with arrhythmia in subsets of older men otherwise vulnerable to the cardiac electrical instability; i.e., those with underlying structural heart disease and those not using calcium channel/β-blocking medication. Although a causal role for PLMS in the pathogenesis of arrhythmias requires prospective and/or intervention studies, these results suggest that patients with underlying heart disease or not taking calcium channel/β-blocking medication may have increased rates of cardiac arrhythmias when PLMS are present.

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