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Periodic Limb Movements in Sleep Contribute to Further Cardiac Structure Abnormalities in Hemodialysis Patients with Restless Legs Syndrome

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SCIENTIFIC INVESTIGATIONS

Study Objectives: In hemodialysis (HD) patients, restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS) constitute common sleep disorders. Recent findings indicate a role for PLMS as a risk factor in the development of new or the aggravation of existing cardiovascular disease. The aim of the current study was to investigate the association of PLMS with indices of cardiac morphology and function in HD patients with RLS as a potential pathway by which PLMS could alter cardiovascular risk.

Methods: Based on PLMS diagnosis by an overnight polysomnographic evaluation, 19 stable HD-RLS patients were divided into the PLMS group (n = 10) and the non-PLMS group (n = 9). During the overnight assessment, nocturnal blood pressure (BP) indices were also assessed. Left ventricular (LV) dimensions were examined by M-mode echocardiography, whereas LV diastolic function was evaluated by conventional Doppler and tissue Doppler imaging the following day.

Results: LV internal diameter in diastole was significantly increased in the PLMS group (4.96 ± 0.61 vs 4.19 ± 0.48 cm, p = 0.007), leading to a significantly increase in LV mass (202 ± 52 vs 150 ± 37 g, p = 0.026). In contrast, no between group differences were observed in diastolic function indices (p > 0.05).

Conclusions: These are the first data to associate severe PLMS with further LV structure abnormalities in HD patients with RLS.

Keywords: Sleep disorders, cardiovascular disease, polysomnography, echocardiography, left ventricular hypertrophy, diastolic function

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Periodic limb movements in sleep (PLMS) is very common in patients receiving hemodialysis (HD) therapy.[1] Briefly, PLMS induces stereotypical repetitive leg movements during sleep, causing significant sleep disturbances through its associated arousals and motor restlessness. Recent studies report that PLMS, as well as a related condition called restless legs syndrome (RLS), are associated with increased cardiovascular risk factors, both in uremic[2,3] and idiopathic RLS patients.[4-6] In addition, in the HD population, PLMS seems to be an independent predictor of all causes mortality.[7] The pathway through which PLMS may confer greater cardiovascular risk in HD patients is not clear but one potential process, via an impact of cardiac structure and function, has not been assessed before.

In RLS patients with normal kidney function, PLMS is associated with a rise in nocturnal blood pressure (BP) (or lack of the dipping effect) and heart rate (HR), probably due to increased sympathetic activity as a result of the leg movements.[8,9] The non-dipping effect of the BP could provide an excessive hemodynamic stimulus that may result in cardiac structure abnormalities[10] such as left ventricular hypertrophy,[11] which in turn could result to a diminished diastolic function.[12,13] By altering cardiac structure and function PLMS could play an important role in the development, or aggravation of cardiovascular disease, which is the main cause of mortality in the HD patients,[14] but this has not yet been studied. This is particularly pertinent given that HD represent a patient population whose cardiac morphology and function is already adversely affected by the chronic uremia as well as the HD therapy per se.[12,13] Consequently, the aim of the current study was to examine whether RLS-HD patients with PLMS have further deterioration in LV cardiac structure and function compared to their PLMS-free counterparts.

BRIEF SUMMARY

Current Knowledge/Study Rationale: The pathway through which PLMS may confer greater cardiovascular risk and higher mortality in hemodialysis patients is still unknown. The current study associated PLMS with further impairments on cardiac structure and function in hemodialysis patients with RLS increasing therefore their cardiovascular risk and mortality.

Study Impact: Severe PLMS seems to contribute further impairments in left ventricular structure in hemodialysis patients with RLS. Successful treatment of PLMS could result to potential reductions in cardiovascular disease risk and lower mortality rates.

METHODS

Subjects

Sixty-five volunteers were initially screened for RLS by a neurologist who specializes in RLS assessment using the criteria of the International Restless Legs Syndrome Study Group (IRLSSG)[15]; syndrome severity was assessed using the IRLSSG severity rating scale.[16] Twenty-five stable HD patients were diagnosed with RLS, but only 19 fulfilled inclusion criteria. Inclusion criteria were RLS positive diagnosis and being on HD therapy ≥ 6 months prior to the study, with adequate HD efficiency (Kt/V > 1.1).

Patients were excluded from the study if they were diagnosed with neuropathies (n = 3), had reasons for being in a catabolic state (including malignancies and opportunistic infections) within 3 months prior to the study (n = 2), were treated with dopaminergic drugs (n = 1), or had uncontrolled hypertension. All patients had a forearm arteriovenous fistula as vascular access in order to receive the HD treatment.

Study Design

This study employed a cross-sectional design. Patients with RLS participated in full-night polysomnography that took place prior to any measurements. Patients then divided into 2 groups according to their PLMS score: the PLMS group (PLMS/h > 25, n = 10) and the non-PLMS group (PLMS/h < 25, n = 9). The status of the patients was coded for blinding purposes. All investigators were blinded to the PLMS status of the patients up to the completion of data analysis. Patients were studied in a single outpatient visit on a non-dialysis day. All patients gave written informed consent to participate in this study. The study conformed to the principles enumerated in the Helsinki Declaration of 1975 and was approved by the Ethics Committee on Human Research at the University Hospital of Larissa.

Polysomnography

The polysomnographic studies were performed at the Sleep Disorders Laboratory of University Hospital of Larissa on a non-dialysis day. Polysomnograms (Somnoscreen, Somnomedics GmbH, Randersacker, Germany), were recorded and scored according to the latest instructions of the American Academy of Sleep Medicine for scoring sleep and associated events.[17] The assessment of PLMS was performed according to the official World Association of Sleep Medicine (WASM) and IRLSSG standards for recoding and scoring of PLMS.[18] Specifically, a PLM was defined as a continuous succession of ≥ 4 leg movements, with 5 to 90 s between movements.[17,18] A movement event was defined as lasting 0.5 to 10 s. The onset of a movement was defined as the point at which there was an 8-μV increase in the EMG voltage above the resting EMG; the end of a leg movement was defined as the start of a period lasting ≥ 0.5 sec after the EMG returned to values not exceeding 2 μV above resting EMG levels.[17,18] The number of PLM per hour of sleep (PLMS/h) was calculated. PLMS/h > 25 indicates moderate or severe PLMS[19] and has been used before as a cutoff point in RLS-HD patient studies[20]; it was thus considered clinically relevant and a cutoff for inclusion in the PLMS group.

Heart rate (HR) during sleep was recorded via an ECG within the PSG device. Minimal and maximal HR, HR accelerations and decelerations, and presence of arrhythmias were recorded. The nocturnal variation of systolic BP was assessed using the pulse transit time (PTT) method, which is a standard tool of the PSG system.[21] Minimum, maximum and average systolic BP, and presence and magnitude of BP dipping (reduction of nocturnal BP compared to the resting value obtained before sleep) were recorded. "Non-dipping" was defined as a reduction of BP of under 10% of the resting average.[22]

Echocardiography

All echocardiographic scans were performed using an iE33 echocardiographic system (Philips Medical Systems, Andover, MA, USA). All image acquisitions were made with the subject lying in the left lateral decubitus position with a 2.5 MHz transducer. For each patient, ≥ 3 consecutive beats were analyzed in each scan, and the mean value was used in the subsequent statistical analysis. All echocardiograms were performed by the same experienced echocardiographer, who was blinded with regards to patient PLMS status. For the recording of HR, a single-lead ECG inherent to the echocardiographic system was used.

Left ventricular dimensions were determined from 2-dimensional guided M-Mode images according to the recommendations of the American Society of Echocardiography (ASE) for chamber quantification,[23] using the parasternal acoustic window. LV mass was calculated from M-Mode traces at the level of mitral valve and determined in *g* by using the recommended ASE formula, whereas the LV mass index was calculated by dividing LV mass by body surface area (using the DuBois and DuBois formula) and height$^{2.7}$ to minimize effects of age, gender, and overweight status.[23]

For the assessment of LV diastolic function, the transducer was applied apically while the pulsed wave Doppler sample volume (4 mm) was located at the tips of the mitral valve leaflets. Doppler gain, pulse repetition frequency, and high-pass filter were all adjusted in order to maximize the signal to noise ratio. The following parameters were evaluated: early peak flow velocity (E), late peak flow velocity (A); thus the ratio of E to A was calculated. Ejection fraction (EF) was calculated using the biplane Simpson's method from 2-dimensional apical 2- and 4-chamber orientation to evaluate the patient's systolic function.

Tissue Doppler velocities were assessed at the basal septum, using pulsed-wave Doppler. The sample volume (2 mm) was placed at the basal septum at the level of the mitral annulus ring in parallel to the longitudinal movement of the septum. The high-pass filter was bypassed, and gains were set to a minimal value to obtain the best signal to noise ratio. Peak early diastolic (E') and peak late diastolic (A') myocardial tissue velocities were assessed and the E'/A' ratio was calculated. In addition, the conventional Doppler E to tissue Doppler E' ratio (E/E') was calculated.

All echocardiographic examinations were performed up to 12 h after the last mid-week HD session in order to have a relatively preload-independent assessment, closer to a normovolemic state.

Blood Chemistry

Routine monthly laboratory results were recorded including albumin, transferrin, ferritin, iron, hematocrit, and hemoglobin. A single-pool Kt/V was calculated from pre- and post-dialysis

BUN measurements using the Daugirdas II equation. The analyses were performed at the clinical biochemistry lab of the University Hospital of Larissa under standard hospital procedures.

Statistical Analysis

Unpaired *t*-tests were used to compare the 2 groups for continuous normally distributed variables; χ^2 for categorical variables. The Pearson correlation test was used to assess the relationship between the examined variables. We conducted a hierarchical regression analysis (i.e., regression analysis where independent variables are inserted in a prespecified sequence to observe changes in regression coefficients amongst models) to predict LV mass (dependent variable) from PLMS, age, and resting SBP (independent variables). The hierarchy of the independent variables was adjusted so that the initial model included PLMS, while age and resting SBP were inserted one by one in subsequent models in order to observe differences in regression coefficients. All analyses were carried out using the Statistical Package for the Social Sciences software (SPSS for Windows, version 15.0, Chicago, Illinois). Data are presented as mean ± SD (95% confidence intervals), and the level for statistical significance was set at $p \leq 0.05$.

Sample Size

Post hoc statistical power analysis calculations were conducted based on the differences in standard echocardiographic indices (e.g., LV mass 202[52] vs 150[37], **Table 3**) between the 2 groups. The resulting statistical power was 71.6% for 2-sided type I and type II errors of 5%.

RESULTS

Patient characteristics are presented in **Table 1**. There were no significant differences between the PLMS and non-PLMS groups in any baseline variables except PLMS/h ($p < 0.001$). The mean value for PLMS/h for the PLMS group was 66.5 ± 27.0, indicating that the patients in the PLMS group suffered from severe PLMS.[19]

The HR and BP data at rest and during sleep are presented in **Table 2**. Resting HR and BP were not different between groups. The minimum systolic BP during sleep was significantly higher in the PLMS group ($p = 0.049$). The percent reduction of BP during sleep, compared to awake values, was 50% smaller in the PLMS

Table 1—Patient characteristics

Variables	PLMS	Non-PLMS	p values
N	10	9	–
Female / Male	3/7	3/6	0.876[a]
Age (y)	59.5 ± 7.3	47.2 ± 17.7	0.069
PLMS/h	66.5 ± 27.0	10.6 ± 7.4	< 0.001
IRLS score	22.2 ± 10.2	14.6 ± 11.9	0.157
Height (cm)	166.5 ± 7.0	163.5 ± 9.9	0.487
Dry weight (kg)	71.6 ± 10.7	74.7 ± 9.8	0.559
BMI (kg/m^2)	25.8 ± 5.3	26.3 ± 2.6	0.776
Kt/V	1.2 ± 0.02	1.3 ± 0.06	0.591
Years in hemodialysis	5.1 ± 2.6	4.8 ± 4.5	0.900
WHR	0.99 ± 0.04	0.97 ± 0.01	0.479
Albumin (g/dL)	4.4 ± 0.3	4.5 ± 0.4	0.828
Ferritin (ng/mL)	244 ± 174	422 ± 285	0.155
Iron (μg/dL)	76.2 ± 17.9	78.0 ± 20.1	0.857
Hct	39.3 ± 3.5	36.5 ± 2.1	0.059
Hb (g/dL)	12.9 ± 1.3	12.3 ± 0.6	0.241
Cardiovascular disease	2 (20%)	2 (22.2%)	0.926[a]
Diabetes prevalence	1 (10%)	1 (11.1%)	0.937[a]

All data are mean ± SD. An Unpaired *t*-test was used to assess the differences between the 2 groups, while for categorical data a χ^2 test was performed. BMI, body mass index; Kt/V, dialysis efficiency; WHR, waist to hip ratio; PLMS, periodic limb movements in Sleep; IRLS, restless legs syndrome severity scale; Hct, hematocrit; Hb, hemoglobin. [a]For categorical data a χ^2 test performed.

Table 2—Heart rate and blood pressure indices at rest and during polysomnography

Variables	PLMS	Non-PLMS	p values
N	10	9	–
Resting Values			
HR (beats/min)	76 ± 12 (66.8 to 85.3)	78 ± 17 (63.7 to 92.4)	0.781
SBP (mm Hg)	131 ± 21 (114 to 147)	119 ± 22 (103 to 140)	0.261
DBP (mm Hg)	71 ± 11 (62 to 79)	72 ± 82 (65 to 80)	0.809
Values during sleep			
Max SBP at PSG	166 ± 29 (143 to 188)	147 ± 25 (128 to 164)	0.143
Max HR at PSG	112 ± 23 (94 to 130)	113 ± 31 (90 to 134)	0.997
Average SBP at PSG	126 ± 26 (106 to 145)	110 ± 19 (96 to 123)	0.143
HR acceleration index	3.23 ± 4.48 (-0.2 to 6.6)	4.23 ± 5.78 (0.1 to 8.3)	0.683
HR deceleration index	4.03 ± 7.08 (-1.4 to 9.4)	4.93 ± 6.73 (0.1 to 9.7)	0.781
Arrhythmia index	14.8 ± 23.6 (-3.2 to 33.0)	3.0 ± 2.8 (1.0 to 5.0)	0.134
Min HR	57 ± 8 (51 to 62)	63 ± 14 (52 to 72)	0.314
Min SBP	119 ± 22 (102 to 136)	97 ± 23 (81 to 113)	0.049
HR systolic	1.04 ± 2.57 (-0.9 to 3.0)	0.52 ± 0.51 (0.2 to 0.8)	0.536
% BP Dipping compared to rest	9.1 ± 5.5 (4.8 to 13.3)	13.6 ± 10.2 (3.9 to 21.0)	0.253

All data are mean ± SD (95% confidence intervals). An Unpaired *t*-tests was used to assess the differences between the two groups. PLMS, periodic limb movements in sleep; RLS, restless legs syndrome; SBP, systolic blood pressure; DPB, diastolic blood pressure, PSG, polysomnography; HR, heart rate; min SBP, minimum systolic blood pressure levels during sleep; min HR, minimum heart rate levels during sleep; BP, blood pressure.

Table 3—Echocardiographic indices

Variables	PLMS	Non-PLMS	p values
N	10	9	–
Standard echocardiographic indices			
IVSTd (cm)	1.07 ± 0.16 (0.94 to 1.19)	1.09 ± 0.15 (0.97 to 1.20)	0.812
LVPWTd (cm)	1.01 ± 0.18 (0.86 to 1.15)	0.98 ± 0.09 (0.90 to 1.05)	0.679
LVIDd (cm)	4.96 ± 0.61 (4.49 to 5.44)	4.19 ± 0.48 (3.84 to 4.53)	0.007
LV mass (g)	202 ± 52 (162 to 242)	150 ± 37 (121 to 179)	0.026
LV mass/BSA (g/m^2)	114 ± 32 (89 to 139)	86 ± 18 (72 to 100)	0.034
LV mass/height$^{2.7}$	51.0 ± 12.3 (41.5 to 60.4)	40.2 ± 9.2 (33.1 to 47.3)	0.050
EF (%)	58 ± 6 (53.4 to 63.2)	58 ± 1 (49.9 to 66.2)	0.957
Doppler Mitral inflow indices			
E (cm/s)	58.2 ± 14.7 (46.9 to 69.5)	67.7 ± 15.6 (55.6 to 79.6)	0.204
A (cm/s)	83.5 ± 19.2 (68.7 to 98.3)	73.6 ± 19.5 (58.6 to 88.5)	0.292
E/A	0.70 ± 0.12 (0.60 to 0.79)	0.99 ± 0.56 (0.61 to 1.12)	0.146
DT (ms)	191 ± 44 (157.0 to 224.1)	178 ± 26 (156.4 to 199.5)	0.489
IVRT (ms)	89 ± 38 (60 to 117)	91 ± 21 (74 to 108)	0.885
Tissue Doppler myocardial velocities indices			
E' (cm/s)	5.71 ± 1.20 (4.7 to 6.6)	6.31 ± 2.40 (4.0 to 7.9)	0.509
A' (cm/s)	8.03 ± 1.77 (6.6 to 9.3)	8.26 ± 2.78 (5.7 to 10.5)	0.838
E'/A'	0.72 ± 0.16 (0.59 to 0.85)	0.85 ± 0.46 (0.4 to 1.2)	0.441
E/E'	10.7 ± 4.0 (7.5 to 13.7)	11.0 ± 2.8 (8.8 to 13.1)	0.841

All data are mean ± SD (95% confidence intervals). An Unpaired *t*-test was used to assess the differences between the 2 groups. IVSTd, interventricular septum thickness in diastole; LVPWTd, left ventricular posterior wall thickness in diastole; LVIDd, left ventricular internal diameter in diastole; LV, left ventricle; BSA, body surface area; EF, ejection fraction; E, early diastolic mitral flow velocity; A, late diastolic mitral flow velocity; E/A, ratio of early to late diastolic flow velocity; DT, deceleration time; IVRT, isovolumic relaxation time, E', early mitral annular velocity, A', late mitral annular velocity; E'/A', ratio of early to late mitral annular velocity; E/E', ratio of early mitral flow velocity to early mitral annular velocity.

Table 4—Polysomnographic data

Variables	PLMS	Non-PLMS	p values
N	10	9	–
Sleep duration (min)	422.8 ± 47.7 (388.6 to 456.9)	386.3 ± 56.8 (342.6 to 429.9)	0.150
Sleep efficiency (%)	93.1 ± 4.3 (90.0 to 96.1)	92.6 ± 6.2 (87.8 to 97.3)	0.858
Light sleep (%)	71.3 ± 15.6 (60.1 to 82.4)	68.6 ± 22.5 (51.3 to 85.8)	0.765
Deep sleep (%)	17.9 ± 17.6 (5.3 to 30.4)	21.7 ± 21.5 (5.1 to 38.2)	0.680

All data are mean ± SD (95% confidence intervals). An Unpaired *t*-test was used to assess the differences between the 2 groups. PLMS, periodic limb movements in sleep.

group, indicative of a reduced "dipping." Echocardiographic data are presented in **Table 3**. LVIDd (p = 0.007), left ventricular mass, LV mass/BSA, and LVM/height$^{2.7}$ were all higher in the PLMS group. Data for EF was not different between groups; neither conventional Doppler nor TDI indices of diastolic function differed significantly between the two groups (p > 0.05).

Data derived from the polysomnographic examination are presented in **Table 4**. There were no significant differences between the PLMS and non-PLMS groups in any of the examined sleep-related variables.

PLMS/h correlated moderately with LV mass (r = 0.492, p = 0.038), LV mass/BSA (r = 0.493, p = 0.038), LV mass/height$^{2.7}$ (r = 0.456, p = 0.050), and LVIDd (r = 0.505, p = 0.027). PLMS/h did not correlate with any LV functional index. Similarly, LV mass did not correlate with sleep duration (r = 0.129, p = 0.610). Resting systolic BP correlated with LVIDd (r = 0.499, p = 0.035) and LV mass (r = 0.724, p = 0.001). Maximal systolic BP during sleep correlated with LVIDd (r = 0.477, p = 0.039) and LV mass (r = 0.729, p = 0.001), while minimal systolic BP during sleep correlated significantly with PLMS/h (r = 0.510, p = 0.026). In contrast to PLMS/h, the RLS severity score (IRLS) did not correlate with any of the examined echocardiographic or PSG parameters. In addition, both diabetes status and previous cardiovascular disease did not correlate with LV mass (r = -0.397, p = 0.102 and r = 0.180, p = 0.474, respectively). The hierarchical regression analysis used to predict LV mass (dependent variable) from PLMS, age, and resting SBP (independent variables) demonstrated linear associations with PLMS and resting SBP. Yet, it is important to highlight that the coefficient of determination (R^2), which demonstrates the amount of variability explained by each model was increased mainly by the resting SBP (R^2 change = 0.349, p = 0.006), while PLMS (R^2 change = 0.223, p = 0.056) was considered marginally significant (**Table 5**).

DISCUSSION

To the best of our knowledge, we present the first evidence of further cardiac structure alternations in RLS-HD patients with

Table 5—Unstandardized regression coefficient table

			Unstandardized Regression Coefficient		
	R^2	F	Model 1	Model 2	Model 3
PLMS/h	0.223*	4.305*	0.66*	0.592	0.365
Age	0.231	2.103		0.317	-0.870
SBP	0.580**	5.974**			1.414**
Constant			154.3	140.3	-7.283

*p = 0.056. **p = 0.006. PLMS, periodic limb movements in sleep; SBP, systolic blood pressure.

severe PLMS, compared to patients without PLMS. While we present evidence that PLMS may contribute to an increase in LVIDd and LV mass, it seems that the magnitude of those alternations in LV structure is not sufficient enough to evoke further impairments in LV function. While speculative, due to the cross-sectional design employed, we hypothesize that PLMS may be associated with alterations in blood pressure during sleep that promote a larger LV size leading to increased cardiovascular risk in the HD patients. This hypothesis requires substantiation in future research.

There is evidence showing that the HD patients with RLS/PLMS experience significant impairments in QoL, and poor sleep[20] and appear to have a higher mortality risk[7] than their RLS/PLMS-free counterparts. Despite these reports on the detrimental impact of PLMS on morbidity and mortality of HD patients, until now, it was unknown what potential pathways to greater cardiovascular risk were associated with PLMS disorder, including altered cardiac structure and function. A link between PLMS and increased LV size and poor LV function is plausible, as we know that HD patients as a group exhibit a diminished cardiac function that consequently leads to an increased risk for a cardiovascular event.[24]

HD patients, *per se*, are characterized by LV structure abnormalities, while LV hypertrophy is considered to be one of the major morphological abnormalities in the HD patient's heart.[13] We observed that the LV chamber and LV mass were significantly larger in the PLMS group of HD patients than their PLMS-free counterparts, supporting our hypothesis that PLMS may be associated with further changes in LV size. In addition, a moderate but significant correlation ($r = 0.492$, $p = 0.038$) between the PLMS/h index and LV mass was found, further supporting the above findings. The later outcomes bear high clinical significance, as LV mass is considered to be a strong and independent predictor of mortality in the HD population.[13] However, we should acknowledge that this is a cross-sectional study, and the association between PLMS and LV mass does not imply causality. Thus it is clear that more research in needed in order to clarify the role of PLMS in LV mass in the HD population.

On the basis of the correlational analysis undertaken, we can hypothesize that the increased LVIDd and LV mass in the PLMS group may also be explained by the repetitive rise in nocturnal BP and HR that occur during PLMS episodes (with or without associated arousals) and/or by the lack of a significant dipping effect.[8,9,25] A high systolic BP during the night is strongly related to LV hypertrophy in HD patients.[26]

The speculative mechanism that PLMS induces increased LV mass via nocturnal BP mechanism is indirectly supported by a large epidemiological trial from Gangwisch and colleagues.[27] In this study, individuals exposed to less than 5 hours of sleep were approximately 60% more likely to develop hypertension than persons enjoying 6 to 8 hours of continuing sleep.[27] It is known that PLMS can significantly disturb sleep through the increased number of arousals that follow leg movements.[28] However, in the current study, sleep duration and sleep efficiency did not significantly differ between the PLMS and the non-PLMS patients.

In recent review articles, it has been hypothesized that the potential detrimental effect of RLS in the CV system could be due to the effect of PLMS in nocturnal BP and HR levels.[3,6] It is noteworthy that 80% of the patients suffering from RLS also co-experience PLMS (PLMS/h > 5).[29] The findings of the current study reveal that PLMS constitute a major contributor to the potential cardiovascular risk that the HD-RLS patients are exposed to. In contrast, RLS severity independent of PLMS did not correlate with any of the examined echocardiographic or PSG parameters.

Diastolic dysfunction is one of the most common abnormalities among patients receiving HD therapy.[12] Many factors are linked to the impaired diastolic function seen in HD patients such as anemia, hypertension, hemodynamic alternations (e.g., volume overload), arteriovenous fistula, increased LV mass, acidosis, hypocalcemia and hypoxia.[12,13] In our study, we did not find statistical differences in indices of LV dysfunction between HD groups, thus rejecting thus our original hypothesis. PLMS does not statistically augment deterioration in LV dysfunction seen in HD patients as a group.

Limitations and Implications

While our study is the first to show evidence of further cardiac structure alternations in RLS-HD patients, our data should be treated cautiously due to the cross-sectional design. Other points to note are that greater variability in LV diastolic functional data may mean that the current study was not adequately powered to detect meaningful differences in diastolic function between PLMS and no-PLMS groups. Ongoing study should follow up this point, potentially looking at other aspects of LV diastolic function such as "untwisting" velocities that can be assessed by myocardial speckle-tracking and represent early elastic recoil during isovolumic relaxation. It is possible that the potential negative effects of PLMS on LV diastolic function could have been masked under the dominant impact of uremia and hemodialysis therapy (i.e., the hemodynamic alterations) per se. While echocardiography is the front-line clinical tool to assess cardiac structure and function, a study employing cardiac magnetic

resonance imaging could provide more accurate measurements of LV mass and avoid some potential pitfalls that characterize the latter technique, such as operator dependence, poor acoustic windows, and the presence of asymmetric hypertrophy or eccentric remodeling, which can invalidate the usual formulas used to calculate LV mass.[30] In addition, the PLMS index of our patients was derived by a single PSG examination due to the nature of the population. Previous data derived from idiopathic RLS patients show a high night-to-night PLMS variability[31]; therefore, a single- night recording of PLMS could limit the reliability of our findings. Further, we should note that we did not assess some polysomnography-derived indices such as the respiratory disturbance index as well as the PLM arousal index, which according to the literature could be associated with LV hypertrophy[32] and BP changes,[25] respectively. Finally, we acknowledge that the study population is small and therefore the results, while warranting further notice, should be treated with caution, and generalization to all sufferers of PLMS requires further study.

Given the very high prevalence of sleep disorders in HD patients, we suggest that PLMS diagnosis should receive special attention from health care providers. PLMS should be treated appropriately to minimize cardiovascular risk and improve the quality of life of sufferers.

In conclusion, this is the first study that has demonstrated increased LVIDd and LV mass in RLS-HD patients who suffer from severe PLMS, compared to matched HD patients with no PLMS. The current findings provide a springboard for future multicenter clinical trials in order to explore the relationship of sleep-movement disorders and cardiac function and structure in uremic and other chronic disease populations.

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