Sleep
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Heart Rate Variability in Restless Legs Syndrome and Periodic Limb Movements of Sleep

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ABSTRACT

Introduction: The relationship between the autonomic nervous system and restless legs syndrome (RLS) and periodic limb movements of sleep (PLMS) consists of varied and somewhat conflicting reports. In order to further elucidate these complexities, a retrospective analysis of polysomnography (PSG) records and clinical data was performed. **Methods:** Records from 233 adult subjects were randomly selected and organized into one of four groups ("non-RLS/PLMS" [n=61], "RLS" [n=60], "PLMS" [n=58], and "RLS/PLMS" [n=54]). Heart rate variability (HRV) analysis was based on 5-minute samples of 2-lead electrocardiogram data isolated from PSG recordings during wakefulness and NREM sleep, and included mean RR interval (labeled "NN") and standard deviation of the RR intervals (labeled "SDNN"), and HRV power, very low frequency (VLF), low frequency (LF), and high frequency (HF) spectral bands. **Results:** A significant reduction in the VLF band in the PLMS group as compared to the non-RLS/PLMS group (542 ± 674 *vs.* 969 ± 1025 ms², *p*=0.038) was found in wakefulness. Statistically significant differences were seen in the PLMS group as compared to the non-RLS/PLMS group with a reduction in SDNN (*p*=0.001) and the HF (*p*=0.001) band, and an increase in HRV power (*p*=0.001), and the VLF (*p*=0.005) and LF (*p*=0.001) bands in NREM sleep. **Conclusions:** The PLMS group exhibited reduced basal sympathetic activity in wakefulness, but basal sympathetic predominance during NREM sleep, distinguishing this group from the RLS and RLS/PLMS groups.

Keywords: Restless Legs Syndrome; Autonomic Nervous System; Heart Rate; Polysomnography; Sleep.

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INTRODUCTION

The relationships between the autonomic nervous system and restless legs syndrome (RLS) and periodic limb movements of sleep (PLMS) are not completely understood. The International Classification of Sleep Disorders, 3rd edition (ICSD-3) diagnostic criteria for RLS includes the urge to move the legs and/or the presence of uncomfortable sensations that occur primarily with rest/inactivity, are at least partially relieved with movement (as long as the movement persists), and have a circadian aspect in that the symptoms occur primarily in the evening or night. Periodic limb movements of sleep are noted during polysomnography (PSG) and are, defined by the ICSD-3 as episodes of repetitive, stereotypical leg movements during sleep, involving the rhythmic extension of the big toe and dorsiflexion of the ankle, occasionally accompanied by knee and hip flexion[1].

Heart rate is modulated through effects of sympathetic and parasympathetic nervous systems, and analysis of changes in heart rate over time provides information about autonomic function. A reliable, non-invasive method to study these changes is heart rate variability (HRV), which has been utilized in patients with sleep disordered breathing and other sleep disturbances as a marker of autonomic dysfunction. In conditions associated with autonomic dysfunction, such as congestive heart failure, diabetes, end-stage renal disease, a decrease in HRV is typically found, with abnormal HRV being considered an independent risk factor for mortality[2].

The literature linking RLS, PLMS, and autonomic disturbances is varied and somewhat conflicting. Small studies of subjects with RLS demonstrate reduced[3,4], indicating a potential elevation of sympathetic activity, whereas others[5] have failed to demonstrate HRV differences between subjects with RLS and healthy controls during NREM sleep. It is known that PLMS are preceded by cardiac acceleration, changes in the oscillatory activity of the cerebral cortex[6], and surges in blood pressure[7], however basal autonomic disturbance has not been demonstrated subjects with PLMS in NREM sleep (as measured through HRV)[8]. Other cardiovascular changes in sleep include increased HRV change during PLMS in subjects with RLS as compared to controls[5] as well as increased blood pressure surges during PLMS in subjects with RLS as compared to controls[7].

A more recent small study failed to demonstrate differences in cardiovascular responses (including HRV) between those patients with RLS and PLMS as compared to those with RLS but without PLMS[4] in wakefulness[8], but these 2 groups only had 6 patients each. Based on the limited literature on this topic, we hypothesize that patients with the combination of RLS and PLMS will demonstrate a basal HRV disturbance during wakefulness and NREM sleep as compared to the non-RLS/PLMS group, reflecting a more pronounced autonomic disturbance than that found in patients with either RLS or PLMS alone.

METHODS

This study was approved by the institutional review board at Weill Cornell Medical College. Polysomnography records and clinical data from adult patients (ages 17-92) collected at the Weill Cornell Center for Sleep Medicine from February, 2011 to October, 2014 were retrospectively analyzed. All patients underwent PSG testing as part of the clinical evaluation of sleep disorders, including snoring, obstructive sleep apnea (OSA), insomnia, and/or hypersomnia. The initial exclusion criterion was an apnea hypopnea index (AHI) > 15/hr and/or missing or corrupt HRV data. Records were then classified into one of four groups depending on the clinical history and PSG findings: "non-RLS/PLMS" (essentially our *control* group; records with no RLS symptoms and PLMS < 15/hr were chosen), "RLS" (records with positive RLS symptoms and PLMS <15/hr were chosen), "PLMS" (records with no RLS symptoms and PLMS ≥ 15/hr were chosen), and "RLS/PLMS" (records with positive RLS symptoms and PLMS ≥ 15/hr were chosen) (Figure 1).

All subjects were provided a questionnaire to complete before the PSG, which includes questions regarding sleep schedules and symptoms, as well as questions regarding parasomnias, including RLS. The RLS-based questions were taken from the RLS Diagnostic Index[9], which is, in turn, based the International Restless Legs Syndrome Study Group rating scale[10,11]. An answer of "yes" for more than 2[9] of the following RLS questions was considered a positive response: 1) kicking legs at night or during sleep; 2) leg movement due to discomfort or disagreeable sensations; 3) need to walk or rub legs to relieve discomfort; 4) symptoms worse when at rest; and/or 5) symptoms worse later in the day or at night.

The scoring of PLMS was performed by registered technologists, according to the American Academy of Sleep Medicine Scoring Manual guidelines[12]. A significant leg movement (LM) event was defined by a duration of 0.5-10 seconds, with an amplitude increase of 8μV in EMG voltage above resting EMG, with a minimum of four consecutive LM events, and a period length between LMs of 5-90 seconds[12]. The EMG criteria were as follows: sampling rate of 200 Hz, low frequency filter of 10 Hz, high frequency filter of 100 Hz, maximum electrode impedance of 5 KΩ, with 16-bit resolution.

For the non-RLS/PLMS group, 749 records were found that fulfilled the selection criteria; for the RLS group, 183 records were found that fulfilled the selection criteria; for the PLMS group, 126 records were found that fulfilled selection criteria; and finally, for the RLS/PLMS group, 69 records were found that fulfilled selection criteria. Of these, we randomly selected 63 per group, based on power analysis. We visually inspected ECG data from each record and if there was excessive artifact (muscle or otherwise), or excessive cardiac ectopy, that record was removed from analysis. For the NREM ECG data, we only used epochs that were free of PLMS. If we could not find PLM-free epochs, that record was discarded. For the non-RLS/PLMS group, 61 records were analyzed; for the RLS group, 60
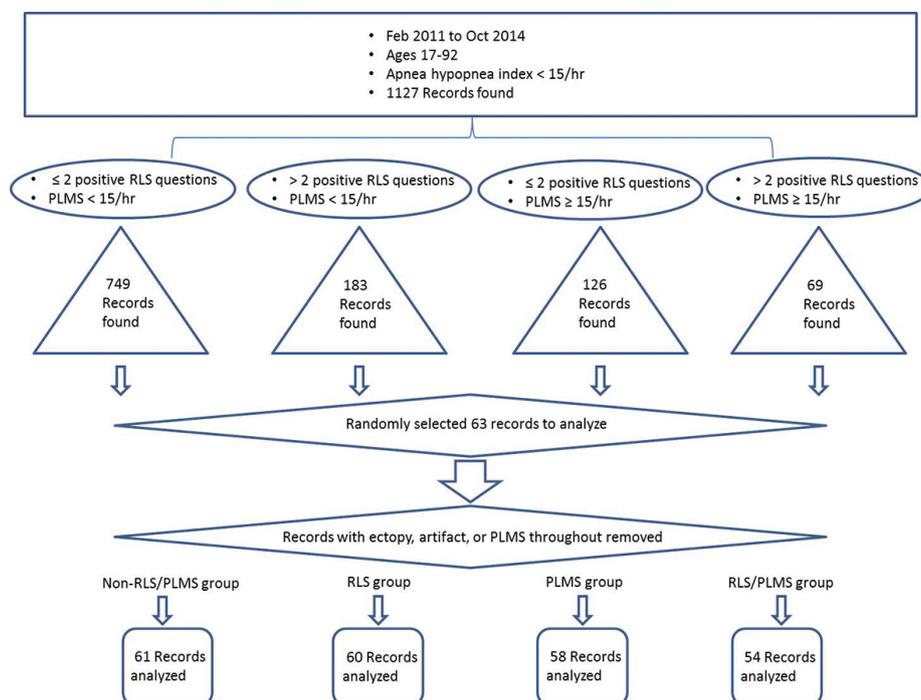
Figure 1. Flow chart for PSG records chosen for analysis. RLS=restless legs syndrome; PLMS=periodic limb movements of sleep.

records were analyzed; for the PLMS group, 58 records were analyzed; and finally, for the RLS/PLMS group, 54 records were analyzed. Demographic data and multiple facets of PSG data were compiled for both groups (see Table 1).

An HRV analysis for each PSG meeting the selection criteria was then performed. The analysis was based on 5-minute PSG epochs of 2-lead ECG data isolated during continuous wakefulness (either at the start of the recording or in the middle of the night), and during NREM sleep, consistent with previous studies[13,14]. The data was then analyzed in the time- and frequency-domains using the SuperECG Package software (Mortara Instrument, Inc., Milwaukee, WI)[15-18]. Time-domain variables included mean RR interval (conventionally labeled "NN" to indicate "normal beats") and standard deviation of the RR intervals (conventionally labeled "SDNN")[13]. Frequency-domain variables included components of RR variability quantified by an autoregressive decomposition algorithm to compute spectral peak powers and their central frequencies, which are then classified into very low frequency (VLF; <0.04 Hz), low frequency (LF; 0.04–0.15 Hz), and high frequency (HF; 0.15–0.4 Hz) bands[13].

Statistics

The HRV data was compiled and further analyzed using SPSS 21 software (IBM, Corp., Armonk, New York). An ANCOVA was performed to test for significant HRV differences between the non-RLS/PLMS, RLS, PLMS, and RLS/PLMS groups. Age was used as a co-variate because it differed significantly between groups as noted above. Of note, all variables were log transformed due to a non-normal distribution. The ANCOVA analysis was performed with the log transformed data to improve the ease of understanding

the data; the means and standard deviations (SD) listed below are the actual values, not the log transformed values. A Holm's sequential Bonferroni procedure was used to control for type I error due to multiple testing[19].

RESULTS

There were no significant differences in any demographic or PSG parameter between the non-RLS/PLMS and RLS groups. However, a significant difference in age was seen between the non-RLS/PLMS (44.4±17 years) and PLMS (55.6±17 years) groups, and between the non-RLS/PLMS and RLS/PLMS (57.3±14 years) groups. The RLS/PLMS group also revealed an elevated BMI and more disturbed sleep architecture, as evidenced by lower sleep efficiency and increased wake after sleep onset (WASO). As expected, there were also significant differences in PLM index between the non-RLS/PLMS and both RLS/PLMS and PLMS groups as shown on Table 1.

HRV in wakefulness

No significant differences were found in SDNN, HRV power, or any other HRV parameter during wakefulness between the non-RLS/PLMS and RLS, RLS/PLMs, and PLMS groups. There was, however, a significant reduction in the VLF band in the PLMS group as compared to the non-RLS/PLMS group (542 ± 674 *vs.* 969 ± 1025 ms², *p*=0.038), as shown on Table 2.

HRV in NREM sleep

There were no significant differences found in SDNN, HRV power, or the VLF, LF or HF bands during NREM sleep between the non-RLS/PLMS group and the RLS or RLS/PLMS groups. Statistically significant differences were seen in

Table 1. Demographic, and PSG characteristics of all four groups.

	Non-RLS/PLMS (n = 61)	RLS (n = 60)	*P*-value	Non-RLS/PLMS (n = 61)	PLMS (n = 58)	*P*-value	Non-RLS/PLMS (n = 61)	RLS/PLMS (n = 54)	*P*-value
Age (years)	44.4 ± 17	47.2 ± 17	0.352	44.4 ± 17	55.6 ± 17*	<0.001	44.4 ± 17	57.3 ± 14*	<0.001
Sex (%M)	32/61 (52)	24/60 (40)	N/A	32/61 (52)	31/58 (53)	N/A	32/61 (52)	22/54 (41)	N/A
BMI (kg/m²)	26.9 ± 6	27.8 ± 6	0.411	26.9 ± 6	27.4 ± 6	0.659	26.9 ± 6	29.5 ± 7*	0.026
AHI (events/hr)	4.5 ± 4	5.3 ± 4	0.272	4.5 ± 4	5.2 ± 4	0.361	4.5 ± 4	6.7± 4*	0.005
Sleep efficiency (%)	76.1 ± 17	77.0 ± 12	0.728	76.1 ± 17	74.9 ± 14	0.683	76.1 ± 17	69.7 ± 17*	0.025
TST (min)	353 ± 86	373 ± 73	0.217	353 ± 86	354 ± 91	0.928	353 ± 86	339 ± 110	0.431
WASO (min)	85 ± 68	91 ± 50	0.578	85 ± 68	98 ± 65	0.251	85 ± 68	116 ± 65*	0.007
PLMI (events/hr)	2.4 ± 4	2.8 ± 4	0.888	2.4 ± 4	35.0 ± 23*	< 0.001	2.4 ± 4	40.3 ± 29*	< 0.001

BMI: Body mass index; AHI=apnea hypopnea index; TST: Total sleep time; WASO: Wake after sleep onset; PLMI: Periodic limb movement index. * Denotes a significant difference compared to non-RLS/PLMS group at *p* < 0.05.

Table 2. HRV parameters of all four groups in wakefulness.

	Non- RLS/PLMS (n = 61)	RLS (n =60)	*P*-value	Non- RLS/PLMS (n = 61)	PLMS (n =58)	*P*-value	Non- RLS/PLMS (n = 61)	RLS/PUMS (n = 54)	*P*-value
NN (ms)	931 ± 125	921 ± 174	0.511	931 ± 125	937 ± 155	0.918	931 ± 125	905 ± 145	0.309
SDNN (ms)	55.7 ± 30.6	54.5 ± 36.5	0.647	55.7 ± 30.6	43.5 ± 24.2	0.095	55.7 ± 30.6	54.4 ± 41.7	0.731
HRV Power (ms²)	4011 ± 4365	4268 ± 7917	0.647	4011 ± 4365	2460 ± 3014	0.094	4011 ± 4365	4654 ± 9215	0.731
VLF (ms²)	969 ± 1025	761 ± 785	0.248	969 ± 1025	542 ± 674	0.038*	969 ± 1025	907 ± 1602	0.519
LF (ms²)	1069 ± 1305	919 ± 1277	0.481	1069 ± 1305	600 ± 763	0.064	1069 ± 1305	820 ± 1094	0.348
HF (ms²)	1448 ± 1700	1714 ± 3610	0.788	1448 ± 1700	955 ± 1465	0.111	1448 ± 1700	1439 ± 2306	0.524

NN=R to R interval length; SDNN=standard deviation of R to R interval lengths; HRV=heart rate variability; VLF=very low frequency; LF=low frequency; HF=high frequency
* Significant after controlling for multiple testing using the Holm's sequential Bonferroni[19]
Please note: analysis was performed with the log transformed data, however to improve the ease of understanding the data the means and standard deviations listed below are the actual values, not the log transformed values

Table 3. HRV parameters of all four groups in NREM sleep.

	Non- RLS/PLMS (n = 61)	RLS (n =60)	*P*-value	Non- RLS/PLMS (n = 61)	PLMS (n =58)	*P*-value	Non- RLS/PLMS (n = 61)	RLS/PUMS (n = 54)	*P*-value
NN (ms)	984 ± 148	957 ± 196	0.258	984 ± 148	976 ± 183	0.739	984 ± 148	967 ± 139	0.696
SDNN (ms)	45.7 ± 19.8	49.1 ± 33.3	0.548	45.7 ± 19.8	37.3 ± 33.6	0.001*	45.7 ± 19.8	51.0 ±45.0	0.665
HRV Power (ms²)	2471 ± 2067	3482 ± 5255	0.548	2471 ± 2067	2489 ± 6161	0.001*	2471 ± 2067	4572 ± 9948	0.665
VLF (ms²)	385 ± 299	503 ± 745	0.379	385 ± 299	472 ± 1177	0.005*	385 ± 299	787 ±2356	0.770
LF (ms²)	689 ± 620	850 ± 1016	0.324	689 ± 620	749 ± 2263	0.001*	689 ±620	1063 ± 2128	0.530
HF (ms²)	1132 ± 1142	1447 ± 2047	0.621	1132 ± 1142	1039 ± 2952	0.001*	1132 ±1142	2044 ± 4862	0.604

NN=R to R interval length; SDNN=standard deviation of R to R interval lengths; HRV=heart rate variability; VLF=very low frequency; LF=low frequency; HF=high frequency
*Significant after controlling for multiple testing using the Holm's sequential Bonferroni[19]
Please note: analysis was performed with the log transformed data, however to improve the ease of understanding the data the means and standard deviations listed below are the actual values, not the log transformed values.

the PLMS group as compared to the non-RLS/PLMS group in regards to HRV parameters, with a reduction in SDNN (*p*=0.001) and the HF (*p*=0.001) band, and an increase in HRV power (*p*=0.001), and the VLF (*p*=0.005) and LF (*p*=0.001) bands, as shown on Table 3.

DISCUSSION

To the best of our knowledge, this is the first study examining basal HRV in a large number of subjects in both wake and NREM sleep across groups of subjects with RLS, PLMS, and the combination of RLS and PLMS, as compared to non-RLS/PLMS subjects during overnight polysomnography. Prior studies utilizing HRV analysis have focused on periods

with leg movements in NREM sleep, given the fact that movement-related surges of sympathetic activity that are known to occur[20,21]; however, only a limited number of studies have investigated basal autonomic regulation in PLMS[8,22]. Our study revealed that the PLMS group had reduced basal sympathetic activity in wakefulness, but basal sympathetic predominance during NREM sleep, when compared to the non-RLS/PLMS group; these findings distinguished the PLMS group from both the RLS and the RLS/PLMS groups.

Altered HRV in the PLMS group in wakefulness

There was a significant reduction in wakefulness in the VLF band in the PLMS group, as compared to the non-

RLS/PLMS group. Physiological interpretation of the VLF band still warrants further elucidation[13], but may be related to sympathetic activity[23]. Additionally, in wakefulness, there was a reduction in the LF band in the PLMS group, which approached significance, and is a marker of sympathetic activity[13,24]. These findings indicate that there might be a reduction of sympathetic activity in wakefulness in the PLMS group, which is in direct contradiction with the prevailing thought of the long term effect of PLMS on the cardiovascular system[25]. The potential etiology of this finding is not clear, but may represent a "burn out" of the sympathetic nervous system, which would be similar to what has been noted in the locus coeruleus of subjects with post-traumatic stress disorder[26,27].

Altered HRV in the PLMS group in NREM sleep

The relationship between the presence of PLMS and basal autonomic function in sleep is unsettled. On the one hand, some failed to produce convincing evidence indicating basal sympathetic predominance in subjects with PLMS[5,8,28], others have reported that the presence of PLMS is related to basal sympathetic predominance and has a potentially negative impact on the cardiovascular system[22]. In our study, the altered HRV in the PLMS group during NREM sleep occurred across all measured parameters, and seems to point towards a basal sympathetic predominance in NREM sleep.

The SDNN and HRV total power parameters are considered to be global measures of variability[14], and in this case there were changes in opposite directions. This suggests the presence of PLMS may have a global impact on the cardiac autonomic nervous system that is not fully understood yet, and/or that these two measurements are not sufficiently precise to detect a meaningful change. Of interest, similar global HRV change has been noted in young subjects with autonomic neuropathy associated with type 1 diabetes mellitus, leading to the authors concluding that young subjects with type 1 diabetes mellitus have autonomic nervous system behavior tending to randomness[29]; a similar behavior may be present in those with PLMS.

The HF band likely represents vagal modulation of sinus rhythm[24]. The fact that it was significantly reduced in the PLMS group compared to the non-RLS/PLMS group suggests that there is reduced parasympathetic influence in NREM sleep in these subjects. The LF band can be viewed either as a surrogate for sympathetic modulations, or may reflect both sympathetic and vagal activity[13,24], or the baroreflex responsiveness to beat-to-beat variations in blood pressure[30]. This parameter was significantly elevated in the PLMS group as compared to the non-RLS/PLMS group in NREM sleep, suggesting that sympathetic influence was stronger in these subjects. Taken together, these two results imply that there exists a sympathetic predominance in the autonomic nervous system of those with PLMS in NREM sleep. Furthermore, there was also a significant elevation in the VLF band in NREM sleep, in the PLMS group compared to the non-RLS/PLMS group, suggesting that in NREM sleep, sympathetic activity may predominate in those with PLMS.

It should be noted that electrocardiographic data time-locked to the occurrence of PLMS were not analyzed in our study, and thus we cannot conclude that there would be further sympathetic surges during PLMS as described in prior studies[5,31-35]. It has been hypothesized that the repetitive abnormal HR rises connected with PLMS might have a long-term negative effect on the cardiovascular system. Despite this, other studies have reported that there is a disconnect of PLMS from arousals[36] and thus leg movements are thought to be either a consequence or a co-occurrence, rather than the cause, of sympathetic activation in PLMS[21]. However, as discussed by Wu et al, basal sympathetic predominance during the intermovement interval in subjects with PLMS may be present[22]; this is in agreement with our findings.

Normal HRV in the RLS and RLS/PLMS groups

Similar to the case with PLMS, the literature regarding basal HRV is disparate for RLS. Whereas large epidemiological surveys have found a significant comorbidity between RLS and cardiovascular disease[37-41], a prior study failed to demonstrate differences in HRV between subjects with RLS and healthy non-RLS/PLMSs during NREM sleep[5]. Another study revealed no difference in HRV measured during wakefulness in six subjects with RLS/PLMS as compared to six non-RLS/PLMSs[4]. Given our large sample size, our study strengthens these two latter results, and suggests that there does not seem to be a basal autonomic disturbance in wake in subjects with either RLS or PLMS, and more importantly, in those with the combined RLS/PLMS condition.

It has been posited that a reduction in HRV across age[42] may occur. Both the PLMS group and the RLS/PLMS combination group in our study were significantly older than the non-RLS/PLMS group, so age could have played some role in reducing HRV in the PLMS group; but this would not explain why the PLMS group and the RLS/PLMS group were not similarly affected. However, the RLS/PLMS group was also significantly older and the HRV in this group was not significantly different to the non-RLS/PLMS group in both wakefulness and sleep. Moreover, we adjusted for age in our analysis, so any effect in this regard should have been minimized.

Limitations

Our study suffers from several limitations, the main issue being its retrospective design, which may have affected the classification of the groups. In particular, the non-RLS/PLMS group, despite acting as our *control* group, was not necessarily without any sleep abnormality. Rather, these were subjects simply free of RLS, PLMS, and OSA, and actually may have been suffering with other conditions such as insomnia, hypersomnia, or other parasomnias, which admittedly may have had effects on HRV. Despite this issue, the retrospective design allowed us to analyze a considerable amount of subjects per group; additionally, our data was comprised of a diverse population of subjects seen in Manhattan, New York, at our comprehensive sleep disorder center.

Similarly, those with RLS may have been falsely deemed so, as this designation was based on information from the questionnaire and chart review. However, all diagnostic algorithms tend to focus on presenting symptoms[43], and in the RLS epidemiology, symptoms, and treatment (REST) primary care study, sleep-related symptoms, daytime sleepiness, and discomfort in the legs (pain, twitching and jerks, uncomfortable feelings) accounted for the most troublesome symptoms[44]. If a patient presents with insomnia/sleep problems and an urge to move, or complains of unpleasant sensations in the legs, it is recommended that follow up questions be asked; these are based on the RLS-Diagnostic Index, a validated diagnostic algorithm[9]. The most important questions concern the urge to move the legs and the worsening of symptoms at rest[9,43]. If a patient answers yes to three or more of these questions[43], there is a high likelihood of RLS being present. Thus, our screening for RLS, while compiled in a retrospective manner, is suitable for grouping purposes.

Another important limitation to mention is our exclusion criteria; there are multiple factors, both known and unknown, that can affect HRV analysis. Among them includes the use of anti-hypertensive medications[45], the use of anti-depressant[46], and the presence of psychiatric diseases[47]. Additionally, there is data suggesting gender-related differences in cardiac autonomic tone that could have potentially impacted HRV analysis in that there has been found a predominance of parasympathetic over sympathetic tone in women, and vice versa in men[48,49]. Finally, obesity is a well-known risk factor of low HRV and overstimulation of the sympathetic nervous system[50]. These factors may have played a role in our study, but given the relatively large number of diverse subjects analyzed, we feel the confounding effects were minimized. Large, prospective studies analyzing HRV in subjects with RLS and PLMS are needed.

Regarding the HRV analysis itself, we attempted to locate 5-minute epochs free of PLMs, but in the case of HRV measured during wakefulness, the presence of PLM in wakefulness and/or RLS may have affected these measurements. The EKG segments during wakefulness that we chose occurred at any point during the PSG record, even in the middle of the night, and HRV could have been affected by this.

Finally, the PLMS group and the RLS/PLMS group were both significantly older than the non-RLS/PLMS group; this should not have been an issue, however, as age was controlled for in analysis. Additionally, while there were significant differences between the non-RLS/PLMS group and the RLS/PLMS groups in sleep efficiency and WASO, these findings were not totally unexpected. The RLS/PLMS group had more sleep disruption, which is what one would except given the presence of both RLS and PLMS. The RLS/PLMS group also had a significantly higher BMI and AHI compared to the non-RLS/PLMS group. These differences, however, should not have played a major role in HRV analysis, as in both groups the BMI was in the overweight range (25–29.9 kg/m^2), and the AHI was very close to the cutoff ($\geq$ 5/hr) for only mild OSA. As evidence of these differences not being a major issue, the non-RLS/PLMS and RLS/PLMS groups had similar HRV values.

CONCLUSIONS

This current report demonstrates somewhat disparate results in that there is reduced basal sympathetic activity in wakefulness in subjects with PLMS, but basal sympathetic predominance during NREM sleep in the same subjects. It argues against a role for basal HRV disturbance in subjects with RLS and the combination of RLS/PLMS during wakefulness and NREM sleep. Although in clinical practice it is tempting to group subjects with RLS and PLMS in the same category, it may be that these conditions are fundamentally different entities. The findings of our current study add to the literature important information regarding HRV on a large sample of subjects with RLS, PLMS and RLS/PLMS combination during wakefulness and sleep and highlight the need for further studies to fully elucidate the effects of these conditions on the autonomic nervous system, and in relation to cardiovascular control.

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