Impact on Clinical Outcomes of Periodic Leg Movements During Sleep in Hospitalized Patients Following Acute Decompensated Heart Failure

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Background: Periodic leg movements during sleep (PLM) are characterized by regularly recurring movement of the legs during sleep. Although PLM is common and a predictor of death in patients with chronic heart failure, the clinical significance of PLM in hospitalized patients with a reduced left ventricular ejection fraction (LVEF) following acute decompensated heart failure (ADHF) remains unknown.

Methods and Results: After initial improvement of acute signs and symptoms of ADHF, 94 consecutive patients with reduced LVEF who underwent polysomnography were enrolled. They were divided into 2 groups based on the presence or absence of severe PLM defined as PLM index ≥ 30 . The risks for clinical events, composite of all-cause death and rehospitalization, were assessed using a stepwise multivariable Cox proportional model including variables showing $P < 0.10$ in univariate analyses. Severe PLM was observed in 21 patients (22%). At a median follow-up of 5.2 months, 30 patients experienced clinical events (32%). In the multivariable analysis, the presence of severe PLM was significantly associated with increasing clinical events (hazard ratio, 2.16; 95% confidence interval, 1.03–4.54; $P = 0.042$) independent of hemoglobin level and the severity of sleep-disordered breathing.

Conclusions: In hospitalized patients with systolic dysfunction following ADHF, severe PLM was prevalent and significantly associated with increased risk of death and/or rehospitalization.

Key Words: Polysomnography; Sleep; Systolic heart failure

Although effective treatments for heart failure (HF) have been recently developed, it remains a major concern in terms of increasing hospitalization and mortality rates.¹ Episodes of worsening of HF, which usually manifest as acute decompensated HF (ADHF), lead to hospitalization and also progression of HF itself, possibly through alterations in cardiovascular physiology and systemic or cardiac metabolic conditions.^{2,3} Thus, hospitalization for ADHF should be identified as a specific entity or risk factor that contributes to the progression of HF.^{4,5} Consequently, among patients hospitalized for ADHF, the identification of potential risk factors that are associated with increased risk of readmission and death is considered an important strategy in comprehensive HF care and may provide benefits by reducing readmission and mortality rates.^{6–8} One such approach may include identification of periodic leg movements during sleep (PLM).

PLM is characterized by regularly recurring movements

of the legs during sleep, affecting 4–8% of the general population.^{9,10} Patients with chronic HF frequently have PLM.^{11–14} In addition, in patients with chronic HF, PLM can be a predictor of all-cause and cardiac death in those with either a reduced left ventricular ejection fraction (LVEF) or with preserved LVEF.^{14,15} However, the effect of PLM in hospitalized patients with reduced LVEF following an episode of ADHF remains to be elucidated. The aim of the present study was to evaluate the relationship between PLM in hospitalized patients with reduced LVEF following ADHF and clinical outcomes such as readmission and/or death.

Methods

Subjects

We enrolled 94 consecutive patients who were hospitalized between May 2012 and May 2014 at the Juntendo University

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Hospital for ADHF in association with LV systolic dysfunction (defined as LVEF <50% on echocardiography) and who underwent overnight polysomnography regardless of symptoms or signs of sleep disorders. ADHF was defined according to modified Framingham criteria.¹⁶ The exclusion criteria were acute coronary syndrome and cardiac surgery during the previous 4 weeks, end-stage renal disease requiring dialysis, cerebrovascular disease with neurological deficits, life-threatening malignancy, apparent obstructive lung disease as demonstrated by a forced expiratory volume <70% in 1 s/forced vital capacity, and known sleep-disordered breathing (SDB). The study protocol was approved by the Juntendo University Hospital Institutional Review Board, and the study complied with the Declaration of Helsinki. Informed consent was given by all patients.

Polysomnography

All patients underwent overnight polysomnography using a digital polygraph system (Alice PDX, Philips Respironics Inc., Murrysville, PA, USA) for a few days after the initial improvement in the acute signs and symptoms of ADHF. Generally accepted definitions and scoring methods were used.¹⁷ Thoracoabdominal motion was monitored via respiratory inductance plethysmography, and airflow was measured by an oronasal thermal airflow sensor and nasal pressure cannula. Oxyhemoglobin saturation (SO₂) was monitored by oximetry. Apneas and hypopneas were quantified, and the severity of SDB was assessed using the frequency of apneas and hypopneas per hour of sleep (i.e., apnea-hypopnea index, AHI). For leg movements, electromyographic recordings were made from the anterior tibialis muscles of both legs. PLM was defined and scored using standard criteria from the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events: a series of 4 consecutive leg movements lasting 0.5–5 s with an amplitude $\geq 8 \mu\text{V}$ above the resting baseline and separated by intervals of 5–90 s.¹⁷ A leg movement was not scored if it occurred during a period from 0.5 s preceding an apnea, hypopnea, or respiratory event-related arousal to 0.5 s following such an event. The PLM index (PLMI) was quantified as the frequency of PLMs per hour of sleep. In this study, patients were divided into 2 groups based on the presence or absence of severe PLM (i.e., PLMI <30/h or ≥ 30 /h).¹⁷ The PLM-related arousal index (PLMAI) was also quantified as the frequency of PLM-related arousals per hour of sleep.

Other Baseline Data and Outcome Data Collection

On the same day of polysomnography, anthropometric data were obtained, and the presence or absence of atrial fibrillation (AF) and the functional status of the patients were determined according to ECG and the New York Heart Association (NYHA) classification system, respectively. Blood pressure (BP) and heart rate were measured just before the functional status assessment. Blood samples were obtained in the early morning after polysomnography was performed. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation with a Japanese coefficient from baseline serum creatinine levels.¹⁸ Complete 2D echocardiography and Doppler ultrasound examination were performed using standard techniques on the day of blood sampling. The LVEF was calculated according to the modified Simpson method.

All patients were followed-up in hospital from the date

of polysomnography until November 2014; outcome data were obtained by reviewing the hospital medical records in which all deaths and readmission events were recorded. The endpoint in the present study was a composite clinical outcome of death and readmission for ADHF. Readmission for ADHF was defined as the first unscheduled readmission to the cardiology ward with progressive symptomatic and/or hemodynamic deterioration.

Statistical Analysis

To compare baseline characteristics between the 2 groups, χ^2 test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U-test for continuous variables were used. The event-free survival curves were established using the Kaplan-Meier method and compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression analyses were performed to evaluate the association between the presence of severe PLM and clinical outcomes. In the univariable analysis, the presence of severe PLM was used as an independent variable along with the following baseline variables: age, sex, body mass index, ischemic etiology, presence or absence of AF, implantable cardioverter defibrillator, cardiac resynchronization therapy, LVEF, systolic and diastolic BP, heart rate, eGFR, hemoglobin level, serum levels of sodium and potassium and C-reactive protein (CRP), plasma B-type natriuretic peptide (BNP) level, medication use, other sleep study parameters (total sleep time, percentage of slow wave sleep, percentage of rapid eye movement [REM] sleep, mean and minimum SO₂, PLMAI [$<$ or ≥ 5 /h],¹⁹ and AHI) and initiation of SDB treatment. Next, variables that showed $P < 0.10$ in the univariable analysis were entered into a multivariable forward stepwise Cox proportional hazards regression analysis with $P < 0.05$ to enter and $P \geq 0.10$ to remove. The natural log-transformed values were used for CRP, BNP, and AHI, as these values were skewed. The assumption of proportional hazards was assessed using a log-minus-log survival graph. All these analyses were performed using a statistical software package (SPSS ver.23.0, IBM Corp., Armonk, NY, USA).

Results

Of the 94 patients, 21 (22%) had severe PLM. The baseline characteristics of the patients with and those without severe PLM are shown in **Table 1**. Patients with severe PLM had a greater NYHA functional class, higher levels of plasma BNP and serum CRP, but lower hemoglobin levels compared with those without severe PLM. They were less likely to take angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. However, there were no significant differences between the 2 groups for the other baseline characteristics. Polysomnographic parameters are listed in **Table 2**. Patients with severe PLM had less REM sleep but greater arousal index and PLMAI than those without severe PLM. Overall, 18 patients were started on treatment for SDB, including 1 of those with severe PLM and 17 of those without severe PLM (4.8% vs. 23.3%, $P = 0.112$).

The outcome data were collected for a median duration of 5.2 (interquartile range, 8.1) months. During this period, 30 clinical events (32%) occurred, of which 13 (62%) were in patients with PLM, and 17 (18%) in those without severe PLM. The cumulative event-free survival curves of these 2 groups are shown in the **Figure**. Patients with severe PLM

Table 1. Baseline Characteristics of Patients With ADHF and PLM

	PLMI <30/h (n=73)	PLMI ≥30/h (n=21)	P value
Age, years	62.2±13.3	66.8±14.9	0.181
Female sex, n (%)	23 (31.5)	6 (28.6)	0.977
BMI, kg/m ²	23.8±5.3	23.2±4.6	0.620
NYHA class	2 [1]	3 [1]	0.004
II, n (%)	46 (63.0)	6 (28.6)	0.011
≥III, n (%)	27 (37.9)	15 (71.4)	
Ischemic etiology, n (%)	22 (30.1)	9 (42.9)	0.407
AF, n (%)	17 (23.3)	4 (19.0)	0.909
Diabetes mellitus, n (%)	17 (23.3)	8 (38.1)	0.283
ICD, n (%)	4 (5.5)	2 (9.5)	0.613
CRT, n (%)	2 (2.7)	3 (14.3)	0.072
Systolic BP, mmHg	106.9±18.7	104.1±15.2	0.533
Diastolic BP, mmHg	60.7±10.9	56.9±8.9	0.148
Heart rate, beats/min	69.4±10.3	73.4±9.5	0.570
LVEF, %	31.4±7.8	29.8±9.4	0.441
Hemoglobin, g/dL	14.1±2.4	12.4±2.2	0.004
eGFR, mL/min/1.73 m ²	60.47±23.0	50.7±25.4	0.101
Sodium, mmol/L	139.3±3.8	138.8±3.8	0.615
Potassium, mmol/L	4.4±0.4	4.4±0.4	0.709
CRP, mg/dL	0.2 [0.4]	0.6 [1.2]	0.026
BNP, pg/mL	266.6 [407.0]	697.1 [825.3]	0.003
β-blockers, n (%)	67 (91.8)	18 (85.7)	0.413
ACEIs/ARBs, n (%)	67 (91.8)	14 (66.7)	0.010
Aldosterone blockers, n (%)	47 (64.4)	16 (76.2)	0.735
Loop diuretics, n (%)	60 (82.2)	18 (85.7)	0.961

Data are expressed as mean±SD or median [interquartile range] for continuous variables and number (%) for nominal variables. ACEI, angiotensin-converting enzyme inhibitors; ADHF, acute decompensated heart failure; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PLM, periodic leg movement during sleep; PLMI, periodic leg movement index.

Table 2. Polysomnographic Parameters of Patients With ADHF and PLM

	PLMI <30/h (n=73)	PLMI ≥30/h (n=21)	P value
Total sleep time, min	367.5±89.0	332.2±120.2	0.144
% of slow wave sleep, % of TST	10.2±8.3	9.0±7.1	0.555
% of REM sleep, % of TST	16.4±6.4	11.0±7.3	0.001
Arousal index, events/h of sleep	18.9 [19.3]	30.3 [21.9]	0.015
AHI, events/h of sleep	22.7 [35.2]	29.4 [32.4]	0.327
Mean SO ₂ , %	96.0±1.7	95.6±1.5	0.355
Minimum SO ₂ , %	85.1±8.5	85.0±7.9	0.945
PLMI, events/h of sleep	0.8 [6.7]	59.9 [57.0]	<0.001
PLMAI, events/h of sleep	0.2 [1.0]	6.0 [12.2]	<0.001

Data are expressed as mean±SD or as median [interquartile range]. AHI, apnea-hypopnea index; PLMAI, PLM-related arousal index; REM, rapid eye movement; SO₂, oxyhemoglobin saturation; TST, total sleep time. Other abbreviations as in Table 1.

had significantly lower event-free survival than those without severe PLM (P=0.002). In the univariate Cox proportional hazards regression analysis, greater heart rate (per 1/min increment; hazard ratio [HR], 1.04; 95% confidence interval [CI], 1.00–1.07; P=0.043), greater NYHA class (per 1 class increment; HR, 1.67; 95% CI, 0.96–2.91; P=0.070), lower hemoglobin (per 1 g/dL increase; HR, 0.82; 95% CI, 0.70–

0.97; P=0.019), lower eGFR (per 1 mL/min/1.73 m² increment; HR, 0.98; 95% CI, 0.97–0.99; P=0.019), use of loop diuretics (HR, 6.04; 95% CI, 0.82–44.4; P=0.077), less REM sleep percentage (1% increment; HR, 0.94; 95% CI, 0.89–0.99; P=0.027), greater natural log-transformed AHI (per 1 increment; HR, 1.80; 95% CI, 1.16–2.81; P=0.009), initiation of SDB treatment (HR, 0.21; 95% CI, 0.05–0.90;

P=0.036), and the presence of severe PLM (HR, 3.04; 95% CI, 1.48–6.28; P=0.003) showed values with P<0.10 and were included in the multivariable analysis (Table 3). The final multivariate forward stepwise Cox proportional hazards regression analysis model is also shown in Table 3. The presence of severe PLM was significantly associated with poor clinical outcomes, together with lower hemoglobin levels and a greater log-transformed AHI.

Discussion

Our findings provide novel insights into the clinical importance of PLM in patients with HF. First, we observed severe PLM defined as PLMI ≥30/h in 22% of unselected hospitalized patients following ADHF in association with reduced LVEF. Second, such severe PLM in hospitalized patients following ADHF was associated with a 2.2-fold greater risk of rehospitalization and/or all-cause death compared with patients without severe PLM after adjustment for other significant variables. In addition, this relationship

between severe PLM and clinical outcomes remained significant even in the multivariable analysis, including severity of SDB, which is a common sleep-related comorbidity of HF. These findings suggest that identification of severe PLM following an ADHF episode could be an important strategy in comprehensive HF care.

In 4 previous studies among HF patients with reduced LVEF, PLM was generally prevalent.^{11–14} However, the reported prevalence is highly variable ranging, from 19% to 52%. One possible explanation for this discrepancy may be differences in the severity of HF. The oldest study by Hanly and Zuberi-Khokhar¹¹ reported that 52% of HF patients with reduced LVEF had moderate to severe PLM, defined as PLMI ≥25/h, which is the highest prevalence rate of PLM among the 4 studies. They reported that their HF patients were stable, but the mean LVEF was 23%, and only NYHA functional class III and IV heart disease was observed, suggesting that the enrolled patients with severely impaired LVEF and highly symptomatic HF may not have really been stable. Three other studies^{12–14} consistently reported a similar prevalence (i.e., 19%, 20% and 37%) even while using a much lower cutoff point for PLMI: ≥5/h. Even among those studies, the study by Yumino and colleagues in which some patients with severely impaired LVEF and with NYHA class IV symptoms were enrolled showed a relatively greater prevalence of PLM (i.e., 37%)¹⁴ compared with the other 2 studies (19% and 20%).^{12,13} On the other hand, a more recent study by Yoshihisa and colleagues in which patients with either reduced or preserved LVEF and those with variable NYHA class (i.e., class I–IV) disease were enrolled showed that the prevalence of severe PLM, defined as PLMI ≥30/h, was 16%; this prevalence is less than that of severe PLM in the present study, in which only patients with reduced LVEF and more symptomatic patients following an episode of ADHF were enrolled. In fact, a recent study by Yoshihisa and colleagues reported that patients with severe PLM have impaired exercise capacity.¹⁵ In addition, in the present study, patients with severe PLM had a worse NYHA functional class and higher CRP and BNP levels than those without severe PLM. Taken together, these findings suggest that patients with more severe HF or those in an unstable state are likely to have severe PLM, and the presence of severe PLM may be an important indicator of such patients' status following ADHF.

A retrospective study in which 29 patients with renal

Table 3. Variables Showing P<0.10 in Univariable Analyses and Variables in the Final Model of Multivariable Stepwise Cox Proportional Hazards Regression Analysis

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Heart rate (1/min increase)	1.04 (1.00–1.07)	0.043	—	—
NYHA class (1 increase)	1.67 (0.96–2.91)	0.070	—	—
Hemoglobin (1 g/dL increase)	0.82 (0.70–0.97)	0.019	0.81 (0.68–0.98)	0.028
eGFR (1 mL/min/1.73 m ² increase)	0.98 (0.97–0.99)	0.019	—	—
Use of diuretics—yes	6.04 (0.82–44.4)	0.077	—	—
% of REM sleep (1% increase)	0.94 (0.89–0.99)	0.027	—	—
Natural log-transformed AHI	1.80 (1.16–2.81)	0.009	1.79 (1.15–2.79)	0.011
Initiation of SDB treatment—yes	0.21 (0.05–0.90)	0.036	—	—
PLMI ≥30/h—yes	3.04 (1.48–6.28)	0.003	2.16 (1.03–4.54)	0.042

CI, confidence interval; SDB, sleep-disordered breathing. Other abbreviations as in Tables 1,2.

failure were included reported that the presence of PLM was associated with increased mortality rate.²⁰ In another retrospective study in which the polysomnographic, echocardiographic, and outcome data of 584 patients referred because of restless leg syndrome were analyzed, severe PLM defined as PLMI $\geq 35/h$ was an independent predictor of severe LV hypertrophy and was associated with increased cardiovascular morbidity and mortality.²¹ In a large observational cohort study, greater severity of PLM was associated with incident cardiovascular disease, particularly peripheral artery disease, in community-dwelling elderly men.²² However, the significance of PLM on clinical outcomes in the field of secondary prevention of cardiovascular disease remains to be elucidated. Nevertheless, there are 2 studies in which the relationship between the presence of PLM and prognosis among patients with HF was investigated. Yumino and colleagues reported that in chronic HF patients with reduced LVEF, the presence of PLM, defined as PLMI $\geq 5/h$, was associated with increased risk of all-cause death.¹⁴ Furthermore, a study by Yoshihisa and colleagues in which HF patients with either reduced or preserved LVEF and those with a variable NYHA class (i.e., class I–IV) were enrolled showed a significant relationship between severe PLM and increased risk of cardiac death.¹⁵ There are no previous data regarding the prognostic significance of PLM in hospitalized patients following ADHF in association with reduced LVEF. Therefore, our study is the first to show that severe PLM in hospitalized patients following ADHF in association with reduced LVEF correlated with an increased risk of rehospitalization and/or all-cause death. Results of the present study indicated that identification of severe PLM even in hospitalized patients following ADHF was important to stratify patients with a high risk for subsequent rehospitalization and/or death.

The mechanisms linking PLM and adverse clinical outcomes in patients with HF remain to be elucidated. The most plausible mechanism is the activation of the sympathetic nervous system. Each episode of PLM causes elevations in BP and heart rate^{23,24} through direct and indirect (via arousal) activation of the sympathetic nervous system.^{25,26} Furthermore, several studies have shown the presence of sustained elevation of BP in association with PLM.^{19,27,28} Such elevations in BP and heart rate during sleep and daytime hypertension in association with PLM may contribute to the LV hypertrophy and increased cardiovascular morbidity and mortality in patients with renal failure, restless leg syndrome, or in community-dwelling elderly men.^{20–22} As well, in a large observational cohort there was a significant association between PLM and cardiac arrhythmias in a subset of community-dwelling elderly men with HF or myocardial infarction.²⁹ In patients with HF, PLM-related hemodynamic changes and possibly cardiac arrhythmias through activation of the sympathetic nervous system may adversely affect cardiac load and function to a greater extent than those without HF and lead to not only increased mortality but also increased rehospitalization rates. Other factors associated with PLM, such as inflammation, may also contribute to the worsening of HF and increased mortality rate.^{30,31} In fact, in the present study, patients with severe PLM showed greater CRP levels than those without severe PLM.

Nevertheless, a cause and effect relationship between the presence of PLM and increased risk of rehospitalization and/or death in patients with HF has not been established

from the results of the present study or other previous studies. An activated sympathetic nervous system in association with HF itself may facilitate the development of PLM.³² Furthermore, there is a possibility that PLM is just an indicator of more impaired cardiac function or unstable HF status. Thus, we cannot determine whether severe PLM in hospitalized patients following ADHF is a therapeutic target or not. Although it is reported that dopamine agonists can alleviate PLM in some subjects,³¹ and specific treatment of PLM by dopamine agonists can be effective in reducing the amplitude of heart rate variability and BP elevation induced by PLM,^{33,34} there is no evidence regarding the cardiovascular effects of PLM-targeted therapy, especially in patients with HF. Thus, further interventional studies to assess the cardiovascular effects of PLM-targeted therapy in hospitalized patients with HF are needed to investigate the cause and effect relationship between PLM and cardiovascular morbidity and mortality in HF patients.

Study Limitations

First, the number of subjects was relatively small. Second, although we took confounders into account, we cannot exclude the possibility that unmeasured factors may have explained some of our findings. Third, although activation of the sympathetic nervous system may play a key role in the relationship between severe PLM and poor clinical outcome, we did not assess sympathetic nervous system activity in patients with HF. Finally, we did not assess for the presence of restless leg syndrome symptoms. Thus, the results of the present study should be viewed as preliminary, and further studies with a larger sample size are needed.

In conclusion, results of the present study shed light on the clinical significance of PLM in patients with HF, suggesting that in hospitalized patients following ADHF in association with reduced LVEF, the presence of severe PLM is associated with increased risk of rehospitalization and/or all-cause death, independent of the severity of SDB.

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