Research Article

Effect of Hypoxia on Periodic Limb Movement in Sleep Related Breathing Disorders

Zeynep Zeren UÇAR¹, Ahmet Emin ERBAYCU², Zühre Sarp TAYMAZ², Cenk KIRAKLI², Ahmet Uğur DEMIR³, Salih Zeki GÜÇLÜ²

¹The Department of Sleep Disorders, Dr Suat Seren Chest Diseases and Surgery Training and Research Hospital, Izmir, Turkey ²The Department of Pulmonary Diseases, Dr Suat Seren Chest Diseases and Surgery Training and Research Hospital, Izmir, Turkey ³The Department of Pulmonary Diseases, Medical Faculty of Hacettepe University, Ankara, Turkey

Summary

Introduction: The relationship between periodic limb movements during sleep (PLMS) and sleep related breathing disorder (SRBD) is not clear. Factors affecting the occurrence of PLMS in patients with SRBD, and a possible relation of PLMS and sleep related hypoxia in patients with obstructive sleep apnea syndrome and sleep related hypoventilation-hypoxemic syndromes was investigated.

Methods: Patients with snoring and/or witnessed apnea were tested with polysomnography. Respiratory events and PLMS were scored. Serology and arterial blood lactate levels were measured.

Results: 80 patients, 58 male and 22 female were included (Mean age: 49.1 years, SD: 9.0). 62 had SRBD and 18 had no SRBD, where 29 were in periodic limb movement index over and equal to 15 (PLMI ≥15) group and 51 were in the PLMI below 15 (PLMI<15) group. The rate of sleep-time spent below 90% oxygen saturation (T90%) and T80% were significantly higher in patients with PLMI ≥15 than patients with PLMI<15. PLMI<15 group spent longer time in NREM III than PLMI≥15 group. Apnea hypopnea index, the rate of sleep-time spent below 90% oxygen saturation (T90%), T80%, T70%, ESS and sleep NREM I-II% were significantly higher in patients with PLMI ≥15 plus SRBD, than patients with PLMI≥15 without SRBD. PLMI was not correlated with overnight lactate change.

Conclusion: As the rate of sleep-time spent below 90% oxygen saturation is longer in patients with PLMI ≥15 than PLMI<15, hypoxemia may play role in the pathophysiology of PLMS. Further studies with nasal CPAP treatment would reveal more information about the etiopathogenesis of PLMS in SRBD.

Key words: Sleep related periodic limb movements, sleep related breathing disorders, obstructive sleep apnea syndrome, hypoxia

Özet


Metodlar: Horlama veya tanıklı apnesi olan hastalara polisomnografi uygulandı. Serum ve arteriyel kan parametreleri ölçüldü ve UPBH skorlandı.

Bulgular: 58’i erkek and 22’si kadın toplam 80 çalışmaya dahil edildi (ortalamça yaş: 49.1 yıl, SS: 9.0 yıl). 62 hasta UISB and 18 had UISB olmayan grupta, bunların da 29‘u periodik bacak...
hareketleri indeksi 15 ve üzeri (PLMI ≥ 15) olan grupta and 51'i ise PLMI 15'in altında (PLMI < 15) grupta yer aldı. Oksihemoglobin saturasyonun %90 altında geçirilen süre oranı (T90%), T80%, T70%, Epworth uykuluk skoru (ESS) ve NREM I-II oranını PLMI ≥ 15 olan ve beraberinde UISB olan hastalarda PLMI ≥ 15 olan and ancaq UISB olmayan hastalara göre daha yüksekti. PLMI ile gece boyunca olan laktat değimi korelasyon bulunmadi. 

Sonuç: Oksihemoglobin saturasyonunun %90 altında geçirildiği süre PLMI ≥ 15 olan hastalarda PLMI < 15 olan hastaları göre daha uzun saptanması, hipoksinin UPBH patofizyolojisinde rol oynamayıbileceğini düşündürmektedir. Nazal CPAP tedavisi ile yapılacak olan ılık çalışmalar UISB olan hastalarda UPBH etiopatogenezi hakkında daha fazla bilgi verecektir.

Anahtar Kelimeler: Uyku ile ilişkili periyodik bacak hareketleri, uyku ile ilişkili solunum bozuklukları, obstrüktif uykı apnesi sendromu, hipoksi

INTRODUCTION
Periodic limb movements in sleep (PLMS) is a common finding in patients with obstructive sleep apnea syndrome (OSAS) (19). They are characterized by dorsiflexion of the ankle, the toes, a partial flexion of the knee and sometimes the hip. PLMS are frequently detected in polysomnograms, appearing as repetitive episodes of muscle contractions, each with the duration of at least 0.5 second and no longer than 10 seconds, separated by an interval of typically 5-90 seconds (1,35). The occurrence of PLMS at a rate of fifteen or more per hour of sleep is regarded as abnormal and is supportive for the diagnosis of periodic limb movement disorder (PLMD) if associated with hypersonmia or insomnia, which could not be better explained by another current sleep disorder or another disorder (1). PLMS is a moderately frequent disorder with a prevalence of about 3.9% in general population (1,27). The prevalence of PLMS has been found to increase with advanced age, with a prevalence of 45% in adults over 65 years old (6,8,13,22,29,34). OSAS is a frequent disorder with a prevalence of about 4% in men and 2% in women aged 30-60 (33). It is characterized by repetitive episodes of upper airway obstruction that occur during sleep causing sleep disruption due to recurrent arousals. Disrupted sleep is responsible for the complaint of excessive sleepiness in OSAS which disappears with continuous positive airway pressure (CPAP) treatment.

PLMS and OSAS are two common sleep disorders. However the relevance of PLMS in OSAS is not yet elucidated. It was reported that 22% of patients with PLMS also had OSAS (14), where 18% of them had both sleep disorders (7). Nearly 38.5% of patients with OSAS also have significant PLMS (19). In a study, 24% percent of the 1124 patients evaluated for sleep related breathing disorder (SRBD) had PLMS frequent enough to satisfy the criteria for PLMD (12). Coexistence of PLMS and OSAS could be due to the presence of a common pathology responsible for the PLMS.

Sleep disorders with frequent PLMS like restless legs syndrome, narcolepsy or rapid eye movement behaviour disorder are hypothesized to be related to dopaminergic hypoactivity, which is involved in the pathophysiology of the disorders (26). Furthermore, dopaminergic agents were reported to reduce the number of PLMS in restless legs syndrome (RLS) (20), narcolepsy (9) and rapid eye movement behaviour disorder (16) patients. PLMS has therefore been suggested to be a potential biological marker of dopaminergic mechanisms (26). Recent studies reported that PLMS might not be on a dopaminergic
control, and this may be for some of them related to SRBD. Although pathophysiology remains largely unknown, anemia, chronic uremia, essential hypertension, alcohol dependency, pregnancy, some other metabolic disorders and medications (tricyclic antidepressants, monoamine oxidase inhibitors) can induce PLMS.

The relationship between PLMS and sleep related breathing disorder (SRBD) and also the pathogenesis of PLMS is not clear.

Aim of our study was to assess the relationship between nocturnal hypoxia associated with SRBD and periodic limb movements and to characterize clinical findings in patients with PLMI ≥ 15 with and without SRBD.

MATERIAL AND METHODS

Patients and Study Design

Adult patients referred to the Department of Sleep Disorders with snoring or witnessed apnea (with or without daytime sleepiness) were invited to participate in this prospective study. Patients were excluded from the study, if they had RLS and any disease or medication that might induce PLMS. Patients with serum ferritin concentration of less than 50 Mg/L were not included in the study. Patients were also excluded if they were suffering from renal failure, hepatic failure, metabolic acidosis or diseases with low O2 delivery to tissues (anemia, hemoglobinopathy, or congestive heart failure), or if they were on medications that might alter lactate metabolism, such as metformin, alcohol, acetaminophen, amoxicillin, amiodarone, chlorpromazine, ciprofloxacin, diclofenac, erythromycin, fluconazole, isoniazid, methylldopa, oral contraceptives, statins (HMG-CoA reductase inhibitors), rifampicin, or valproic acid. Other exclusion criteria included refusal to participate in the study, central sleep apnea, Cheyne-Stokes respiration, and sleep efficiency under 70% on polysomnography (PSG).

Diagnosis of sleep disorders was based on the International Classification of Sleep Disorders (ICSD-2) of the American Academy of Sleep Medicine (AASM). The occurrence of PLMS at rates of 15 or more per hour of sleep is regarded as abnormal and is supportive for the diagnosis of periodic limb movement disorder (PLMD) if associated with hypersonia or insomnia and these symptoms are not better explained by another current sleep disorder or other disorders according to ICSD-2 statement for PLMD. Patients with PLMI ≥ 15 hypersonia or insomnia symptoms were not classified as PLMD group, since hypersonia or insomnia symptoms might be due to SRBD other than PLMS.

The study protocol was approved by the Institutional Review Board Ethics Committee of the Hospital. A signed informed consent was obtained from each patient.

Polysomnography (PSG)

Polysomnography was performed in the Sleep Laboratory with Embla polysomnograph running Somnologica software version 4.0 (Flaga hf. Medical Devices, Iceland) and included four electroencephalography (EEG) channels (C3 to A1, C4 to A2, O1 to A2, O2 to A1), right and left electroocculography (EOG) channels, one chin electromyography (EMG) channel and four tibialis anterior EMG channels, finger pulse oxymeter, strain gauges for thoraco-abdominal movements, one electrocardiography (ECG) lead, a nasal airflow (pressure cannula) and a digital microphone for snoring detection.

PSG recordings were scored in 30 second epochs for sleep, breathing and oxygenation according to the standard criteria of AASM. Obstructive apneas were defined as a complete cessation of oro-nasal airflow for at least 10 seconds in the presence of chest-wall motion. Hypopnoeas were defined as a reduction in respiratory airflow of 50% or more or a
clear reduction in airflow associated with more than 3% arterial oxygen desaturation or an arousal lasting for at least 10 seconds. Apnea hypopnea index (AHI) was calculated as the total number of apneas and hypopneas per hour of sleep. Sleep was staged manually according the methods of Rechtschaffen and Kales. According to ICSD-2 classification, the diagnosis of SRBD is based on PSG and includes:

- OSAS: AHI ≥ 5 per hour of sleep.
- SRHH-NMCWD: Obese patient (BMI: body mass index > 30 kg/m²(7)) with one of the following:
  - An oxyhaemoglobin saturation with pulse oxymeter (SpO₂) during sleep of less than 90% for more than five minutes with a nadir of at least 85%
  - More than 30% of total sleep time with an SpO₂ of less than 90%
  - Sleeping arterial blood gas with PaCO₂ that is abnormally high or disproportionately increased relative to levels during wakefulness.

And the disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use or substance use disorder.

- SRHH-LAO: Lower airway obstruction defined as FEV₁/FVC < 0.7 with at least one of the following:
  - An SpO₂ during sleep of less than 90% for more than five minutes with a nadir of at least 85%
  - More than 30% of total sleep time at SpO₂ of less than 90%
  - Sleeping arterial blood gas with PaCO₂ that is abnormally high or disproportionately increased relative to levels during wakefulness.

And the disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use or substance use disorder.

Subjects, who had normal PSG findings, with no diagnosis of SRBD were considered as the control group (No-SRBD).

**Polysomnographic and PLMS Recordings**

The PLMS were scored according to standard criteria: a minimum of 4 consecutive anterior tibialis electromyogram contractions, each lasting 0.5 to 10.0 seconds, with an interval between contractions of 5 to 90 seconds. Surface electrodes were placed at 2-3 centimeter apart or 1/3 of the length of the anterior tibialis muscle. Electrodes were placed longitudinally on the muscles, symmetrically around the middle. Impedance was ≤ 5KΩ. Filters were 10-200 Hz. Calibration also has been done in accordance with that of the official World Association of Sleep Medicine (WASM) standards for recording and scoring PLMS and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG)²⁵. The diagnosis of PLMD was based on the minimal criteria provided by the International Classification of Sleep Disorders. The periodic limb movements index (PLMI) exceeds five per hour in children and 15 per hour in most adults according to ICSD-2 statement for PLMD.²¹

A movement event and arousal are considered as related with each other when there is less than 0.5 second between the end of one event and the onset of the other event.

Limb movements occurring simultaneously with the end of apneas were excluded. PLMS were not classified according to the presence or the absence of an arousal.³⁵,¹¹ Patients were classified into two group as with PLMI below 15 (PLMI<15) and patients with PLMI equal to and over 15 (PLMI≥15) group.

**Measurement of Blood Lactate and Calculation of Overnight Difference in Blood Lactate**

Two arterial blood gases samples from each subject were collected in heparinised
syringes (PICO 70, Radiometer Copenhagen, Denmark). First sample was collected at the beginning of PSG recording at night, awake, supine position, and the second sample was collected in the morning after the PSG recording, awake, supine position. Samples were immediately analyzed by blood gas and lactate analysing system (Rapidlab Analyzer 860, Bayer Health Care Systems, USA).

Overnight difference in lactate was calculated according to the formula:

Overnight difference in Lactate = Blood lactatemorning − Blood lactatenight

**Other Measurements**

Haemoglobin, hematocrite, ferritin and biochemical parameters including fasting glycaemia and lipid profile were measured on fasting venous blood samples collected the following morning.

Pulmonary function testing was performed according to the methodology proposed by the American Thoracic Society and European Respiratory Society, in standing position and with nose clips (ZAN 100, Flowhandy, Germany) (24). At least three, up to five forced expiratory maneuvers were performed to obtain three technically satisfactory blows. The highest forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) values were reported. For the diagnosis of SRHH-LAO, post bronchodilator values were considered after inhalation of 400 µg aerosolised salbutamol.

**Statistical Analysis**

Descriptive data of continuous variables were presented as mean and standard deviation, and median (range) where applied. Normality of distributions was tested by Kolmogorov-Smirnov test. Comparisons between continuous variables were carried out by Student's or Mann-Whitney U test for the presence and lack of normal distribution, respectively. Proportions were compared using Chi-square. Fisher's exact test was used when the value of expected count was less than 5, in at least 25% of the cells. Association between PLMI, AHI, Epworth sleepiness scale (ESS) and blood lactate measurements was tested with nonparametric correlation analysis. Multiple linear regression analysis was used to adjust the significant findings in the correlation analysis and findings in the univariate analysis of disease groups, for age and gender. Analyses were repeated in the subgroup of PLMI≥15 patients. All statistical testing was two tailed, and p values less than 0.05 were considered as significant. Statistical analysis was carried out using SPSS software (package version 13.0, SPSS Inc, Chicago, IL).

**RESULTS**

80 patients, 58 male and 22 female were included in the study with a mean age of 49.1 years. Of the 80 patients, 18 had no SRBD and 62 had SRBD. All SRBD patients had OSAS, five patients had also sleep-related hypoventilation / hypoxemia due to neuromuscular or chest wall disorders (SRHH-NMCWD) and nine patients presented sleep-related hypoventilation/hypoxemia due to lower airway obstruction (SRHH-LAO). Of the eighty patients enrolled in the study, 29 were in PLMI≥15 group and 51 were in the PLMI<15 group. Demographic, laboratory, vigilance evaluation of patients and polysomnographic data of the two groups are reported in Table 1. The rate of sleep-time spent below 90% oxygen saturation (T90%) and T80% were significantly higher in patients with PLMI≥15 than patients with PLMI<15. PLMI<15 group spent longer time in slow wave sleep than PLMI≥15 group. There was no significant difference between proportions of time spent at stage of rapid eye movement (REM) between both groups. Other laboratory results including arterial blood gases, haemoglobin, haematocrit, FEV1/FVC, ESS score, triglyceride, cholesterol and fasting glycaemia were similar in both groups.
Table 1. Patients’ demographic, laboratory and polysomnographic parameters among two groups with or without PLMD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Periodic limb movement index below 15 (n: 51)</th>
<th>Periodic limb movement index over and equal to 15 (n: 29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female / Male, n</td>
<td>14 / 37</td>
<td>8 / 21</td>
<td>0.990</td>
</tr>
<tr>
<td>Age, years</td>
<td>49.29 (26-74)</td>
<td>49.0 (35-73)</td>
<td>0.873</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.4 (21-53)</td>
<td>30.5 (23-47)</td>
<td>0.249</td>
</tr>
<tr>
<td>Apnea hypopnea index, /h</td>
<td>17 (0-76)</td>
<td>34.6 (0-154)</td>
<td>0.009</td>
</tr>
<tr>
<td>PLMI, /h</td>
<td>1.3 (0-14.8)</td>
<td>40.7 (16.5-188.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>Haemoglobin, gr/dl</td>
<td>14.543 (11-19.1)</td>
<td>14.9 (12.2-16.7)</td>
<td>0.156</td>
</tr>
<tr>
<td>Haemotocrit, %</td>
<td>41.8 (33.6-50.2)</td>
<td>42.6 (35-48.4)</td>
<td>0.118</td>
</tr>
<tr>
<td>T90%</td>
<td>1.4818 (0-74.36)</td>
<td>6.6432 (0-98.97)</td>
<td>0.035</td>
</tr>
<tr>
<td>T80%</td>
<td>0.0283 (0-81.88)</td>
<td>0.193 (0-79.4)</td>
<td>0.011</td>
</tr>
<tr>
<td>T70%</td>
<td>0.0024 (0-10.45)</td>
<td>1.9283 (0-55.24)</td>
<td>0.054</td>
</tr>
<tr>
<td>Epworth sleepiness scale</td>
<td>7.86 (0-22)</td>
<td>10.33 (0-22)</td>
<td>0.270</td>
</tr>
<tr>
<td>Minimum SaO2 , %</td>
<td>84.29 (55-97)</td>
<td>82 (57-93)</td>
<td>0.079</td>
</tr>
<tr>
<td>FEV1 / FVC, %</td>
<td>84.333 (3-48.97)</td>
<td>82 (60-100)</td>
<td>0.534</td>
</tr>
<tr>
<td>Stage I-II, %</td>
<td>59.59 (20.56-93.3)</td>
<td>63.84 (24.62-91.9)</td>
<td>0.164</td>
</tr>
<tr>
<td>Stage III-IV, %</td>
<td>22.25 (0-74.47)</td>
<td>9.27 (0-49.58)</td>
<td>0.002</td>
</tr>
<tr>
<td>REM, %</td>
<td>8.68 (0-34.2)</td>
<td>8.39 (0-30.17)</td>
<td>0.841</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.41 (7.33-7.45)</td>
<td>7.40 (7.31-7.49)</td>
<td>0.604</td>
</tr>
<tr>
<td>pO2, mmHg</td>
<td>88 (54-99)</td>
<td>84 (44-99)</td>
<td>0.083</td>
</tr>
<tr>
<td>pCO2, mmHg</td>
<td>41.17 (33-53)</td>
<td>42.38 (35-62)</td>
<td>0.491</td>
</tr>
<tr>
<td>Bicarbonate, mEq/L</td>
<td>25.35 (21.8-32.6)</td>
<td>26.05 (22-32.2)</td>
<td>0.196</td>
</tr>
<tr>
<td>SaO2,%</td>
<td>96.47 (85.8-99)</td>
<td>96.3 (76-98.3)</td>
<td>0.406</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>225.67 (114-344)</td>
<td>224.67 (144-311)</td>
<td>0.830</td>
</tr>
<tr>
<td>Triglycerid, mg/dl</td>
<td>148 (46-551)</td>
<td>149 (72-760)</td>
<td>0.441</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>100.25 (16-197)</td>
<td>100 (75-250)</td>
<td>0.737</td>
</tr>
<tr>
<td>Morning lactate, mmol/L</td>
<td>1.57 (0.68-2.80)</td>
<td>1.56 (0.72-3.27)</td>
<td>0.996</td>
</tr>
<tr>
<td>Overnight change in lactate, mmol/L</td>
<td>0.05 (-1.76-0.94)</td>
<td>-0.11 (-1.28-1.79)</td>
<td>0.426</td>
</tr>
</tbody>
</table>

Median and range of the values are given for the variables unless specified.
PLMI : periodic limb movement index
T90% : the rate of sleep-time spent below 90% oxygen saturation
Minimum SaO2 : lowest oxyhaemoglobin saturation along night with pulse oxymeter
FEV1 / FVC : The ratio of forced expiratory volume in one second to forced vital capacity
REM : rapid eye movement
pO2 : the partial arterial oxygen pressure
pCO2 : the partial arterial carbon dioxide pressure
Patients' demographic, laboratory and polysomnographic parameters were analyzed in two groups of having PLMI ≥ 15 with or without SRBD. Apnea hypopnea index, the rate of sleep-time spent below 90% oxygen saturation (T90%), T80%, T70%, ESS and sleep Stage I-II% were significantly higher in patients with PLMI ≥ 15 plus SRBD, than patients with PLMI ≥ 15 without SRBD. Minimum oxygen saturation, FEV1/FVC and arterial pH were significantly higher in patients with PLMI ≥ 15 without SRBD (Table 2).

There was no statistically significant correlation between PLMI and overnight lactate change (rho: -0.03, p: 0.73) (Figure 1).

![Figure 1](scatterplot.png)  
*Figure 1: Scatterplot graph of PLMI and lactate overnight change (rho: -0.03 , p: 0.73)*
Table 2. Patients’ demographic, laboratory and polysomnographic parameters among two groups having PLMD with or without SRBD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PLMI≥15 with SRBD (n: 12)</th>
<th>PLMD≥15 without SRBD (n: 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female / Male, n</td>
<td>2 / 10</td>
<td>6 / 11</td>
<td>0.408</td>
</tr>
<tr>
<td>Age, years</td>
<td>48.5 (39-65)</td>
<td>50 (35-73)</td>
<td>0.877</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.8 (23-47)</td>
<td>30 (23-39)</td>
<td>0.287</td>
</tr>
<tr>
<td>PLMI, /h</td>
<td>34.4 (16.5-118)</td>
<td>42.1 (17.1-188.7)</td>
<td>0.535</td>
</tr>
<tr>
<td>Haemoglobin, gr/dl</td>
<td>15.9 (13.7-16.7)</td>
<td>14.7 (12.2-16.6)</td>
<td>0.163</td>
</tr>
<tr>
<td>Haemotocrit, %</td>
<td>44.1 (40.5-48)</td>
<td>41.5 (35-48.4)</td>
<td>0.097</td>
</tr>
<tr>
<td>T90%</td>
<td>57.9 (0-99.0)</td>
<td>0.6 (0-26.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>T80%</td>
<td>15.5 (0-79.4)</td>
<td>0.0742 (0-2.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>T70%</td>
<td>7.1 (0-55.2)</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>Epworth sleepiness scale</td>
<td>16.5 (10-22)</td>
<td>6 (0-15)</td>
<td>0.000</td>
</tr>
<tr>
<td>Minimum SaO2, %</td>
<td>68.7 (57-91)</td>
<td>86.3 (71-93)</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>77.6 (60-92)</td>
<td>86 (70-100)</td>
<td>0.028</td>
</tr>
<tr>
<td>Stage I-II, %</td>
<td>75.2 (53.1-91.9)</td>
<td>58.64 (24.6-89.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>Stage III-IV, %</td>
<td>10.4 (0-18.1)</td>
<td>8.53 (0-49.6)</td>
<td>0.363</td>
</tr>
<tr>
<td>REM, %</td>
<td>7.9 (0-20.1)</td>
<td>9.52 (0-30.2)</td>
<td>0.740</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.37 (7.31-7.44)</td>
<td>7.4225 (7.32-7.49)</td>
<td>0.007</td>
</tr>
<tr>
<td>pO2, mmHg</td>
<td>77.5 (46-91)</td>
<td>87 (44-99)</td>
<td>0.076</td>
</tr>
<tr>
<td>pCO2, mmHg</td>
<td>46.8 (40-62)</td>
<td>39.75 (35-46)</td>
<td>0.003</td>
</tr>
<tr>
<td>Bicarbonate, mEq/L</td>
<td>27.2 (22-32.2)</td>
<td>25.8 (22.6-28.3)</td>
<td>0.080</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>95.3 (76.9-98)</td>
<td>97.0 (76-98.3)</td>
<td>0.069</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>229 (180-270)</td>
<td>210 (144-311)</td>
<td>0.138</td>
</tr>
<tr>
<td>Trigliserid, mg/dl</td>
<td>138.7 (72-760)</td>
<td>193 (100-517)</td>
<td>0.207</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>96.5 (75-250)</td>
<td>101.5 (83-239)</td>
<td>0.610</td>
</tr>
<tr>
<td>Morning lactate, mmol/L</td>
<td>1.73 (0.87-2.10)</td>
<td>1.42 (0.72-3.27)</td>
<td>0.983</td>
</tr>
<tr>
<td>Overnight change in lactate, mmol/L</td>
<td>-0.14 (-1.28-0.47)</td>
<td>-0.02 (-0.89-1.79)</td>
<td>0.419</td>
</tr>
</tbody>
</table>

Median and range of the values are given for the variables unless specified.
PLMI: periodic limb movement index
T90%: the rate of sleep-time spent below 90% oxygen saturation
Minimum SaO2: lowest oxyhaemoglobin saturation along night with pulse oxymeter
FEV1 / FVC: the ratio of forced expiratory volume in one second to forced vital capacity
REM: rapid eye movement
pO2: the partial arterial oxygen pressure
pCO2: the partial arterial carbon dioxide pressure
DISCUSSION

Patients with a combined diagnosis of PLMI≥15 and SRBD had significantly more severe hypoxia, were more sleepy (as measured by ESS), and had a higher proportion of light sleep than PLMI≥15 subjects without SRBD. Also patients with PLMI≥15 had significantly more severe hypoxia and had more light sleep than PLMI<15 group. There was no statistically significant correlation between PLMI and overnight lactate change.

To our knowledge, no other previous studies have tested the hypothesis of tissue hypoxia on PLMI. This is the first study, to investigate the correlation between PLMI and hypoxia and lactate. We hypothesized that hypoxia may also evoke PLMS like anemia, chronic uremia, some other metabolic disorders and medications and we found that the PLMI≥15 group had spent more time at oxyhemoglobin saturation below 90% and 80% than in patients with PLMI<15. However, overnight lactate change was not significantly different between groups with PLMI≥15 and PLMI<15.

Increase in PLMI was positively correlated with higher AHI in Baran et al’s study. (5) Previously the similarity in periodicity of PLMS and OSAS led a study to hypothesize the existence of a common central generator responsible for the periodicity of both OSAS and PLMS. This study showed that the periodicity of PLMS was different from that of OSAS, suggesting that sleep apneas and PLMS are not generated by a common central generator. (11)

A PLMI (the number of PLMS per hour of sleep) above 5 per hour is often used as a cut off for differentiating normal from elevated values in most studies, according to previous ICSD(4,12,19). The diagnosis of PLMD was based on the minimal criteria provided by the latest ICSD in this study. The PLMI is required to be 15 per hour in adults according to ICSD-2 statement for PLMD diagnosis. (1)

PLMS is frequently observed in NREM I-II sleep and less commonly in NREM III-IV and REM sleep. (25) The proportion of NREM I-II in sleep was significantly higher in patients with PLMI≥15 plus SRBD than patients with PLMI≥15 without SRBD. It was also observed that PLMI<15 group to spent longer time at slow wave sleep than PLMI≥15 group in our study. Seo CS et al. found that PLMI was negatively correlated with duration of NREM III-IV in patients with OSAS. (30)

Briellmann et al. and Baran et al. proposed that PLMS in patients with OSAS have more than one etiologies and types. (5,10) They suggested that there were two types of PLMS in patients with OSAS: one is spontaneous and the other is induced by EEG arousals due to the respiratory effort. They suggested that each had different clinical significance and treatment options. Like Carelli et al did, we did not score the PLMS of respiratory origins which could benefit from CPAP by improving oxygenation of patients with SRBD.

One of the limitations in our study was that EEG arousals related with PLMS were not scored and a PLM arousal index was not calculated, similar to the study of Baran et al. (5). PLMS are either related to apnea-hypopnea or are idiopathic in origin. There are only a few PLMS occurring independently of any respiratory event related arousal. Apnea-hypopnea related PLMS were not necessarily occurring just at the end of respiratory event. Therefore, all the PLMS during the respiratory event should be considered as respiratory event related PLMS. Other limitation of the study is the lack of the investigation of the correlation of PLMS and lactate levels after CPAP. The effects of CPAP on PLMS in patients with OSAS are inconsistent among studies, with findings of increment and reduction of PLMS after CPAP treatment.
Baran et al. reported that severity of OSAS might determine the effect of CPAP on PLMS. The PLMS may increase in moderate to severe OSAS due mainly to unmasking of underlying PLMI ≥15. The PLMS may decrease in mild OSAS after CPAP due to resolution of PLMS associated with respiratory effort-related arousals⁵. In the follow-up period of our study, we are planning to find out how and PLMI change by hypoxia, lactate change after CPAP treatment. It is difficult to differentiate intrinsic leg movements from secondary movements before CPAP treatment and there are only a few PLMS occurring independently of any respiratory event. Therefore Carelli et al. suggested comparing the occurrence of PLMS in the absence of apneas during CPAP treatment and with apneas before CPAP treatment. For the same reason, leg movements initiating within 0.5 second of an end of arousal were not scored as PLM. These two events were considered as related.

CONCLUSION
The hypoxic sleep period is longer in patients with PLMI ≥15 plus SRBD than patients with PLMI ≥15 alone, though serum lactate is similar in these two groups. Serum lactate level has no effect on occurrence of PLMS. As the rate of sleep-time spent below 90% oxygen saturation is longer in patients with PLMI ≥15, nocturnal hypoxemia may play role in the pathophysiology of PLMS and induce the hypoactivity of dopaminergic system in some patients with PLMS. But this result allows for only preliminary conclusion because of it may be impossible to define whether a movement or not it is secondary to an episode respiratory unless they are disposed of with the use of nasal CPAP. Further studies with nasal CPAP treatment would reveal more information about the etiopathogenesis of PLMS in SRBD.

Conflict of Interest: None of the authors had declared any financial or personal relationship that may inappropriately influence their actions on the preparation of the manuscript.

Correspondence to:
Zeynep Zeren Ucar
E-mail: zeynepzucar@yahoo.com

Received by: 17 October 2009
Revised by: 21 December 2009
Accepted: 28 December 2009

The Online Journal of Neurological Sciences (Turkish) 1984-2010
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova,
Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

REFERENCES
5. Baran AS, Richert AC, Douglass AB, et al. Change in periodic limb movement index