Periodic Limb Movements During Sleep in Patients With Congestive Heart Failure*

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The prevalence of periodic limb movements (PLM) during sleep and their effect on sleep and daytime alertness were determined in 23 men with severe, stable congestive heart failure (CHF) and 9 healthy control subjects. Each subject had overnight polysomnography and the following day completed a subjective assessment of daytime sleepiness (Epworth Sleepiness Scale [ESS]) and a multiple sleep latency test (MSLT). The proportion of CHF patients with moderately severe PLM (>25/h) was significantly higher (52%) than control subjects (11%). CHF patients were subdivided into two groups, those with more than 10 PLM per hour (group 1, n=15) and those with less than 10 PLM per hour (group 2, n=8). Group 1 a significantly higher frequency of PLM (group 1, 73±50; group 2, 4±4; control, 11±12/h) and associated arousals from sleep (group 1, 14±13; group 2, 2±3; control subjects, 1±1/h) than group 2 and the control group, and had more stage 1 and 2 nonrapid eye movement sleep than the control group (group 1, 77±11; group 2, 71±11; control, 63±9% total sleep time). Mean sleep latency on the MSLT was significantly shorter in group 1 than the control group (group 1, 6.1±2.9; group 2, 9±6.7; control subjects, 12.4±1.9 min). Although the ESS score was highest in group 1, this did not reach statistical significance. We conclude that PLM are more prevalent in patients with CHF and may contribute to their sleep/wake complaints. (CHEST 1996; 109:1497-1502)

Key words: Cheyne-Stokes respiration; daytime sleepiness; heart failure; periodic limb movements; sleep

Abbreviations: AH1=apnea-hypopnea index; BMI=body mass index; CHF=congestive heart failure; CSR=Cheyne-Stokes respiration; EMG=electromyogram; EEG=electroencephalogram; ESS=Epworth Sleepiness Scale; LVEF=left ventricular ejection fraction; MSLT=multiple sleep latency test; NREM=nonrapid eye movement sleep; PLM=periodic limb movements; SaO2=oxygen saturation; tCO2=transcutaneous Pco2; TST=total sleep time

Periodic limb movements (PLM) during sleep are characterized by recurrent episodes of repetitive, stereotyped limb movements that occur predominantly in the legs.1 They have been described in association with a variety of medical disorders, including uremia and hemodialysis,2 chronic myelopathies and peripheral neuropathies,3 anemia,4 chronic lung disease,5 and rheumatoid arthritis.6 They are also reported to be more prevalent in patients with other sleep disorders, such as sleep apnea7 and narcolepsy.1 Although PLM may be asymptomatic, they can be associated with recurrent arousals from sleep leading to complaints of insomnia and daytime hypersomnolence.1

We have previously reported PLM during sleep in a single patient with congestive heart failure (CHF) that resolved after heart transplantation.8 Although this suggests that PLM may be associated with CHF, to our knowledge, there have been no studies that have systematically addressed this issue. The development of PLM in patients with CHF may contribute to the pathogenesis of daytime fatigue, which is a frequent complaint in these individuals. The objective of our study was to determine the prevalence of PLM in patients with CHF and evaluate their effect on sleep and daytime alertness.

Materials and Methods

Patient Population

We studied 23 patients with severe, stable CHF (New York Heart Association, class III to IV) whose resting left ventricular ejection fraction (LVEF) was less than 35%. A history of insomnia, excessive daytime sleepiness, or fatigue was not required for entry into the study. Patients were excluded if they had (1) significant pulmonary, renal, neurologic, or musculoskeletal disease, and (2) medication prescribed that is associated with PLM or excessive daytime sleepiness. In addition, we studied a control group of nine healthy individuals who were not taking medication and were age- and sex-matched with the CHF group. Each subject had an overnight sleep study and the following day, daytime sleepiness was assessed. The protocol was approved by the Ethics Committee of our institution and informed consent was obtained from each patient.

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Manuscript received June 13, 1995; revision accepted December 29.
Sleep Study

The following variables were monitored during overnight polysomnography. We recorded two-channel EEG (C3-A2, C4-A1), electro-oculogram (EOG), and submental electromyogram (EMG) using surface electrodes. Airflow was detected by monitoring expired CO2 at the nose and mouth through nasal cannulas adapted for this purpose and attached to a CO2 analyzer (Datex; Helsinki, Finland). Respiratory effort was monitored by respiratory plethysmography with transducers placed around the chest and abdomen (Respirtrac; Ambulatory Monitoring: Ardsley, NY). Arterial oxygen saturation (SaO2) was recorded with a pulse oximeter (Biox 3740; Ohmeda; Boulder, Colo) set at its fastest response with the probe placed on the patient's ear. Transcutaneous Pco2 (tc02) was recorded by a Pco2 sensor placed on the anterior chest wall and attached to a CO2 monitor (Kontron Instruments; Switzerland). The EOG and heart rate were recorded from standard limb leads. All movements of the left and right leg were recorded independently from the anterior tibialis EMG using surface electrodes. All variables were continuously recorded on a polygraph (model 78E; Grass Instruments; Quincy, Mass) at a paper speed of 10 mm/s. The tc02 was displayed on a slow recorder (paper speed, 20 cm/h) that was synchronized to the polygraph.

All polysomnograms were scored manually and sleep stage and arousals were determined by established criteria using the EEG, EOG, and EMG.9 Sleep onset was defined as the time (minutes) from “lights out” to the first epoch of sleep. Sleep efficiency was defined as the total sleep time (TST) expressed as a percentage of the total study time. An arousal was defined as an awakening from sleep for more than 3 s, as evidenced by simultaneous alpha activity on the EEG, EMG activation, and eye movements. Arousal were classified into those associated with PLM and those associated with Cheyne-Stokes respiration (CSR). PLM were scored if they occurred independently of an arousal from sleep and were part of a series of 4 of more consecutive, involuntary leg movements, lasting 0.5 to 5.0 s with an intermovement interval of 5 to 90 s.2 CSR was defined as periodic breathing with central apnea or hypopnea alternating with hypopnea in a crescendo/descrescendo pattern, and the duration of CSR was expressed as a percentage of TST. Central apnea was defined as absence of airflow for more than 10 s due to loss of respiratory effort. Hypopnea was defined as a reduction in the amplitude of respiratory effort of at least 50% from the sleeping baseline level for more than 10 s. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. SaO2 during sleep was expressed as mean SaO2 calculated by averaging the high and low SaO2 for each 30-s epoch. The tc02 during sleep was expressed as mean tc02, calculated from the average tc02 over 36-s intervals.

Cardiac Function

LVEF was estimated at rest by radionuclide angiography. Circulation time from the lung to the carotid body was estimated either from the overnight sleep study or during a voluntary breath-hold the following day by measuring the time from the end of an apnea or voluntary breath-hold to the nadir of oxygen desaturation estimated with an ear oximeter set at its fastest response. Only apneas with an abrupt termination and onset of respiration were chosen so that a clear increase in SaO2 could be detected. The average circulation time from at least ten apneas or breath-holds was obtained in each patient.

Daytime Sleepiness

Daytime sleepiness was assessed by a subjective rating (Epworth Sleepiness Scale [ESS]) in each patient the morning after his overnight sleep study. The ESS is a self-administered questionnaire that asks the patient to rate on a numeric scale the likelihood of falling asleep in different situations such as watching TV or sitting in a car. The scale ranges from 0 (“would never doze”) to 3 (“high chance of dozing”) and the potential score ranges from 0 to 24 with a higher score indicating increased sleepiness. The ESS has been correlated with the multiple sleep latency test (MSLT) and a score of 5.9±2.2 has been reported in normal control subjects and 16±4.4 in patients with severe obstructive sleep apnea.10

Daytime sleepiness was also measured objectively by an MSLT that was done in a standardized fashion11 the day after the overnight sleep study. Sleep stage was determined from surface electrodes that recorded three-channel EEG (C3-A2, C4-A1, O1-A2), two-channel EOG (F7-A1, F3-A2), and submental EMG. During the MSLT, the patient lay on a bed in a quiet, darkened room and was invited to fall asleep. The patient took 4 naps throughout the day at 9 and 11 AM and at 1 and 3 PM. Sleep onset was defined as the time from lights out to the first of 3 consecutive epochs of stage 1 nonrapid eye movement (NREM) sleep or 1 epoch of any other sleep stage. Our definition of sleep onset was more conservative than what is conventionally used to score an MSLT (one 30-s epoch of NREM sleep)11 because we believed that these criteria were required to identify established sleep. Once sleep onset was identified, the patient was awakened to prevent consolidated sleep improving his performance on subsequent naps. In addition, the patient was observed between naps to ensure that he did not sleep.

Statistical Analysis

Significant differences between groups were analyzed by x2 test (nonparametric data) or one-way analysis of variance (parametric data) with p<0.05 considered significant.

Results

We studied 23 patients with stable CHF due to ischemic heart disease and 9 healthy control subjects. Because all CHF patients referred to us were male, we excluded female subjects from the control group to keep the groups well matched. Each CHF patient’s LVEF was less than 35% (mean LVEF, 23±5%), and their New York Heart Association functional class was III or IV. Ejection fraction was presumed to be normal in the control subjects because they had no history or physical evidence of impaired ventricular function. Mean age and body mass index (BMI) were the same in CHF patients and control subjects (age, 64±6 vs 65±4 years; BMI, 27.3±3.8 vs 26.6±3 kg/m2). None of the control subjects were taking medication, whereas the CHF patients were taking a variety of cardiac drugs. In addition to their cardiac status, the outstanding difference between the two groups of patients was the prevalence of PLM during sleep (Figs 1 and 2). The proportion of CHF patients with more than 25 PLM per hour was significantly higher (52%) than control subjects (11%) and 33% of the CHF patients had more than 50 PLM per hour of sleep.

To evaluate the effect of PLM on sleep and daytime function in CHF patients, we divided them into two groups based on the frequency of PLM during sleep (Table 1). Group 1 consisted of patients with more than 10 PLM per hour and group 2 included those with less than 10 PLM per hour. Both groups were a similar age and weight and had comparable left ventricular dysfunction as evidenced by LVEF and circulation time.
Normal circulation time in our control subjects was 9±1.4 s. In addition, both groups were taking similar cardiac medications, although more patients in group 2 were receiving digoxin and vasodilators. There was no significant difference in the duration of CHF between groups 1 and 2, and no association between the duration of heart failure and the severity of PLM.

The effect of PLM on sleep in patients with CHF and control subjects is summarized in Table 2. By definition, group 1 patients had a higher frequency of PLM, which was associated with a significantly higher number of arousals from sleep. In addition, group 1 had more stage 1 and 2 NREM sleep than the control group and tended to have less slow-wave sleep. However, other parameters of sleep architecture were not significantly different between heart failure groups. Respiratory data during wakefulness and sleep in the two heart failure groups are shown in Table 3. None of our patients were hypoxemic or hypercapnic while awake and none had obstructive sleep apnea. Although CSR frequently developed during sleep, the duration of CSR was similar in both groups and there was no significant intergroup difference in the AHI. Furthermore, the mean frequency of arousals associated with CSR was identical in both groups. Finally, mean SaO2

Table 1—Characteristics of CHF Patients With More Than 10 PLM per Hour (Group 1) and Less Than 10 PLM per Hour (Group 2)*

<table>
<thead>
<tr>
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<th>Group 1</th>
<th>Group 2</th>
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<tbody>
<tr>
<td>No.</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Age, yr</td>
<td>64±6</td>
<td>64±6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6±4</td>
<td>26.6±3</td>
</tr>
<tr>
<td>EF, %</td>
<td>24.5±6</td>
<td>20.2±8</td>
</tr>
<tr>
<td>Circulation time, s</td>
<td>17.2±6</td>
<td>16.8±7</td>
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<tr>
<td>Cardiac medications, % of group</td>
<td></td>
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<tr>
<td>D</td>
<td>60</td>
<td>100</td>
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<td>Di</td>
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<td>V</td>
<td>13</td>
<td>38</td>
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<td>AA</td>
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*EF=ejection fraction; D=digoxin; Di=diuretic; A=angiotensin-converting enzyme inhibitor; N=nitrates; V=vasodilator; AA=anti-arrhythmic.
and $tCO_2$ were not significantly different between those patients with and without PLM during sleep.

The effect of PLM on daytime alertness was assessed subjectively by the ESS and objectively by MSLT (Table 4). The ESS scores were higher in group 1 than group 2 and the control group, but this did not reach statistical significance. Mean sleep latency on the MSLT was lowest in group 1 but was significantly different only from the control group and not group 2.

**Discussion**

We found that patients with severe CHF have a higher prevalence of PLM than a group of healthy individuals (Fig 2). The groups were carefully age-matched because the prevalence of PLM increases with advancing age. Although all our subjects were male, the same results are likely in a female population because a gender difference has not been reported in this disorder. We excluded subjects with coexisting illnesses that are known to be associated with PLM, such as renal failure, pulmonary, neurologic, and musculoskeletal disease, and individuals taking medications that have been reported to cause PLM during sleep such as antidepressants and withdrawal from anticonvulsants, benzodiazepines, and other hypnotics. The only demographic differences between the CHF group and control subjects were the presence of severe left ventricular dysfunction and their cardiac medications. However, when CHF patients with and without significant PLM were subdivided, both groups were taking similar cardiac medications (Table 1). Consequently, we believe that CHF patients have an increased prevalence of PLM and that this is not related to coexisting illness or medical therapy.

We compared sleep architecture in CHF patients with and without PLM and in healthy subjects (Table 2). PLM were associated with an increased frequency of arousals from sleep. Although patients with PLM (group 1) had reduced TST and more light sleep, these differences were statistically significant only from the control group and not from heart failure patients without PLM (group 2). This suggests that these changes in sleep architecture may have been due to something other than PLM. Although the disruption of sleep by coexisting CSR may have diminished the impact of PLM, the prevalence of CSR and the frequency of associated arousals were very similar in CHF patients with and without PLM (Table 3). Nevertheless, it is possible that recruitment of more CHF patients without CSR may have demonstrated a greater effect of PLM on sleep quality.

Although there was a trend for CHF patients with PLM to experience greater daytime sleepiness, neither the ESS nor MSLT results were significantly different...
between CHF patients with and without PLM. Compared with healthy subjects, mean sleep latency was significantly lower only in CHF patients with PLM, suggesting that PLM and associated sleep disruption may have contributed to the development of daytime sleepiness.

Although the pathophysiology of PLM is not known, a number of hypotheses can be considered to explain the development of PLM in patients with CHF. First, because PLM have been reported in association with both obstructive and central sleep apnea, it is possible that they developed secondary to CSR. However, this hypothesis is not supported by our finding of a similar prevalence of CSR in CHF patients with and without PLM (Tables 2 and 3). Second, electrolyte and acid-base abnormalities associated with CHF may have contributed to the development of PLM. Although we did not measure serum electrolytes, it is unlikely that they were significantly different between CHF patients with and without PLM because the same proportion of both groups were taking diuretics (Table 1). Furthermore, arterial blood gas values both during wakefulness and sleep were not different between these groups (Table 3). Third, PLM may develop through stimulation of a spinal reflex in conjunction with cortical inhibition during sleep. Reduced peripheral blood flow may serve as anafferent stimulus that triggers this reflex. It is possible that CHF patients with a critical reduction in pedal blood flow, due to diminished cardiac output or coexisting peripheral vascular disease, are more likely to develop PLM. PLM have been reported in association with alteration in peripheral blood flow. Interestingly, our CHF patients with low frequency of PLM received vasodilators more frequently than those with a high frequency of PLM. It is possible that the peripheral vasodilation induced by these medications may have reduced the frequency of PLM. However, this is speculative and requires further study.

What are the clinical implications of PLM in patients with CHF? Although our results do not conclusively demonstrate that PLM cause sleep disruption and daytime sleepiness in patients with CHF, it is likely that severe PLM contribute to sleep and daytime complaints in individual subjects. Second, the increased frequency of arousals from sleep associated with PLM may have a direct impact on ventricular function in patients with CHF. Arousals from sleep are associated with increased sympathetic nervous system activity, which is an important determinant of survival in the natural history of CHF. Increased sympathetic nervous system activity during sleep may increase left ventricular afterload and elevate systemic BP, which has been reported in patients with idiopathic PLM.

Third, arousals associated with PLM may influence the development of CSR in patients with CHF. The pathogenesis of CSR is closely related to oscillation of arterial Pco2 above and below the apnea threshold. Arousals from sleep frequently induce hyperventilation, which lowers PaCO2. If PaCO2 falls below the apnea threshold, CSR may develop if other predisposing conditions exist such as prolonged circulation time and increased gain of the metabolic control system. Furthermore, the duration of apnea within the periodic breathing cycle has been correlated with the degree of hyperventilation associated with arousals from sleep. Accordingly, PLM may both initiate and perpetuate CSR in patients with CHF and thereby impair sleep quality and daytime function, which are frequent sequelae of CSR. If PLM do contribute to morbidity in patients with CHF, effective treatment may improve not only sleep/wake complaints but also cardiac function.

In summary, we have found that CHF patients have an increased prevalence of PLM and associated arousals from sleep. Although the pathogenesis of PLM in this common medical disorder is not clear, we suggest that PLM may contribute to the patients’ sleep/wake complaints and possibly to their impaired cardiac function. Further studies are required to test these hypotheses and to determine whether they are influenced by medical therapy.

ACKNOWLEDGMENT: The authors wish to thank Elvice Garcia for typing the manuscript.

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