Periodic Limb Movements during Sleep and Prevalent Hypertension in the Multi-Ethnic Study of Atherosclerosis

Brian B. Koo, Stefan Sillau, Dennis A. Dean II, Pamela L. Lutsey, Susan Redline

Abstract—Periodic limb movements during sleep (PLMS) are associated with immediate increases in blood pressure. Both PLMS and hypertension have different distributions across racial/ethnic groups. We sought to determine whether PLMS is associated with hypertension among various racial/ethnic groups. A total of 1740 men and women underwent measurement of blood pressure and polysomnography with quantification of PLMS. Hypertension was defined as systolic blood pressure (SBP) ≥140, diastolic BP ≥90, or taking antihypertensive medication. For those taking antihypertensives, an estimated pretreatment SBP value was derived based on observed SBP and medication type/dose. Measures of PLMS, PLMS index, and PLMS arousal index were the main explanatory variables. Hypertension and SBP were modeled with logistic and multivariable regression adjusted for age, sex, body mass index, cardiovascular risk factors, lifestyle/habitual factors, apnea-hypopnea index, and race/ethnicity. In the overall cohort, prevalent hypertension was modestly associated with PLMS index (10 U; odds ratio, 1.05; 95% confidence interval, 1.00–1.10) and PLMS arousal index (1 U; 1.05; 1.01–1.09) after adjusting for confounders. Association in the overall cohort was influenced by large effect sizes in blacks, in whom the odds of prevalent hypertension increased by 21% (1%–45%) for 10 U PLMS index increase and 20% (2%–42%) for 1-U PLMS arousal index increase. In blacks, every 1-U PLMS arousal index increase was associated with SBP 1.01 mm Hg higher (1.01; 0.04–1.98). Associations between PLMS and blood pressure outcomes were also suggested among Chinese-Americans but not in whites or Hispanics. In a multiethnic cohort of community-dwelling men and women, prevalent hypertension and SBP are associated with PLMS frequency in blacks. (Hypertension. 2015;65:70-77. DOI: 10.1161/HYPERTENSIONAHA.114.04193.)

Key Words: blood pressure □ continental population groups □ ethnicity □ hypertension □ PLMS

Periodic limb movements during sleep (PLMS) are repetitive, forceful contractions of leg and foot muscles often associated with arousal from sleep, affecting 7.6% of middle-aged adults and 45% of community-dwelling elderly.1,2 The motor phenomenon of PLMS not only occurs in ≤80% of patients having the neurosensory condition, restless legs syndrome (RLS) but also can occur in those with hypertension and even in the normal elderly.3–5 Once thought to be primarily a sleep-related peculiarity, PLMS recently has been recognized as associated with cardiovascular disease, at least in elderly and health-compromised populations.5–7 Pathophysiologic mechanisms that link PLMS and cardiovascular disease are not well understood, but hypertension may play a role. Individual movements of a PLM cluster are associated with discrete elevations in blood pressure on the order of 20 systolic and 10 diastolic mm Hg.8,9 When considering daytime hypertension, there is no clear association with PLMS; however, this question has not been studied adequately.

Hypertension itself is a robust predictor of cardiovascular disease across all ages and racial/ethnic groups.10 Meta-analyses of blood pressure-lowering trials suggest that reduction of heighten ed blood pressure by 10 mm Hg systolic decreases incident coronary heart disease by one fifth and cerebrovascular disease by one third.11 For this reason, it is important to identify secondary causes of hypertension, which can be treated to optimize blood pressure and cardiovascular risk.

There is racial/ethnic variation in the prevalence of PLMS, RLS, and hypertension. PLMS occurs in ≤9% of middle-aged European-Americans, and 4% of similarly aged blacks.1,12 RLS is most common in whites, intermediate in Mexican-Hispanics, and least common in Sub-Saharan Africans.13,14 Conversely, hypertension affects 60% of blacks, 44% of Hispanic-Americans, and 42% of white-Americans.15 For these reasons, it is important to examine the association between PLMS and hypertension in a multiethnic population and to determine whether either race/ethnicity or RLS influences this association.

To address whether PLMS is associated with hypertension, we analyzed data from the Multi-Ethnic Study of Atherosclerosis (MESA) Sleep ancillary study. MESA is a large US population-based study of white, black, Hispanic, and Chinese adults, designed to examine racial/ethnic, age, and sex variation in cardiovascular outcomes. Recently, a subset of MESA participants underwent comprehensive sleep assessment in the MESA Sleep ancillary study. Using these data, we tested our hypothesis that frequency of PLMS with and without arousal would be cross-sectionally associated...
with daytime hypertension and blood pressure. We also explored whether race/ethnicity or RLS modified any relationship between PLMS and hypertension.

Methods

Study Population

The MESA prospective cohort includes 6814 men and women (45–64 years at baseline) initially recruited in 2000 to 2002 from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; Manhattan, NY; and St. Paul, MN). The primary objective of MESA is to investigate risk factors for cardiovascular disease in a racially/ethnically diverse community population, free of cardiovascular disease at baseline.16 Five clinic examinations have taken place, the most recent occurring between 2010 and 2011, being attended by 4716 original MESA participants. Of these individuals, 4077 were approached shortly after the fifth clinic examination to take part in the MESA Sleep ancillary study, of which 2060 participated. When compared with participants in MESA examination 5 who did not undergo the sleep examination, participants in the sleep examination were slightly younger (68.4 versus 71.0 years), less likely to be white (36.1% versus 44.5%), and less likely to be smokers (7.1% versus 8.4%). However, they were comparable in regards with sex, body mass index (BMI), physician diagnosed sleep apnea, asthma, diabetes mellitus, and previous myocardial infarction. Institutional review board index (BMI), physician diagnosed sleep apnea, asthma, diabetes mel-

Sensitivity analyses were performed with the exposure variables in 4 groups: <$25 000 per year, $25 000 to $39 999 per year, $40 000 to 74 000 per year, and >$75 000 per year. Physical activity was assessed using the MESA Typical Week Physical Activity Survey. Reported time spent performing several physical tasks in a typical week were multiplied by the metabolic equivalent level and summed to create a physical activity score.24 Waist:hip ratio was calculated as waist circumference/hip circumference, and BMI as weight(kg)/height(m)2.

RLS was assessed with 1 main question and 3 additional subquestions. The main question was (1) Do you ever experience a desire to move your legs because of discomfort or disagreeable sensations in your legs? Three subquestions were answered only if the response to this main question was yes. The subquestions were (1a) Do you sometimes feel the need to move to relieve the discomfort, for example, by walking, or rubbing your legs? (1b) Are these symptoms worse when you are at rest, with at least temporary relief by activity? (1c) Are these symptoms worse later in the day or at night? Response choices to each of the 4 questions were identical: no, yes, and don’t know. Participants were considered to have RLS only if all 4 questions were answered yes.

Statistical Analysis

Participant characteristics were compared across PLMI and PLMAI categories using χ2 tests for categorical variables and ANOVA for continuous variables. The effects of PLMI and PLMAI on the odds of hypertension were analyzed using multiple logistic regression; results are presented as odds ratios with 95% confidence intervals. Odds of hypertension were presented for every 10 U of PLMI and 1 U of PLMAI, reflecting meaningful changes across the relevant distribution of these variables. Multivariable regression modeled SBPimputed and DBPimputed; SBPmeasured and DBPmeasured was considered as an outcome in sensitivity analysis among those not taking antihypertensive medication. PLMI and PLMAI were treated both as continuous and as categorical variables. Covariates were added to the models in stages: unadjusted, minimally adjusted, and fully adjusted. Minimally adjusted models controlled for sex, age, and BMI. Fully adjusted models added race/ethnicity, education, income, smoking status, alcohol use, atrial fibrillation, diabetes mellitus, depression scale, physical activity scale (log transform), apnea-hypopnea index, and arousal index.

Polysomnography

Between 2010 and 2013, unattended in-home polysomnography was conducted using the Compumedics Somte System (Compumedics, Abbotsford, Australia) with recording of 3 EEG channels (C3-M1, O1-C3, and F4-C4), bilateral electrooculogram, chin EMG, thoraco-abdominal respiratory inductance plethysmography; airflow (nasal-oral thermocouple and nasal pressure transduction); ECG, bilateral leg movements (piezoelectric sensors), and finger pulse oximetry. Recordings were transmitted to the Brigham and Women’s centralized reading center, and data were scored by trained technicians using standardized criteria.17,18 Apneas were identified by near absence of airflow for ≥10 s. Hypopneas were identified by ≥30% breathing amplitude reduction lasting for ≥10 s when followed by ≥2% oxygen desaturation or arousal. The apnea-hypopnea index was calculated as the total number of apneas and hypopneas per hour of sleep. Arousals were scored when EEG frequency increased ≥3 s and were summarized as the total number of arousals per hour of sleep (arousal index). Individual leg movements were scored if there was a clear amplitude increase from baseline and lasted for 0.5 to 5 s. To be considered periodic, a minimum of 4 movements needed to occur in succession 5 to 90 s apart.19 Leg movements after respiratory events were excluded unless they were part of a 4 (or more) movement cluster with ≥2 movements occurring independently of respiratory events. Computed were periodic limb movement index (PLMI), total number of periodic leg movements per hour of sleep; and periodic limb movement arousal index (PLMAI), total number of periodic leg movements per hour of sleep in which arousal occurred within 3 s of the PLM. Inter-and intrascore reliability for PLMI was high (intraclass correlation coefficients, 0.93–0.98).

Exposure and Outcome Data

The main exposure variables were PLMI and PLMAI, which were examined continuously in logistic and linear multivariable models. Sensitivity analyses were performed with the exposure variables in categories; PLMI: (1) <5, (2) ≥5 and <30, and (3) ≥30 and PLMAI: (1) <1, (2) ≥1 and ≤5, and (3) ≥5.

Blood pressure was based on measurements from MESA examination 5, which occurred a median of 300 days before polysomnography. Blood pressure was measured in triplicate at 2-minute intervals using an automated oscillometric device (Dinamap MonitorPro 100; GE Healthcare, Milwaukee, WI). The second and third readings were averaged to yield systolic (SBPmeasured) and diastolic blood pressure (DBPmeasured). Antihypertensive drug use was determined by medication inventory. Antihypertensive drug classes included β-blockers, diuretics, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, α-blockers, calcium channel blockers, or other peripheral vasodilators. Prevalent hypertension was considered if a participant was taking antihypertensive medication or if Joint National Committee VII hypertension criteria (SBP≥140 or DBP≥90) were met.19 A large proportion of participants were taking antihypertensive medications. For these participants, we estimated pretreatment blood pressure values using previously described methods,20,21 In brief, the blood pressure imputation model was derived from before and after blood pressures from a subset of new antihypertensive drug users, and included data were on-treatment blood pressures, age, sex, race/ethnicity, BMI, diabetes mellitus, total and high-density lipoprotein cholesterol, smoking, antihypertensive medication class, and 2-way interactions between sex, race/ethnicity, and medication type. From these procedures, 10 imputed blood pressure data sets were created and averaged separately for SBP and DBP to yield SBPimputed and DBPimputed, respectively.

Covariate Data

Other information was also collected during MESA clinic examination 5. Questionnaires documented information on demographics, medical history, medication use, physical activity, education, income, depression, atrial fibrillation, diabetes mellitus, smoking, and alcohol use. Diabetes mellitus was defined by fasting glucose ≥126 mg/dL or medical treatment with insulin/oral hypoglycemic.22 Depression symptoms were measured using the Center for Epidemiologic Studies Depression scale.23 Smoking status was categorized as never, former, and current. Alcohol use was categorized as current or not current. Education was categorized into 3 groups: high school or less, some college, and bachelors/graduate degree. Income was categorized into 4 groups: <$25 000 per year, $25 000 to $39 999 per year, $40 000 to 74 000 per year, and >$75 000 per year. Physical activity was assessed using the MESA Typical Week Physical Activity Survey. Reported time spent performing several physical tasks in a typical week were multiplied by the metabolic equivalent level and summed to create a physical activity score.24 Waist:hip ratio was calculated as waist circumference/hip circumference, and BMI as weight(kg)/height(m)2.

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To allow for the possibility of different effects by race/ethnicity, the unadjusted and minimally adjusted models were stratified by race/ethnicity through interaction terms. The sample sizes in some races/ethnicities were not large enough to accommodate fully adjusted stratified models, so only PLMI/PLMAI and minimally adjusting covariates were allowed racial/ethnic heterogeneity. The effects of the other covariates in the full model were combined over the different races/ethnicities. For the continuous responses, the residual variance was allowed to differ by race/ethnicity, and Satterthwaite denominator degrees of freedom were used for $T$ and $F$ tests. The interaction terms between PLMI/PLMAI and race/ethnicity were jointly tested for statistical significance to determine whether race/ethnicity modified the relationship between PLMI/PLMAI and the response. To determine whether RLS was associated with hypertension, multiple logistic regression was performed with RLS diagnosis as the main exposure variable both with and without PLMI or PLMAI in the models.

### Results

#### Overall Characteristics

A total of 1740 participants had a mean age of 68.3±9.1 years and 46.0% (n=801) were men. Table 1 shows demographic, anthropomorphic, and health characteristics of the overall cohort and the cohort stratified by PLMI and PLMAI categories. Participants in high when compared with low PLMI and PLMAI categories were older with no difference in BMI. The majority of participants fall in the lowest PLMI and PLMAI categories; 16.8% with PLMI≥30 and 9.1% with PLMAI≥5. Participants with hypertension were disproportionately represented in the PLMI≥30 and PLMAI≥5 groups (Table 1). Having PLMI≥30 was equally prevalent in whites, Hispanics,
and Chinese-Americans, affecting 18.8%, 20.1%, and 19.1%, respectively, but less prevalent in blacks (10.5%). Having PLMAI≥5 in Chinese-American, white, Hispanic, and black groups was 12.1%, 11.4%, 8.3%, and 5.6%, respectively.

**Models for Hypertension**

Approximately 60% of the overall cohort was hypertensive (Table 1). As shown in Table 2, the unadjusted frequencies of hypertension differed significantly among races/ethnicities with blacks having highest and Chinese-Americans having lowest frequencies (P<0.0001). When subset to race/ethnicity, prevalence of hypertension increased with increasing PLMI or PLMAI category in Chinese-Americans but not in other groups (Table 2).

For the overall cohort, PLMI, considered as a continuous index, showed a weak association with hypertension in unadjusted analyses (Table 3). When stratifying by race/ethnicity, there were associations between PLMI and hypertension in unadjusted models for blacks, Chinese-Americans, and whites (Table 3), which were also apparent when hypertension frequency was examined by PLMI category (Table 2). In adjusted analyses, the association between PLMI and hypertension persisted only in blacks in whom every increase of PLMI by 10 U was associated with a 21% increased odds of hypertension (odds ratio, 1.21; 95% confidence interval 1.01,1.45; P=0.02; Table 3). The P value for interaction of race and PLMI was 0.19.

For PLMAI modeled continuously in the overall cohort, there were significant associations between PLMAI and hypertension in unadjusted and fully adjusted models (Table 3). In race/ethnicity-specific models, there were significant associations between PLMAI and hypertension for blacks, Chinese-Americans, and whites (Table 3), which were also apparent when hypertension frequency was examined by PLMAI category (Table 2). In adjusted analyses, the association between PLMAI and hypertension persisted only in blacks in whom every increase of PLMAI by 1 unit was associated with a 21% increased odds of hypertension (odds ratio, 1.21; 95% confidence interval 1.01,1.45; P=0.02; Table 3). The P value for interaction of race and PLMAI was 0.19.

**Table 2. Hypertension by PLMI/PLMAI Category and Race/Ethnicity**

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>Overall (n=1740)</th>
<th>PLMI&lt;5 (n=1001)</th>
<th>5≤PLMI&lt;30 (n=446)</th>
<th>PLMI≥30 (n=293)</th>
<th>P Value</th>
<th>PLMAI&lt;1 (n=1218)</th>
<th>1≤PLMAI&lt;5 (n=364)</th>
<th>PLMAI≥5 (n=158)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP measured mm Hg</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>122.4±19.8</td>
<td>125.2±19.8</td>
<td>120.0±19.4</td>
<td>124.0±20.1</td>
<td>0.07</td>
<td>122.3±19.8</td>
<td>121.6±18.7</td>
<td>125.5±21.6</td>
<td>0.10</td>
</tr>
<tr>
<td>Black</td>
<td>126.4±19.2</td>
<td>125.7±19.1</td>
<td>126.4±19.3</td>
<td>130.6±19.8</td>
<td>0.23</td>
<td>126.0±19.2</td>
<td>125.3±17.5</td>
<td>134.4±21.5</td>
<td>0.08</td>
</tr>
<tr>
<td>White</td>
<td>119.6±19.2</td>
<td>120.1±19.6</td>
<td>118.7±18.7</td>
<td>121.6±18.8</td>
<td>0.20</td>
<td>119.6±19.5</td>
<td>119.2±19.2</td>
<td>120.9±17.4</td>
<td>0.83</td>
</tr>
<tr>
<td>Hispanic</td>
<td>123.1±20.1</td>
<td>123.9±20.5</td>
<td>121.8±19.4</td>
<td>124.4±19.8</td>
<td>0.62</td>
<td>123.1±20.6</td>
<td>123.4±17.9</td>
<td>122.1±21.8</td>
<td>0.94</td>
</tr>
<tr>
<td>Chinese-American</td>
<td>120.2±20.7</td>
<td>116.7±19.2</td>
<td>121.5±20.2</td>
<td>129.2±23.0</td>
<td>0.004</td>
<td>117.4±18.6</td>
<td>121.1±19.6</td>
<td>134.6±27.3</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

**Diastolic BP measured mm Hg**

| Overall                    | 68.1±9.9        | 68.5±9.7        | 67.3±9.9          | 67.8±10.4       | 0.09   | 68.2±9.7        | 67.6±10.0         | 68.2±10.7       | 0.51   |
| Black                      | 69.7±9.7        | 70.1±9.6        | 69.5±9.1          | 67.5±11.0       | 0.19   | 68.9±9.5        | 68.3±9.7          | 70.6±11.3       | 0.43   |
| White                      | 66.8±9.8        | 67.0±9.6        | 66.0±9.9          | 67.4±10.0       | 0.40   | 66.6±9.8        | 67.3±9.8          | 66.4±9.7        | 0.68   |
| Hispanic                   | 68.0±10.1       | 68.5±9.4        | 67.5±11.3         | 67.5±10.4       | 0.62   | 68.2±9.7        | 67.8±10.8         | 67.0±11.6       | 0.74   |
| Chinese-American           | 68.4±9.8        | 68.1±10.2       | 68.0±7.7          | 69.0±10.8       | 0.58   | 68.3±9.7        | 66.7±9.5          | 72.1±10.3       | 0.11   |

**Diastolic BP imputed mm Hg**

| Overall                    | 129.8±19.6      | 129.1±19.6      | 129.3±20.1        | 133.2±18.8      | 0.08   | 129.2±19.8      | 129.6±18.6        | 135.0±20.2      | 0.08   |
| Black                      | 135.6±17.2      | 134.5±17.1      | 136.2±17.8        | 142.2±15.1      | 0.21   | 135.0±17.3      | 136.3±15.4        | 143.7±17.1      | 0.29   |
| White                      | 126.1±19.7      | 125.4±19.7      | 125.6±20.8        | 128.7±17.7      | 0.56   | 125.5±20.2      | 126.2±19.2        | 129.5±18.6      | 0.58   |
| Hispanic                   | 130.1±19.7      | 129.7±20.4      | 129.0±18.3        | 132.6±19.2      | 0.68   | 129.4±20.1      | 131.0±17.4        | 134.0±19.6      | 0.58   |
| Chinese-American           | 126.7±21.5      | 122.2±20.0      | 130.2±22.4        | 136.2±21.4      | 0.02   | 123.0±19.6      | 129.8±21.3        | 143.0±24.2      | 0.01   |

Diastolic BP imputed indicates imputed diastolic blood pressure; diastolic BP measured indicates measured diastolic blood pressure; PLMAI, periodic limb movement arousal index; PLMI, periodic limb movement index; systolic BP imputed indicates imputed systolic blood pressure; and systolic BP measured indicates measured systolic blood pressure.
Chinese-Americans, and whites (Table 3). After full adjustment for multiple potential confounders, a significant relationship between PLMAI and hypertension remained only for blacks in whom a 1-U PLMAI increase was associated with a 20% increased odds of hypertension (1.20; 1.02–1.42; P=0.005). In Chinese-Americans, there was a marginal association between PLMAI and hypertension after adjusting for multiple confounders; for every 1-U PLMAI increase, the odds of hypertension increased 10% (P=0.08). The P value for interaction of race/ethnicity and PLMAI for hypertension was 0.07.

When modeling PLMI and PLMAI as categorical exposures, similar although less significant associations were observed when compared with models using continuous exposure variables. Associations were strongest in blacks (data not shown). When considering a potential relationship between RLS symptoms and hypertension (without PLMI or PLMAI), there was no association between RLS symptoms and hypertension (unadjusted 1.23; 0.98–1.55; P=0.07), minimally adjusted (1.21; 0.95–1.55; P=0.07), or fully adjusted models (1.15; 0.89–1.49; P=0.30).

### Systolic Blood Pressure

In the overall cohort, SBP<sub>imputed</sub> was associated with PLMI and PLMAI only in unadjusted models (Table 4). In models adjusted fully for multiple potential confounders, neither PLMI nor PLMAI was associated with SBP<sub>imputed</sub> in whites, Hispanics, or Chinese-Americans (Table 4). In blacks, there was a significant association between PLMAI and SBP<sub>imputed</sub>; for every 1-U PLMAI increase, SBP<sub>imputed</sub> was 1.01 mm Hg higher. Also in blacks, there was a marginal but nonsignificant association between PLMI and SBP<sub>imputed</sub> (P=0.09). The P value for interaction of race and PLMAI when considering SBP<sub>imputed</sub> was 0.27.

Mean SBP<sub>imputed</sub> differed significantly among the races, with blacks having the highest and whites the lowest values (P<0.0001; Table 2). In the overall cohort, SBP<sub>imputed</sub> was highest in both PLMI≥30 and PLMAI≥5 groups, but these differences were not statistically significant. SBP<sub>imputed</sub> was significantly different among PLMI (P=0.02) or PLMAI (P=0.01) categories only in Chinese-Americans, where high PLMI or PLMAI category was associated with highest SBP<sub>imputed</sub> (Table 2). There was a trend toward increased SBP<sub>imputed</sub> in higher PLMAI categories for blacks.

In sensitivity analysis restricted to those not taking antihypertensive medication (n=802), SBP<sub>measured</sub> was associated with both PLMAI and PLMI after considering multiple potential confounders in blacks and Chinese-Americans. In blacks for every 10-U PLMAI increase, SBP<sub>measured</sub> was 2.47 mm Hg higher (1.25–3.69; P<0.0001); and for every 1-U PLMAI increase, SBP<sub>measured</sub> was 3.71 mm Hg higher (1.69–5.72; P=0.0004).

In Chinese-Americans, for every 10-U increase in PLMI, SBP<sub>measured</sub> was 1.31 mm Hg higher (0.13–2.50; P=0.03); and for every 1-U increase in PLMAI, SBP<sub>measured</sub> was 1.45 mm Hg higher (0.17–2.72; P=0.03).

### Diastolic Blood Pressure

Mean imputed DBP (DBP<sub>imputed</sub>) differed significantly among the races/ethnicities with blacks having the highest and whites the lowest values (P<0.0001; Table 2). DBP<sub>imputed</sub> did not differ according to PLMI or PLMAI category (Table 1) in the overall cohort or cohort stratified by race/ethnicity. DBP<sub>measured</sub> in the overall cohort was not associated with PLMI or PLMAI in unadjusted or adjusted models (data not shown).
In race-ethnicity-specific models of DBP_{imputed}, there was no significant association with PLMI or PLMAI in any race/ethnicity group, but there were marginal associations in both blacks and Chinese-Americans. In blacks, after adjusting for multiple confounders, DBP_{imputed} was associated with PLMI; every 10-U increase, DBP_{imputed} was 1.26 mm Hg higher (−0.21 to 0.96; 0.09). In sensitivity analysis, for Chinese-Americans after adjusting for multiple confounders, every 1-U PLMAI increase, DBP_{imputed} was 1.01 (−0.69 to 2.71) 0.24.

### Table 4. Linear Regression of Imputed Systolic Blood Pressure By Periodic Limb Movements Indices

<table>
<thead>
<tr>
<th>Group</th>
<th>Systolic Blood Pressure; Estimate (95% Confidence Interval)</th>
<th>Unadjusted</th>
<th>P Value</th>
<th>Minimally Adjusted</th>
<th>P Value</th>
<th>Fully Adjusted</th>
<th>P Value</th>
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<tbody>
<tr>
<td>PLMI (10 U)</td>
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<td>By race</td>
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<tr>
<td>Overall</td>
<td>0.65 (0.00 to 1.30)</td>
<td>0.05</td>
<td>0.09</td>
<td>(−0.51 to 0.70)</td>
<td>0.70</td>
<td>0.08 (−0.28 to 0.87)</td>
<td>0.87</td>
</tr>
<tr>
<td>Black</td>
<td>1.53 (0.06 to 2.99)</td>
<td>0.04</td>
<td>1.05</td>
<td>(−0.39 to 2.50)</td>
<td>0.051</td>
<td>1.26 (−0.21 to 2.73)</td>
<td>0.09</td>
</tr>
<tr>
<td>White</td>
<td>0.54 (−0.39 to 1.47)</td>
<td>0.25</td>
<td>−0.07</td>
<td>(−0.98 to 0.84)</td>
<td>0.72</td>
<td>−0.08 (−0.98 to 0.82)</td>
<td>0.86</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.35 (−0.88 to 1.58)</td>
<td>0.57</td>
<td>−0.22</td>
<td>(−1.39 to 0.96)</td>
<td>0.052</td>
<td>−0.21 (−1.39 to 0.96)</td>
<td>0.71</td>
</tr>
<tr>
<td>Chinese-American</td>
<td>2.23 (0.41 to 4.05)</td>
<td>0.02</td>
<td>1.04</td>
<td>(−0.65 to 2.73)</td>
<td>0.07</td>
<td>1.01 (−0.69 to 2.71)</td>
<td>0.24</td>
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<tr>
<td>PLMAI (1 U)</td>
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<td>By race</td>
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<tr>
<td>Overall</td>
<td>0.52 (0.06 to 0.97)</td>
<td>0.03</td>
<td>0.19</td>
<td>(−0.23 to 0.62)</td>
<td>0.37</td>
<td>0.35 (−0.09 to 0.79)</td>
<td>0.12</td>
</tr>
<tr>
<td>Black</td>
<td>1.07 (0.09 to 2.04)</td>
<td>0.03</td>
<td>0.84</td>
<td>(−0.11 to 1.79)</td>
<td>0.08</td>
<td>1.01 (0.04 to 1.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>White</td>
<td>0.32 (−0.28 to 0.93)</td>
<td>0.29</td>
<td>−0.02</td>
<td>(−0.60 to 0.56)</td>
<td>0.94</td>
<td>−0.01 (−0.59 to 0.58)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.50 (−0.30 to 1.30)</td>
<td>0.22</td>
<td>0.14</td>
<td>(−0.62 to 0.90)</td>
<td>0.71</td>
<td>0.20 (−0.62 to 1.01)</td>
<td>0.63</td>
</tr>
<tr>
<td>Chinese-American</td>
<td>1.71 (0.33 to 3.08)</td>
<td>0.02</td>
<td>0.88</td>
<td>(−0.40 to 2.16)</td>
<td>0.17</td>
<td>0.82 (−0.50 to 2.14)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Minimal adjustment included covariates sex, age and BMI. Full adjustment included covariates sex, age, BMI, race/ethnicity, education, income, smoking status, alcohol use, atrial fibrillation, diabetes mellitus, depression scale, exercise scale (log transform), apnea-hypopnea index, and arousal index. BMI indicates body mass index; PLMAI, periodic limb movement arousal index; and PLMI, periodic limb movement index.

### Discussion

This is the first study to examine the association of PLMS and hypertension across race/ethnic groups. Using objective measures of PLMS, we found that the likelihood of prevalent hypertension and measurements of SBP were significantly associated with PLMS frequency, and report the novel finding that associations were strongest among blacks. In blacks, an increase by 10 U for PLMI and 1 U for PLMAI was associated with a systolic unit higher for every 1-U PLMAI increase. Both PLMS and arousal, even when occurring alone, are associated with discrete blood pressure increases.9,31 When PLMS and arousal occur together, these increases in blood pressure are greater.9 This interaction between PLMS and arousal may provide new insight into the relationship between fragmented sleep (ie, arousal) and the
development of hypertension, which has been frequently studied but not clarified.

There are other potential physiological interactions that are worth mentioning. Because many participants were receiving blood pressure medications, it is important to consider the effects of antihypertensive medications on PLMs. In general, PLMS frequency is decreased with dopamine agonists; pharmacological effects of antihypertensive medications on PLMS have not been defined and thus is a potential confounder. Obstructive sleep apnea often co-occurs with PLMS and is a well-studied independent risk factor for hypertension. The statistical adjustment for apnea-hypopnea index may not have fully accounted for this potential physiological confounder. Finally, the phenomenon of PLMS itself can be seen in a large variety of conditions, including RLS, hypertension, neuropathy, and senility. The frequency of these conditions varies across racial/ethnic and socioeconomic lines and may also have confounded the results.

In this study, RLS symptoms were not associated with hypertension and did not influence the relationship between PLMS and hypertension. Other large population studies have reported an association between RLS and hypertension in unadjusted models but not in models adjusted for potential confounders. In these previous reports, patients with frequent RLS symptoms were most likely to have hypertension. RLS symptom frequency was not assessed in MESA, which may account for the disparate and negative findings about RLS.

A challenge in evaluating blood pressure in the community relates to consideration of antihypertensive medication effects. We addressed this limitation using a robust approach for integrating longitudinal blood pressure data and information on medication type to impute pretreatment blood pressure levels. Although robust, the imputation methods could have resulted in blood pressure estimates that lacked precision. We also performed sensitivity analysis on SBP measured limited to those not taking antihypertensive medication. The latter analysis confirmed the association between SBP and PLMS frequency in blacks and found that in Chinese-Americans, SBP measured was 1.5 mm Hg higher for every 10-U PLMI increase and 1-U PLMAI increase. These findings indicate that differences in antihypertensive use or imputation effects were unlikely to explain associations between hypertension and PLMS.

This study has several strengths. Participants with diverse ethnic and racial backgrounds were studied, providing an opportunity to explore associations across population groups. Participants were not chosen according to predilection for PLMS or hypertension, allowing generalizability to other similarly aged populations. Data were rigorously collected and scored by highly trained and centralized polysomnologists, with high PLMS intrascorer reliability. Clinic visits and blood pressure measurement were also standardized across institutions.

There are also some limitations to consider. The study was cross-sectional that weakens an argument for causality. Blood pressure, anthropomorphic, and questionnaire data were ascertained a median of 300 days before polysomnography testing. Although the measures of interest are generally stable for >1 year in individuals studied in community settings, this time difference could have contributed to some misclassification of exposure and outcome associations. The diagnosis of hypertension was based on a point sample of blood pressure. PLMS were measured using piezoelectric sensors and not standard electromyography. Previously, we had performed in-laboratory validation in 51 subjects where PLMS was assessed concurrently using piezoelectric leg sensors and leg electromyography and showed a correlation of r=0.81. Also, despite the large overall sample, the number of participants within each race/ethnicity group was limited, reducing the power to detect significant interactions.

In summary, PLMS are associated with hypertension and SBP, with findings strongest in blacks and Chinese-Americans. Given the high prevalence of hypertension in minority groups, these data suggest novel targets for improving blood pressure control. Further research is needed to identify the pathophysiological links between PLMS and hypertension and to determine whether environmental or genetic factors that vary with ancestry modify these associations.

Perspectives
PLMS are repetitively occurring limb movements during sleep that are often associated with arousal from sleep. Individual movements of a PLM cluster are each associated with elevations in blood pressure on the order of 20 systolic mm Hg. Because the prevalence of both PLMS and hypertension differs by race/ethnicity, we determine whether PLMS was associated with prevalent hypertension and whether this association was modified by race/ethnicity. We found that PLMS are associated with hypertension and SBP, with findings strongest in blacks and Chinese-Americans. Given the high prevalence of hypertension in minority groups, these data suggest novel targets for improving blood pressure control in these groups.

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Disclosures
None.

References


Novelty and Significance

What Is New?

In this study, we found that the frequency of periodic limb movements during sleep (PLMS) is associated with hypertension and systolic blood pressure, especially in the black and Chinese-American populations. After adjusting for multiple potential confounders, PLMS frequency both with and without arousal was associated with significant increases in measured systolic blood pressure.

What Is Relevant?

Minority groups, particularly blacks, have a high prevalence of hypertension. In this study, it was interesting that blacks were least likely (compared with other racial/ethnic groups) to have PLMS, but when PLMS was present in blacks, it was most predictive of prevalent hypertension. It will be important to determine whether this strong association between PLMS and hypertension in blacks is consistent with mechanisms of hypertension, which also differ by race/ethnicity, such as greater salt sensitivity in blacks. Given the high prevalence of hypertension in minority groups, these data suggest novel targets for improving blood pressure control in these populations.

Summary

PLMS frequency both with and without arousal is associated with prevalent hypertension and systolic blood pressure in blacks and Chinese-Americans.
Periodic Limb Movements During Sleep and Prevalent Hypertension in the Multi-Ethnic Study of Atherosclerosis

Brian B. Koo, Stefan Sillau, Dennis A. Dean II, Pamela L. Lutsey and Susan Redline

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