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SCIENTIFIC INVESTIGATIONS

Reduced sympatho-vagal responses to orthostatic stress in drug-naïve idiopathic restless legs syndrome

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Study Objectives: Restless legs syndrome (RLS) is known to be a risk factor for cardiovascular disease. However, there are no electrophysiological biomarkers to assess this risk. This study aimed to evaluate heart rate variability (HRV) and cardiovascular reflexes in the supine and standing positions during wakefulness in patients with RLS.

Methods: Fourteen drug-naïve patients with RLS (12 women and 2 men, mean age, 42.14 ± 7.81 years) and 10 healthy control patients underwent tests for blood pressure, heart rate when in the supine and standing positions, and deep breathing and handgrip tests in controlled laboratory conditions. Data on 5-minute R-R intervals at each position were collected and analyzed for HRV.

Results: Expected cardiovascular reflexes were within the normal range and were similar between the 2 groups. In HRV analysis, the normalized unit of the low-frequency component and the low-frequency/high-frequency ratio during standing were lower in patients with RLS than in the control patients. The low-frequency/high-frequency ratio responses during the change from the supine to the standing position were significantly reduced in patients with RLS (mean ± standard deviation, 2.94 ± 3.11; control patients: 7.51 ± 5.58; $P = .042$.) On Spearman rank correlation, questionnaires related to sleep problems were associated with the parameters of HRV.

Conclusions: Patients with RLS showed reduced sympatho-vagal responses during the change from the supine to the upright position during wakefulness, and RLS-related sleep disturbance was a contributing factor for autonomic nervous system dysfunction. This case-control study showed a difference in HRV response to position change in a considerably small group of patients with RLS. The relevance of this finding is uncertain, but it may be worthy of further investigation in longitudinal studies on RLS and cardiovascular disease.

Keywords: restless legs syndrome, heart rate variability, cardiovascular disease

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Numerous cross-sectional and longitudinal observational studies have shown an association between restless legs syndrome and cardiovascular disease risk. However, there is no physiologic biomarker for cardiovascular disease risk in patients with restless legs syndrome.

Study Impact: After evaluating the autonomic control of cardiovascular reflexes using heart rate variability with positional changes in drug-naïve patients with idiopathic restless legs syndrome during wakefulness, we found that low-frequency/high-frequency ratio responses during the change from the supine to the standing position were significantly reduced in patients, suggesting reduced sympatho-vagal responses during positional change. Restless legs syndrome–related sleep disturbance was a contributing factor for autonomic nervous system dysfunction.

INTRODUCTION

Restless legs syndrome (RLS) is a common neurological sensorimotor disorder characterized by an uncomfortable sensation in the legs that worsens in the evening and night, resulting in sleep disturbances.[1] The association between RLS and cardiovascular disease (CVD) has been reported in both cross-sectional and prospective studies, although these are limited in number and have yielded conflicting results.[2] Several clinical studies have explored this association through physiologic measures such as blood pressure, vascular stiffness, and reactivity.[3–6]

Heart rate is regulated by the balance between the sympathetic and parasympathetic nervous systems. Heart rate variability (HRV) is a commonly examined marker for autonomic nervous system (ANS) dysfunction and is a well-accepted noninvasive marker for evaluating cardiac autonomic function.[7] Low HRV has been positively associated with CVD and mortality.[8] Recently, a large prospective study showed that short-term HRV testing can be used as a novel digital-health

mortality indicator for enhanced risk assessment in individuals without known CVD.[9]

Some studies that assessed HRV in patients with RLS reported reduced sympatho-vagal activity during the daytime[10,11] and increased sympathetic activity associated with periodic leg movements during sleep.[12] However, such previous studies had some limitations. Two studies that examined sympatho-vagal activity included patients who were not drug-naïve, and patients in another study were older and had higher blood pressure than the control patients at baseline. Dopaminergics and aging may affect sympatho-vagal activity.

The supine-standing HRV test measures dynamic loading of the ANS in the form of an increase in sympathetic activity and a simultaneous decrease in vagal activity in the standing position and vice versa in the supine position.[13] Therefore, we hypothesized that autonomic dysfunction would manifest during positional change and that the ANS responses during the change of position from supine to standing would differ between patients with RLS and healthy control patients during wakefulness.

This study aimed to evaluate the autonomic control of cardiovascular reflexes in the supine and standing positions in middle-aged patients (age range, 30–55 years) with normal blood pressure and drug-naïve idiopathic RLS during wakefulness; the study also assessed the utility of HRV as a tool for predicting cardiovascular risk in patients with RLS.

METHODS

Study participants

Patients with drug-naïve idiopathic RLS were recruited at the outpatient clinic of the CHA University Hospital, Korea, between June 2017 and February 2019. The study was approved by the CHA Medical Center Institutional Review Board. All patients were diagnosed by a neurologist in the outpatient neurological clinic using face-to-face interviews and sleep questionnaires at the first visit. Participants were included if they (1) met the International Restless Legs Syndrome Study Group diagnostic criteria[1] and (2) were aged 30–55 years at the time of diagnosis. The exclusion criteria included the following: (1) previous diagnosis or evidence of specific sleep disorders, such as obstructive sleep apnea, narcolepsy, and rapid eye movement sleep behavior disorder (screened using clinical interviews and sleep questionnaires including Sleep-50[14] and the Korean version of the self-reported rapid eye movement sleep behavior disorder questionnaire[15]); (2) underlying conditions that may induce RLS, such as iron-deficiency anemia, pregnancy, neuropathy, multiple sclerosis, or renal failure[16]; (3) use of concomitant medications that cause or exacerbate RLS; (4) disorders with symptoms similar to those of RLS such as positional discomfort, leg cramps, essential tremor, Parkinson's disease, neuroleptic-induced akathisia, vascular claudication, neurogenic claudication, myelopathy, and arthritis; and (5) history of receipt of any medication or presence of other medical disorders such as diabetes mellitus, hypertension, cardiac, endocrine disease, metabolic disease, and renal disease.

To assess RLS severity, we used the Korean version of the International Restless Legs Syndrome (IRLS) rating scale,[17] which has 10 items scored using a 5-point scale (no symptoms of RLS = 0 to very severe symptoms = 4) and provides a total score out of 40 (mild, 0–10; moderate, 11–20; severe, 21–40). We used the Insomnia Severity Index (ISI)[18] and the Pittsburgh Sleep Quality Index (PSQI)[19] to evaluate sleep quality. The ISI is a 7-item self-reported questionnaire that assesses insomnia severity; a 5-point scale (no problem = 0 to very severe = 4) is used for each item, with a total score out of 28 (subthreshold insomnia, 0–7; moderate insomnia, 15–21; severe insomnia, 22–28). The PSQI is a 19-item questionnaire evaluating sleep quality and disturbance over the past month. The tool yields 7 component scores, which range from 0–3. A total score ranging from 0 to 21 is obtained by adding the 7 component scores; a score > 5 suggests poor sleep quality.

Age- and sex-matched healthy participants served as controls and were screened for any sleep-related symptoms and neurological or psychological diseases by a structured questionnaire and clinical interview. Informed consent was obtained from all participants.

HRV and cardiovascular reflexes

At the second visit, all the study participants were evaluated in a laboratory at the same time slot (8:00 AM–10:00 AM) after they had fasted overnight and refrained from strenuous exercise for > 48 hours and from alcohol and caffeine for 24 hours to avoid any possible influence on the circadian rhythm that could affect cardiovascular function. Measurements were obtained using DiCAN (Medicore, Seoul, Korea), a device that is used to test ANS function and orthostatic intolerance in HRV; it consists of an electrode cable (3-channel), a noninvasive blood pressure module, a Valsalva tube (Galemed Corp., Taipei, Taiwan), and a handgrip dynamometer and is used after a 10-minute period of rest and heart rate stabilization.

Cardiovascular reflexes were assessed using standard cardiovascular reflex tests, as described by Ewing and Clarke.[20] Changes in the R-R interval with deep-breathing standing and changes in blood pressure in response to the handgrip test, which corresponds to the maximal voluntary isometric contraction, were evaluated. The difference in the R-R interval with deep breathing was taken as the mean of the differences between the maximum and minimum R-R intervals during 6 respiratory cycles. The ratio of the longest R-R interval around the 30th beat after standing to the shortest R-R interval around the 15th beat after standing was 30:15. In all study participants, the test sequence was standardized as follows: supine position, standing test, deep breathing, and handgrip test.

Analyses of HRV were conducted using an analyzing software embedded in DiCAN (Medicore). The electrocardiography signal was collected at a sampling rate of 500 samples/second for 5 minutes. The R-R interval was measured by detecting the QRS complex; several errors during the detection of the QRS complex and noise from arrhythmias were not included in the analysis. To express the responsiveness of sympatho-vagal activity to postural stress, parameters of HRV were recorded for 10 minutes in the supine and standing positions. All parameters were analyzed during the final 5 minutes in the supine position and in the following 5 minutes after change of posture in the standing position. The frequency-domain analysis concerned the following parameters: high

frequency (HF; 0.15–0.4 Hz), low frequency (LF; 0.04–0.15 Hz), very low frequency (0.01–0.04 Hz), and the LF/HF ratio. The HF power (expressed in ms^2) illustrated the vagal control over the heart rate. The LF and HF values were also calculated in normalized units defining the relative values of each frequency spectrum compared to the total spectral power, from which the very low frequency component was excluded during calculation. The time domain of HRV features included the mean R-R interval, the standard deviation of the normal-to-normal intervals, and the root mean square of difference between adjacent R-R intervals.

Statistical analysis

Data were reported as means ± standard deviation. The normally distributed data were compared using the Student unpaired 2-tailed *t* test. HRV, expressed as normalized units not normally distributed, was analyzed using the Mann-Whitney rank-sum test for intergroup analysis and the Wilcoxon matched-pairs signed rank test for intragroup analysis within the sample. To avoid type 1 statistical errors, the Bonferroni correction was applied when required. Associations between the variables were determined using nonparametric partial correlation with the Spearman rank correlation. All statistical analyses were performed using SPSS (version 23.0, IBM Corp., Armonk, NY).

RESULTS

Clinical features and demographics

Fourteen patients with RLS (12 women and 2 men; mean age, 42.14 ± 7.81 years) with a mean disease duration of 9.33 ± 5.46 years and 10 healthy control patients (8 women and 2 men; mean age, 39.10 ± 6.44 years) participated in the study. RLS patients and control patients did not significantly differ in terms of age and body mass index (unpaired *t* test: age, $P = .285$; body mass index, $P = .312$).

Patients had moderate to severe symptoms at the first visit to our clinic (mean IRLS score, 28.07 ± 4.84), 5 patients (35%) were categorized as having a very severe degree of RLS. All patients with RLS were poor sleepers (mean PSQI, 12.07 ± 3.15), as measured by the PSQI (score > 5). Six of 14 patients (42.8%) had moderate to severe insomnia (ISI ≥ 15), and the mean ISI score of all the patients with RLS was 14.86 ± 6.61. All of the healthy control patients were good sleepers, without any symptoms of insomnia (**Table 1**).

HRV analysis and cardiovascular reflexes

Blood pressures during systole and diastole in the supine position were within normal limits in all participants, and there was no difference between the 2 study groups. **Table 1** shows the results of the cardiovascular responses to deep breathing and isometric handgrip. These results were within normal limits and were similar between the patients with RLS and the control patients.

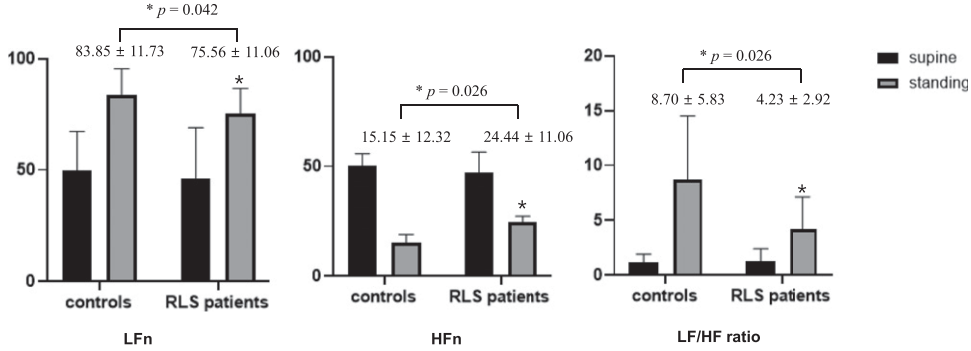
On spectral analysis of HRV, the LF normalized unit components (75.56 ± 11.06 vs 83.85 ± 11.73; $P = .042$) and the LF/HF ratio (4.23 ± 2.92 vs 8.70 ± 5.83; $P = .026$) during standing were significantly lower in the patients with RLS than in the control patients (**Figure 1**). Changes in the LF/HF ratio during the change from the supine to the standing position were reduced in patients with RLS in comparison to the control patients (2.94 ± 3.11 vs 7.51 ± 5.58; $P = .042$). In the supine

Table 1—Clinical characteristics and cardiovascular reflexes between patients with RLS and control patients.

Variables	Patients with RLS (n = 14)	Control Patients (n = 10))	*P* Value*
Age (y)	42.14 ± 7.81	39.10 ± 6.44	.285
Sex (women; %)	12 (85.7)	8 (80)	.563
BMI (kg/m^2)	22.05 ± 2.29	21.59 ± 3.35	.312
IRLS	28.07 ± 4.84	0.60 ± 1.26	< .001
PSQI	12.07 ± 3.15	4.00 ± 1.49	< .001
ISI	14.86 ± 6.60	4.80 ± 2.57	< .001
Self-reported sleep duration, h (by PSQI)	5.60 ± 1.50	6.35 ± 0.67	.036
Blood pressure, supine (mm Hg)			
SBP	107.43 ± 11.35	112.20 ± 12.27	.341
DBP	71.93 ± 9.17	76.60 ± 12.58	.371
HR	72.86 ± 9.46	69.80 ± 10.41	.472
Cardiovascular reflexes			
Deep breathing			
E/I ratio	1.32 ± 0.11	1.33 ± 0.19	.709
Isometric handgrip			
△DBP (mm Hg)	23.36 ± 11.68	21.20 ± 12.81	.585

Data are expressed as means ± standard deviation. *$P < .05$ is the significance level as obtained by the Wilcoxon and Mann-Whitney *U* tests. BMI = body mass index, DBP = diastolic blood pressure, E/I ratio = Expiration/Inspiration ratio, HR = heart rate, IRLS = International Restless Legs Syndrome Rating Scale, ISI = Insomnia Severity Index, PSQI = Pittsburgh Sleep Quality Index, RLS = restless legs syndrome, SBP = systolic blood pressure.

Figure 1—LF and HF normalized units and LF/HF ratio in supine and standing position in patients with RLS and control patients.



Values are mean ± standard deviation. *P < .05. The Mann-Whitney U test was used to compare variables between the groups. HFn = high-frequency normalized units (HF/total power-very low frequency) × 100, LFn = low-frequency normalized units (LF/total power-very low frequency) × 100.

position, there was no significant difference in the parameters of HRV between RLS patients and controls.

The relationship between the parameters of HRV, IRLS, and sleep disturbance

Correlation analyses were performed between the parameters of HRV and demographics with sleep parameters, including the IRLS score. A significant negative correlation was observed between the ISI (r = –.564; P = .036), the PSQI (r = –.538; P = .047), and the LF normalized units and LF/HR ratio; a positive correlation was observed between the ISI (r = .592; P = .026), the PSQI (r = .611; P = .020), and the HF normalized units in the supine but not the standing position. However, the IRLS score, disease duration of RLS, and sleep duration did not show any significant correlation with the HRV parameters (**Table 2**).

DISCUSSION

Our study showed a blunted HRV response to orthostatic stress in patients with RLS compared with healthy control patients. In the supine position, the mean heart rate, mean standard deviation of the normal-to-normal intervals value, and LF and HF power in patients with RLS were similar to those of the control patients. In addition, there was no significant difference in cardiovascular reflexes between the groups. However, patients with RLS exhibited a lesser increase in LF power and a lesser decrease in HF power compared with the control patients when the position was changed from supine to standing. Hence, our findings replicate those of previous studies that have reported reduced sympatho-vagal activity during orthostatic stress in patients with RLS. These specific alterations may serve to elevate cardiovascular risk in patients with RLS.

Evidence of the association between HRV and CVD, including myocardial infarction,[21] stroke,[22] coronary heart disease,[23] and sudden cardiac death[24] has been reported. Furthermore, studies have suggested that HRV has predictive value for CVD outcomes.[25,26] In the general population, reduced HRV has a high correlation with incident coronary heart disease and death.[27] Therefore, the reduced HRV of patients with RLS during wakefulness may be related to an increased incidence of CVD.

Two previous studies have examined the association between HRV and cardiovascular reflexes in patients with RLS during wakefulness; however, their methodologies differed slightly from ours.[10,11] In 1 study,[10] there was no significant difference in HRV between patients with RLS and control patients. However, in the within-group analysis, the control patients showed statistically significant variations in most HRV components during the head-up tilt test compared to when they were in the supine position; such variations did not occur in patients with RLS. The other study[11] showed that moderate to severe RLS was associated with lower baroreflex gain and higher leg vascular resistance and that the lower gain was associated with higher blood pressure. Therefore, the authors suggested that the decreased baroreflex gain resulted from increased sympathetic activity from baseline because of increasing arterial resistance.

In our study, the LF normalized units and LF/HF ratio during standing were lower in patients with RLS than in the control patients; similar to previous studies, reduced sympatho-vagal responses were observed in the patients with RLS during orthostatic stress. LF power is modulated by baroreflexes, with combined sympathetic and parasympathetic efferent nerve traffic to the sinoatrial node. Because standing and the head-up tilt test typically cause a modest increase in LF power,[28] a lack of variability during the head-up tilt test or standing during wakefulness may occur as a result of exaggerated sympathetic nerve activity during sleep at night; this possibility is supported by the fact that RLS symptoms are aggravated during the evening and at night and are associated with increased sympathetic activation.[12,29]

Several factors may contribute to increased cardiovascular risk in patients with RLS; the related sympathetic activation is one. Periodic leg movements during sleep are associated with large increases in heart rate and blood pressure. Sleep fragmentation that is seen with sleep deprivation in RLS is known to affect the neural, metabolic, oxidative, inflammatory, and vascular systems and is also associated with a shift in the sympatho-vagal balance toward heightened sympathetic nervous system activity. Iron deficiency, which is an emerging risk

Table 2—Spearman rank correlation between clinical characteristics and parameters of HRV in patients with RLS.

Variables		Age	BMI	LFn (S)	LFn (U)	LFn (D)	HFn (S)	HFn (U)	HFn (D)	LF/HF Ratio (S)	LF/HF Ratio (U)	LF/HF Ratio (D)	Disease Duration	PSQI	Sleep Duration	ISI	IRLS
Age	*R*	1.000	.189	.181	.196	–.084	–.059	–.196	.084	.181	.196	.148	–.168	.227	–.285	–.126	–.420
	P	—	.517	.537	.502	.776	.840	.502	.776	.537	.502	.615	.566	.435	.322	.667	.135
BMI	*R*	.189	1.000	.011	–.222	–.095	.073	.222	.095	.011	–.222	–.279	–.196	–.047	–.337	.013	–.173
	P	.517	—	.970	.446	.748	.805	.446	.748	.970	.446	.334	.501	.874	.239	.964	.555
Disease duration	*R*	–.168	–.196	.274	.022	–.172	–.382	–.022	.172	.274	.022	–.137	1.000	–.507	.803**	–.343	–.300
	P	.566	.501	.344	.940	.556	.178	.940	.556	.344	.940	.641	—	.064	.001	.230	.297
PSQI	*R*	.227	–.047	–.538*	–.116	.422	.611*	.116	–.422	–.538*	–.116	.149	–.507	1.000	–.791**	.779**	.692**
	P	.435	.874	.047	.694	.133	.020	.694	.133	.047	.694	.611	.064	—	.001	.001	.006
Sleep duration	*R*	–.285	–.337	.470	.142	–.369	–.586*	–.142	.369	.470	.142	–.122	.803**	–.791**	1.000	–.629*	–.497
	P	.322	.239	.090	.627	.195	.028	.627	.195	.090	.627	.678	.001	.001	—	.016	.070
ISI	*R*	–.126	.013	–.564*	.013	.524	.592*	–.013	–.524	–.564*	.013	.338	–.343	.779**	–.629*	1.000	.788**
	P	.667	.964	.036	.964	.055	.026	.964	.055	.036	.964	.237	.230	.001	.016		.001
IRLS	*R*	–.420	–.173	–.513	–.108	.381	.522	.108	–.381	–.513	–.108	.102	–.300	.692**	–.497	.788**	1.000
	P	.135	.555	.060	.712	.180	.055	.712	.180	.060	.712	.729	.297	.006	.070	.001	

*$P < .05$; **$P < .005$. BMI = body mass index, D = difference between values of supine and upright position, HFn = high-frequency normalized units (HF/total power-very low frequency) × 100, HRV = heart rate variability, IRLS = International Restless Legs Syndrome Rating Scale, ISI = Insomnia Severity Index, LFn = low-frequency normalized units (LF/total power-very low frequency) × 100, PSQI = Pittsburgh Sleep Quality Index, *P* = *P* value, *R* = rho for Spearman rank correlation coefficient, RLS = restless legs syndrome, S = supine, U, upright.

for CVD, may be a contributing factor, although it is not directly associated with sympathetic activity.[2]

According to the Spearman rank correlation in this cohort, the ISI and PSQI were contributing factors for ANS dysfunction. Approximately 75% of patients with RLS report various sleep problems, including difficulty in falling asleep and maintaining sleep, interrupted sleep, and insufficient sleep.[30] Polysomnography studies have also shown that sleep latency and arousal index scores are higher in patients with RLS.[31] Thalamocortical abnormalities have been implicated in the pathophysiology of RLS,[32] and sleep disturbances may be mediated by a combined deficit in spindle and slow oscillation activities with slow oscillation-spindle coordination because of thalamocortical dysfunction.[33] Because ISI and PSQI scores are correlated with IRLS scores, blunted sympatho-vagal responses in patients with RLS in the standing position may be related to poor sleep quality secondary to severe RLS symptomatology. In a recent study on patients with coronary artery disease, the prevalence of RLS was relatively high compared to that in the general population, and the presence of RLS was associated with disrupted sleep quality and health-related quality of life in these patients.[34] Thus, sleep quality seems to be important for autonomic control in RLS.

Generally, normal aging is often associated with diminished cardiac autonomic modulation during postural stress.[35] This effect could be a compounding variable in the interpretation of ANS function results and may explain the lack of significant difference in HRV between patients with RLS and control patients, although it was observed neither while supine nor during head-up tilt tests in a previous study, which included older patients (patients' ages, mean ± standard deviation, 58.41 ± 15.36).[10] In contrast to previous studies, our study had a large proportion of younger participants (ages 20–49 years, n = 12; ages 50–59 years, n = 2). Our results suggest that younger adult patients with RLS who do not have hypertension may exhibit autonomic dysfunction, which ultimately affects the development of CVD in the long term.

Previous research and our study have shown that the spectral analysis of HRV in the frequency domain is a useful noninvasive technique for quantifying progressive alterations in sympatho-vagal balance. The supine-standing test measures a dynamic loading of the ANS in the form of a sequential increase in sympathetic activity and a concomitant decrease in vagal activity in the standing position.[13] A reduced sympatho-vagal response during positional change during wakefulness may be a good predictor of the risk of CVD in a patient with RLS. It is unclear as to why other cardiovascular reflex indices have not shown statistical differences between control patients and patients with RLS in previous research. Further studies are necessary for evaluating the effect of dopaminergic therapy on improving responsiveness to reduced HRV. Positive results with dopaminergic therapy would reinforce the importance of actively treating RLS.

Our study has certain limitations. First, the sample size was small; therefore, our results are hypothesis-generating. Further larger cohort studies are necessary for confirming our results. HRV is a useful tool; however, there are wide variations in autonomic responses to orthostatic maneuvers based on sex and age.[35] Therefore, while interpreting patient data, clinicians should not use absolute values as the norm. Instead, they are to be compared with the data obtained from normal control patients matched for age and sex; these parameters were difficult to obtain. Second, there was no objective measure for sleep and periodic leg movement during sleep using polysomnography in our study. Because periodic leg movement during sleep in RLS is itself related to sympathetic activation, there may have been some discrepancy in the interpretations. However, a previous study has shown no association between periodic leg movement during sleep and baroreflex function.[11]

CONCLUSIONS

RLS is a known risk factor for CVD. This study aimed to evaluate the HRV and autonomic control of cardiovascular reflexes in the supine and standing positions in patients with RLS during wakefulness. We found that the LF/HF ratio responses during the change from the supine to the standing position were significantly reduced in patients with RLS, suggesting reduced sympatho-vagal responses during positional change. Increases in the sympathetic drive during sleep may impair ANS function; this measurement may be a good predictor for the risk of CVD. Because RLS-related deteriorated sleep quality is an important risk factor for ANS dysfunction, active treatment of RLS for improving sleep quality is necessary in patients with cardiovascular risks. Further studies with larger populations are needed to confirm our findings and to explore active treatment modalities to improve the reduced HRV in RLS.

ABBREVIATIONS

ANS, autonomic nervous system
CVD, cardiovascular disease
HF, high-frequency
HRV, heart rate variability
IRLS, International Restless Legs Syndrome Rating Scale
ISI, Insomnia Severity Index
LF, low-frequency
PSQI, Pittsburgh Sleep Quality Index
RLS, restless legs syndrome

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