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SCIENTIFIC INVESTIGATIONS

Association of heart rate variability with REM sleep without atonia in idiopathic REM sleep behavior disorder

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Study Objectives: Idiopathic rapid eye movement sleep behavior disorder (iRBD), characterized by rapid eye movement sleep without atonia (RSWA) and dream-enactment behavior, has been suggested to be a predictor of α-synucleinopathies. Autonomic instability, represented by heart rate variability, is a common characteristic of both iRBD and α-synucleinopathies. Previous studies reported that RSWA was associated with autonomic dysfunction and was a possible predictor of phenoconversion. Therefore, we sought to compare heart rate variability between iRBD and control groups and explore the relationship between heart rate variability and RSWA in patients with iRBD.

Methods: Nocturnal polysomnographic data on 47 patients (28 men, 19 women) diagnosed with iRBD based on video-polysomnography and 26 age-matched and sex-matched controls were reviewed. The first 5-minute epoch with a stable electrocardiogram lead II on video-polysomnography was selected from stage N2, wake, and rapid eye movement. For quantification of RSWA, tonic activity was analyzed from the submentalis electromyogram and phasic activity from the submentalis and bilateral anterior tibialis electromyogram channels.

Results: Compared to the control group, the iRBD group showed significant reductions in the standard deviation of the R-R intervals, the root mean square of successive R-R interval differences, and high-frequency values. Quantified tonic activity was inversely correlated with normalized low-frequency values and low-frequency/high-frequency ratios and positively correlated with normalized high-frequency values.

Conclusions: This study implied decreased cardiac autonomic function in patients with iRBD, which showed parasympathetic predominance. Heart rate variability of the patients with iRBD in this study was associated with quantified tonic RSWA, which was previously reported to be a possible predictor of phenoconversion.

Keywords: REM sleep behavior disorder, heart rate variability, autonomic nervous system

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Previous studies reported idiopathic rapid eye movement sleep disorder (iRBD) to be highly associated with α-synucleinopathies, with both diseases showing autonomic denervation represented by heart rate variability (HRV) changes. Moreover, rapid eye movement sleep without atonia itself is reportedly associated with autonomic dysfunction and the risk of phenoconversion. The goals of this study were to reveal decreased autonomic function based on HRV in patients with iRBD and to determine the correlation of HRV with quantified rapid eye movement sleep without atonia.

Study Impact: Our study showed decreased cardiac autonomic function in patients with iRBD with parasympathetic predominance. Moreover, HRV parameters were correlated with tonic rapid eye movement sleep without atonia in patients with iRBD.

INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia that is primarily characterized by loss of the atonia normally present in REM sleep or REM sleep without atonia (RSWA), with resultant dream-enactment behavior. RBD is reportedly related to α-synucleinopathies such as Parkinson disease (PD), dementia with Lewy bodies, and multiple systemic atrophy.[1] RBD converted to α-synucleinopathies in over 73.5% of patients after a 12-year follow-up in a recent study.[2] The idiopathic form of RBD (iRBD) is now considered an early manifestation of neurodegenerative disease with α-synuclein deposition.[3]

In previous studies to date, RBD has been reported to be associated with dysfunction of the autonomic nervous system.[4] Patients with iRBD have shown more autonomic symptoms than controls, predominantly in the gastrointestinal, genitourinary, and cardiovascular domains.[5,6] In addition, heart rate variability (HRV), an objective marker of cardiovascular autonomic function, was lower in RBD, consistent with mainly

sympathetic impairment, such as a reduced low-frequency (LF) band[7–9] or low-frequency/high-frequency (LF/HF) ratio.[10] This decline in autonomic function was consistent with the pattern seen in α-synucleinopathies including PD, and the degree was intermediate between control and PD.[5,7] In addition, a decrease in cardiac uptake in 123I-labeled meta-iodobenzylguanidine scintigraphy implied a decrease in cardiac sympathetic activity, and patients with iRBD reportedly showed a remarkable decrease in cardiac uptake compared to symptomatic patients with RBD secondary to narcolepsy.[11]

RSWA, mentioned above as a core feature of RBD, has also been associated with autonomic dysfunction. Barone et al[12] reported that patients with isolated RSWA, which does not correspond to clinical RBD, also had decreased HRV compared to a control group. However, in a recent paper, HRV declined in patients with isolated RSWA compared to healthy controls, although the difference was not statistically significant.[13] The authors regarded this as a result of the small sample size (33 patients and 28 controls) and a failure to correct for covariates such as age and sex. However, only a few studies have examined the association between RSWA and autonomic dysfunction, and the correlation between RSWA and HRV in patients with RBD has not been analyzed.

Recently, RSWA has been found to be associated with α-synucleinopathies in patients with RBD.[14] In previous studies, the degree of REM atonia loss on baseline polysomnography (PSG) predicted progression to PD.[2,15] Another study reported that phenoconversion to neurodegenerative disease was predicted by mixed RSWA, defined as simultaneous tonic and phasic RSWA.[16] Two other studies also reported that greater RSWA on baseline PSG in patients with iRBD was associated with a higher rate of progression to PD or mild cognitive impairment.[17,18] In those studies, the degree of RSWA, a key manifestation of RBD, was associated with increased risk of α-synucleinopathies. If the linear correlation between RSWA and HRV can be confirmed, it will provide another important clue to the process of phenoconversion from RBD to α-synucleinopathies.

The purpose of our study was to assess HRV, an objective measure of autonomic dysfunction, in patients with iRBD to clarify the decrease in HRV on nocturnal PSG in patients with iRBD in a study with a larger sample size and age-matched and sex-matched controls, while effectively controlling for factors such as age, sex, and electrocardiogram (ECG) artifacts that might affect assessment of HRV and RSWA.[19] Moreover, we intended to analyze the correlation between autonomic dysfunction as represented by HRV and quantified RSWA. We hypothesized that HRV parameters would be decreased in iRBD compared to age-matched and sex-matched controls and would show correlations with quantified RSWA data in patients with iRBD.

METHODS

Participants

We retrospectively reviewed the medical records of older (age over 50 years) patients who visited the sleep clinic of psychiatry department and underwent nocturnal video polysomnography (v-PSG) at the Sleep and Chronobiology Center of Seoul National University Hospital between January 1, 2016, and May 31, 2019. The exclusion criteria were a history of major psychiatric illness (schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder) or neurodegenerative disease including α-synucleinopathies; current signs or symptoms of parkinsonism; a history of diabetes mellitus, arrhythmia, ischemic heart disease, or any serious medical illness; apnea-hypopnea index (AHI) > 15 events/h; and periodic limb movement index (PLMI) > 15 events/h.

Fifty-seven patients (36 men, 21 women) who underwent v-PSG during the study period were diagnosed with iRBD and did not meet the exclusion criteria were enrolled in the study. The control group was defined as participants who underwent v-PSG during the same period; did not have a diagnosis or clinical suspicion of a sleep disorder including RBD, obstructive sleep apnea (OSA), or restless legs syndrome; and did not meet the exclusion criteria. We selected 28 age-matched and sex-matched healthy controls (17 men and 11 women) from among those who met the criteria for the control group.

For the HRV analysis, participants with a lead II abnormality on their ECG, such as arrhythmia, or poor ECG signals on their PSG were also excluded from the study. Finally, 47 patients with iRBD (28 men, 19 women) and 26 controls (14 men, 12 women) were included in the analysis.

This retrospective study was approved by the institutional review board of Seoul National University Hospital (approval no. H-1809-080-97). Informed consent was waived for retrospective review of patients by iRB. All procedures followed the ethical standards of the research committee and were implemented in accordance with the 1964 Declaration of Helsinki and subsequent amendments.

Video-polysomnography

Data from overnight v-PSG (Profusion3, Compumedics, Charlotte, NC) at the Center for Sleep and Chronobiology of Seoul National University Hospital, comprising electroencephalograms (electrodes at F3, F4, C3, C4, O1, and O2, with A1 and A2 as reference sites), bilateral electrooculograms, a single-lead ECG (lead II), submental and bilateral tibialis anterior electromyography (EMG), airflow measurement via a nasal pressure transducer and oronasal thermal sensor, a respiratory inductance plethysmography band to monitor the movements of the chest and abdomen, and a finger pulse oximeter, were analyzed in each patient. PSG data were scored by experienced technicians and physicians in accordance with the American Academy of Sleep Medicine (AASM) recommendations.[20] Parameters including the AHI, PLMI, time in bed, total sleep time, sleep efficiency, wake after sleep onset, sleep latency, REM latency, and percentage of sleep in each stage were calculated and recorded.

HRV analysis

HRV differs between sleep and wakefulness and also among different sleep stages.[21] To analyze HRV across different sleep stages, HRV data from non-REM sleep stage 2 (N2), awake (W), and REM stage (R) were selected.

The first 5-minute epochs with stable ECG lead II values were selected from stages N2, W, and R from the nocturnal PSG data. Some participants did not develop stage N1 (30 of 73) or N3 (57 of 73) sleep for 5 consecutive minutes; hence, the analysis in these cases was not performed for these stages. ECG

data during wakefulness before sleep onset were excluded from the analysis. Epochs with arrhythmia, arousals, motor or respiratory events, poor ECG signals, or other artifacts were excluded from the analysis. HRV parameters for both the time and frequency domains were analyzed for each epoch. ECG recordings with a pulse rate > 180 or < 30 beats/min or regarded as artifacts on manual inspection were excluded.

To remove noise and baseline drift, the ECG signals were filtered through high-pass filtering (cutoff frequency: 0.5 Hz) and were then sequentially low-pass filtered (cutoff frequency: 30 Hz, fifth order, infinite impulse response, Butterworth). ECG R peaks were detected using a self-developed automatic peak detection algorithm[22] and then manually corrected.

HRV parameters for the time and frequency domains were extracted as follows. In the time domain, the mean heart rate, standard deviation of the R-R intervals (SDNN), and root mean square of successive R-R interval differences (RMSSD) were computed. Furthermore, to extract frequency domain HRV, cubic interpolation was applied to the R-R intervals. Then, the spectral power was computed using fast Fourier transform. The spectral power in the LF (0.04–0.15 Hz) and HF (0.15–0.4 Hz) bands was computed by summing all spectral components in each band. Normalized LF and HF values were computed by dividing by the sum of the LF and HF values. The formulas were

$$\text{Normalized LF} = \text{LF}/(\text{LF} + \text{HF}),$$

$$\text{Normalized HF} = \text{HF}/(\text{LF} + \text{HF}).$$

In addition, the ratio of the LF value to the HF value (LF/HF) was extracted. Eight HRV parameters were computed every 30 s with a 5-minute window. The HRV was analyzed using MATLAB R2018b (MathWorks, Natick, MA) software.

Two patients with RBD and two controls showed no 5-minute consecutive-stage W data on PSG, so their HRV variables were excluded from the analysis of stage W.

RSWA analysis

RSWA was quantified as proposed by Lapierre and Montplasir[23] by dividing the entire PSG into epochs and mini-epochs and calculating the rates of tonic epochs and phasic mini-epochs among all epochs and mini-epochs. In our study, we defined epochs as 30 seconds and mini-epochs as 3 seconds, based on the AASM scoring manual.[20,24] In accordance with the AASM manual, tonic activity was measured using chin EMG, whereas phasic activity was measured using chin or limb EMG. In previous studies, phasic activity was measured only in the mentalis or submentalis muscle; in the bilateral anterior tibialis muscle and the mentalis or submentalis muscle[25]; or in other limb muscles such as the flexor digitorum superficialis, biceps brachii, or extensor digitorum brevis muscles, in addition to the mentalis or submentalis and bilateral anterior tibialis.[24,26,27] However, among 85 patients, EMG of the flexor digitorum superficialis was recorded in only 49 (45 of 57 patients with RBD and 4 of 28 control participants), but EMG of both the submentalis and anterior tibialis muscle was performed in all participants. Accordingly, we used only the bilateral anterior tibialis and submentalis to evaluate phasic activity.

In our study, when an epoch of REM sleep had an EMG amplitude of more than 10 μV in the submentalis EMG channel during at least 50% of the duration of the epoch, it was defined as an epoch with tonic activity. On the other hand, when determining phasic activity, a 30-second epoch of REM sleep was divided into 10 sequential 3-second mini-epochs. When at least 5 (50%) of the mini-epochs contained bursts of transient muscle activity, in which the duration of bursts was more than 3 seconds and the amplitude was more than 10 μV in the submentalis or anterior tibialis EMG channel, the epoch was defined as having phasic activity.[20] The cutoff value for the amplitude of tonic and phasic activity was set to 10 μV (rather than 4 times the background EMG activity, as defined by the AASM, because the background EMG activity of the samples was not always easily determined).[24] The RSWA of tonic activity was defined as the rate of tonic epochs of all the epochs of REM sleep, and the RSWA of phasic activity was defined as the rate of phasic mini-epochs of all the mini-epochs of REM sleep.

Statistical analysis

To summarize the demographic, clinical, polysomnographic, and HRV parameters, descriptive statistical analysis was performed. The Kolmogorov–Smirnov test was used to confirm that the data were normally distributed. As most characteristics were not normally distributed, the demographic, clinical, and polysomnographic differences between groups were assessed using nonparametric methods, namely the Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables.

We used a linear mixed model (LMM) to evaluate HRV differences between the 2 groups and to assess relationships between HRV and RSWA in the iRBD group across different sleep stages. As most HRV parameters, except the normalized LF and HF values, were not normally distributed, log transformation was performed prior to LMM analysis.

In the first analysis, changes in HRV by sleep stage and the presence of iRBD were evaluated. As no significant group × sleep-stage interaction was observed for any HRV parameter, the association of iRBD and sleep stage on HRV was analyzed without considering such interactions. The second analysis was limited to iRBD participants. The changes in HRV by sleep stage and quantified tonic/phasic RSWA were evaluated. For certain parameters for which significant interactions between RSWA and sleep stage were observed, those interactions, RSWA, and sleep stage were analyzed as fixed effects. Other parameters were analyzed without considering interactions.

P values < 0.05 were regarded as statistically significant. Statistical tests were performed using the Statistical Package for the Social Sciences version 23.0. Seoul National University Hospital Medical Research Collaboration Center was asked to advise on statistical analysis; we followed that advice.

RESULTS

Demographic and clinical characteristics

The demographic and polysomnographic characteristics of the iRBD and control groups are shown in **Table 1**. No significant difference in demographic or polysomnographic parameters

Table 1—Comparisons of demographic and polysomnographic characteristics between the iRBD and control groups.

Variable	iRBD (n = 47)	Control (n = 26)	*P* Value
Age	67.17 ± 6.79	67.19 ± 6.41	.989
Sex (female)	19 (40.4%)	12 (46.2%)	.805
TIB, min	480.93 ± 30.02	479.85 ± 23.96	.875
TST, min	385.24 ± 48.63	378.19 ± 63.31	.624
Sleep efficiency, %	80.47 ± 11.11	91.34 ± 69.04	.292
WASO, min	76.61 ± 51.69	91.44 ± 54.19	.252
Sleep latency, min	18.49 ± 22.86	11.62 ± 11.07	.154
R latency, min	125.61 ± 65.82	98.29 ± 53.61	.075
Stage N1, %	24.65 ± 13.81	19.58 ± 9.07	.097
Stage N2, %	52.15 ± 12.96	56.66 ± 7.63	.066
Stage N3, %	4.20 ± 5.77	3.77 ± 5.50	.755
Stage R, %	18.99 ± 7.76	20.00 ± 6.56	.579
AHI, events/h	6.89 ± 4.10	5.63 ± 3.72	.202
PLMI, events/h	26.79 ± 38.89	12.37 ± 19.65	.082
Hypertension	17 (36.2%)	6 (22.2%)	.300
Coronary vascular disease	6 (12.8%)	2 (7.4%)	.703

AHI = apnea-hypopnea index; iRBD = idiopathic rapid eye movement sleep behavior disorder, PLMI = periodic limb movement index, TIB = time in bed, TST = total sleep time, WASO = wake after sleep onset.

Table 2—Linear mixed model analysis of fixed effects of factors (iRBD and sleep stage) on heart rate variability parameters.

	iRBD (n = 47)			Control (n = 26)			*P*
	Wake# (n = 45)	NREM sleep	REM sleep	Wake# (n = 24)	NREM sleep	REM sleep	
Mean HR (L)	67.34 (8.51)	63.00 (8.22)	64.95 (7.61)	68.67 (10.75)	63.22 (11.10)	67.07 (10.88)	Group: .554 Stage: < .001*
SDNN (L)	42.61 (26.53)	24.33 (12.00)	34.75 (18.11)	53.26 (27.56)	33.02 (21.04)	48.38 (36.76)	Group: .006* Stage: < .001*
RMSSD (L)	40.26 (34.64)	23.44 (19.44)	23.83 (20.09)	56.26 (31.41)	36.43 (30.32)	40.51 (59.78)	Group: .006* Stage: < .001*
LF (L)	417.37 (606.81)	166.84 (262.68)	250.84 (268.07)	597.36 (716.38)	349.43 (685.95)	586.46 (1318.40)	Group: .103 Stage: < .001*
HF (L)	541.50 (835.20)	187.66 (266.91)	205.54 (341.40)	678.93 (746.50)	399.72 (546.20)	802.01 (2766.11)	Group: .010* Stage: < .001*
Normalized LF	0.52 (0.22)	0.51 (0.22)	0.63 (0.22)	0.46 (0.19)	0.43 (0.22)	0.61 (0.25)	Group: .208 Stage: < .001*
Normalized HF	0.48 (0.22)	0.49 (0.22)	0.37 (0.22)	0.54 (0.19)	0.57 (0.22)	0.39 (0.25)	Group: .208 Stage: < .001*
LF/HF ratio (L)	2.04 (2.63)	1.85 (2.48)	3.56 (3.80)	1.13 (0.89)	−1.22 (1.53)	3.28 (3.39)	Group: .507 Stage: < .001*

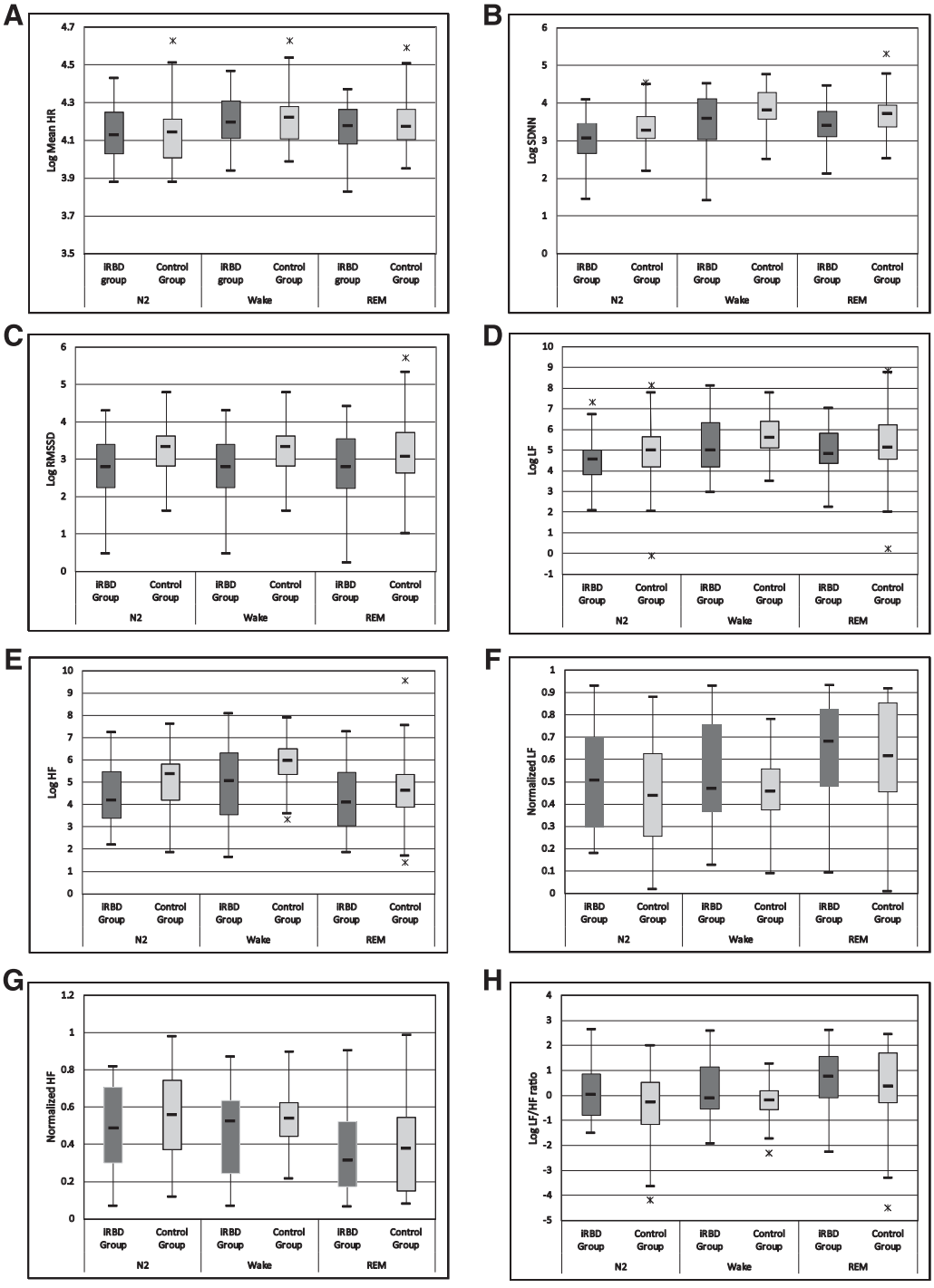
(L) Parameters were log-transformed before performing linear mixed model analysis. #Two participants with iRBD and 2 controls showed no stage W for 5 consecutive minutes on PSG, so their HRV variables were excluded from the analysis of stage W. *$P < .05$. iRBD = idiopathic rapid eye movement disorder, HF = high frequency, LF = low frequency, RMSSD = root mean square difference of successive R-R intervals, SDNN = standard deviation of R-R intervals.

between the 2 groups was observed. As the iRBD and control groups were matched for age and sex, the 2 groups showed no statistically significant difference in age (67.17 ± 6.79 vs 67.19 ± 6.41, $P = .989$) or sex (19 of 47 [40.4%] female vs 12 of 26 [46.2%] female, $P = .805$). There were no significant differences in AHI (6.89 ± 4.10 vs 5.63 ± 3.72, $P = .202$), PLMI (26.79 ± 38.89 vs 12.37 ± 19.65, $P = .082$), prevalence of hypertension (17 of 47 [36.2%] vs 6 of 26 [22.2%], $P = .300$), or prevalence of coronary vascular disease (6 out of 47 [12.8%] vs 2 out of 26 [7.4%], $P = 0.703$) between the 2 groups. The duration percentage of each sleep stage and other polysomnographic parameters did not differ significantly between the groups.

Comparisons of HRV parameters between groups

The HRV parameters and the results of LMM analysis of the association between fixed-effect factors (iRBD and sleep stage) and HRV are shown in **Table 2** and **Figure 1**. Although 2 participants from the iRBD group and 2 from the control group did not exhibit 5 consecutive minutes of stage W, the LMM allowed these participants to be included even though some values were missing. To summarize

Figure 1—Box plots of HRV parameters across sleep stages in iRBD group and control group.



The values of the first and third quartiles are shown in boxes. Values showing a difference of more than 10 times the IQR from the average value are marked with * as outliers. HF = high frequency, HRV = heart rate variability, iRBD = idiopathic rapid eye movement sleep disorder, LF, low frequency, REM = rapid eye movement, RMSSD = root mean square difference of successive R-R intervals, SDNN = standard deviation of R-R intervals.

in advance, we found associations of sleep stage with HRV parameters and of iRBD with SDNN, RMSSD, and HF. No group × sleep stage interaction was observed for any HRV parameter. No interactions are included in the LMM analysis shown in the **Table 2**.

LMM analysis of the log-transformed mean HRs revealed an association with sleep stage ($P < .001$), but not with iRBD ($P = .554$). The mean heart rate was lower in stage N2 than in stages W and R (all $P < .001$; **Figure 1A**). LMM analysis of the log-transformed SDNN and RMSSD revealed a significant main effect of sleep stage (all $P < .001$). SDDN was lower in stage N2 than in stages W and R (all $P < .001$), whereas RMSSD was higher in stage W than in the other 2 stages ($P = .009$ vs

Table 3—Linear mixed model analysis of fixed effects of factors (tonic/phasic RSWA, sleep stage) on heart rate variability parameters in participants with iRBD.

	Association of Tonic RSWA with HRV				Association of Phasic RSWA with HRV			
	B	95% CI Boundary		*P*	B	95% CI Boundary		*P*
		Lower	Upper			Lower	Upper	
Normalized LF								
RSWA	−0.00263	−0.00437	−0.00089	.004*	0.00141	−0.00267	0.00550	.490
Sleep stage				.003*				.003*
W	0 (ref)				0 (ref)			
N2	−0.08274	−0.16309	−0.00239		−0.01005	−0.07897	0.05887	
R	0.09869	0.01304	0.18434		0.11306	0.04698	0.17915	
RSWA × sleep stage				.016*				
W	0 (ref)							
N2	0.00271	−0.00437	0.00453					
R	0.00062	0.00090	0.00255					
Normalized HF								
RSWA	0.00263	0.00089	0.00437	.004*	0.00141	−0.00550	0.00267	.490
Sleep stage				.003*				.003*
W	0 (ref)				0 (ref)			
N2	0.08274	0.00239	0.16309		−0.01005	−0.05887	0.07897	
R	−0.09869	−0.18434	−0.01304		0.11306	−0.17915	−0.04698	
RSWA × sleep stage				.016*				
W	0 (ref)							
N2	−0.00271	−0.00453	0.00437					
R	−0.00062	−0.00255	−0.00090					
LF/HF ratio (L)								
RSWA	−0.12924	−0.02132	−0.00453	.003*	0.00531	−0.01453	0.02514	.593
Sleep stage				.003*				.004*
W	0 (ref)				0 (ref)			
N2	−0.40574	−0.80675	−0.00472		−0.05614	−0.39795	0.28568	
R	0.49382	0.04655	0.94109		0.56396	0.21876	0.90916	
RSWA × sleep stage				.020*				
W	0 (ref)							
N2	0.01305	0.00398	0.02211					
R	0.00302	−0.00705	0.01309					

(L) Parameters were log-transformed before performing linear mixed model analysis. *$P < 0.05$. HF = high frequency, LF = low frequency, RMSSD = root mean square difference of successive R-R intervals, RSWA = rapid eye movement sleep without atonia, SDNN = standard deviation of R-R intervals.

stage N2; $P = .004$ vs stage R). These 2 HRV parameters were lower in the iRBD group than in the control group; the association of iRBD and these parameters was thus significant (all $P = .006$; **Figure 1B** and **Figure 1C**).

The log-transformed LF values revealed a significant association with sleep stage ($P < .001$), being lower in NREM sleep than in stage W ($P = .006$). We found no significant association with iRBD ($P = .103$). Log-transformed HF values were also associated with sleep stage ($P < .001$), being higher in stage W than in N2 and R ($P = 0048$, $P = .003$, respectively), as well as with iRBD ($P = .010$), with lower HF values in the iRBD group than in the control group (**Figure 1D** and **Figure 1E**).

In terms of the normalized LF values, the association with sleep stage was significant ($P < .001$), but not that with iRBD ($P = .208$). Stage R was associated with significantly higher normalized LF values (vs. N2, $P = .001$; vs W, $P = .003$; **Figure 1F** and **Figure 1G**) than those of the other sleep stages. When the normalized HF value changed in a manner symmetrical to the normalized LF value change, only the association with sleep stage was confirmed ($P < .001$). There was no association of the parameters with iRBD ($P = .208$). Stage R was associated with significantly lower changes than stages N2 ($P = .001$) or W sleep ($P = .003$).

LMM analysis of the log-transformed LF/HF ratios revealed a significant association with sleep stage ($P < .001$). LF/HF ratios were higher in REM sleep than in stage W ($P = .012$)

and N2 ($P < .001$); we found no significant effect of iRBD ($P = .507$, **Figure 1H**).

Correlation of HRV parameters with RSWA in the iRBD group

The correlations between HRV parameters and the tonic and phasic RSWA values of patients with iRBD are shown in **Table 3**.

LMM analysis of the association between tonic RSWA and sleep stages with HRV showed that sleep stage was associated with all HRV parameters. The quantified tonic activity was positively correlated with log-transformed normalized HF (B = 0.00263, $P = .004$) and inversely correlated with log-transformed normalized LF (B = −0.00263, $P = .004$) and the LF/HF ratio (B = −0.12924, $P = .003$). Significant interactions of group with sleep stage were observed for normalized LF values, normalized HF values ($P = .016$), and LF/HF ratios ($P = .020$); the correlation remained significant after inclusion of these interactions.

Analysis of the association of phasic RSWA and sleep stage with HRV showed that phasic RSWA was not correlated with HRV, but sleep stage was significantly associated with all HRV parameters. No group × sleep stage interaction was observed. No parameter other than the normalized LF and HF values, and the LF/HF ratio, had any significant effect on either tonic or phasic RSWA; these effects are not included in **Table 3**.

DISCUSSION

Our study revealed differences in HRV between patients with iRBD and controls, and these differences remained significant during sleep stages. As hypothesized, HRV parameters were significantly lower in the iRBD group than in the control group. Moreover, normalized LF values and the LF/HF ratio were negatively correlated with the quantified tonic RSWA, whereas HF values showed a positive correlation.

Comparison of HRV between the iRBD and control groups

We found that HRV parameters including SDNN, RMSSD, and HF values were significantly lower in the iRBD group than in the control group, consistent with the findings of previous studies that reported HRV decreases in patients with RBD.[7–9,12] These findings indicate the presence of cardiac autonomic dysfunction in Asian patients with iRBD as well, which previous studies did not address. Previous studies reported HRV decreases in both the frequency and time domains, and most reports focused on decreases in LF values rather than in HF values. Two studies that showed significant dysfunction only in LF values also showed borderline significance in terms of HF dysfunction.[8,12] The other 2 studies compared patients with PD with and without RBD and may have recruited participants with more advanced neurodegeneration than occurs in the early stage of the disease. Regarding HF, 1 previous study reported that patients with RBD had lower HF values than controls, which is consistent with current results.

In previous studies of HRV, SDNN reflected both sympathetic and parasympathetic functions, whereas RMSSD reflected mainly parasympathetic functions and was highly associated with HF.[28] We found that RMSSD, SDNN, and HF values were lower in patients with iRBD than in controls, implying, unlike previous reports, that iRBD may be associated with dysfunction of the parasympathetic rather than the sympathetic nervous system.

The dorsal motor nucleus of the vagus nerve has been reported to exert a major effect on autonomic nervous dysfunction in the early stages of PD.[29] Also, patients with early PD in whom motor deterioration is not significant have been reported to exhibit parasympathetic rather than sympathetic dysfunction.[30,31] Parasympathetic dysfunction reported in early synucleinopathies was dominant in the iRBD group in the current study, which supports the conventional hypothesis that RBD and synucleinopathies represent the same spectrum of neurodegenerative disorders.

Association of HRV with quantified RSWA in patients with iRBD

To our knowledge, no previous study has directly examined the correlation between HRV parameters and quantified RSWA. We found a correlation of HRV with tonic rather than phasic RSWA in patients with iRBD as well as inverse correlations of tonic RSWA with normalized LF values and the LF/HF ratio and a positive correlation with normalized HF values.

The normalized LF and normalized HF values, which are calculated using all LF and HF values, respectively, serve as markers of sympathovagal balance, as does the LF/HF ratio.[32] In our study, tonic RSWA was positively correlated with normalized HF values, but not with HF values. As mentioned in the Methods section, normalized HF values are derived from the ratio of HF values and LF values. HF values were lower in the iRBD group in the first part of our analysis, which may imply that steeper decline of sympathetic function than control group, represented by LF values, was correlated with tonic RSWA. This finding is in line with previous studies reporting predominant sympathetic dysfunction in patients with RBD, as represented by low LF values or a low normalized LF value and LF/HF ratio, together with a high normalized HF value, in patients with PD/RBD, which can be regarded as an advanced phase of RBD, compared with patients with only PD.[7,9]

The results of our study revealed that the quantified RSWA in patients with iRBD was related to changes in cardiac autonomic dysfunction. However, this correlation was observed only for tonic (not phasic) RSWA, probably because the clinical implications of these 2 indicators in terms of iRBD may differ. Recent studies indicated that the RSWA pattern may change over the course of iRBD, with tonic RSWA becoming predominant[17] in the late phase of the disease, and that tonic RSWA is a marker of phenoconversion to α-synucleinopathies in patients with iRBD.[2,15–17] Considering the results of previous studies, it is possible that autonomic dysfunction is more strongly correlated with tonic than with phasic activity in more severe and advanced forms of iRBD.

Strengths and limitations

To the best of our knowledge, we recruited more patients with RBD than any previous case–control study. This is the first study to analyze HRV in Asian patients with iRBD. In previous studies, HRV differed with race, including between Asians and Whites,[33] enhancing the clinical significance of our current study. We recruited age-matched and sex-matched controls and controlled for

factors that may affect or interfere with HRV measurement, such as AHI and PLMI. We performed high-pass and low-pass filtering and used an automatic peak detection technique (combined with manual inspection) to eliminate noise from HRV data.

Our study has several limitations. It was a retrospective study and thus cannot reveal causal relations between variables. Moreover, we could not control for the effects of medication on HRV. Various medications affect HRV, including antihypertensives such as beta-blockers, angiotensin-converting enzyme inhibitors, and antidepressants.[34–36] However, patients with a history of depression or use of antidepressants were excluded from the study, and there were no significant differences in the prevalence of hypertension and coronary artery disease between the iRBD and control groups. Another limitation is that neurodegenerative diseases were excluded based only on a medical-record review without structured evaluation of cognitive function. At our sleep clinic, participants who were enrolled in this study underwent detailed history taking for medical, neurological and psychiatric, and sleep signs/symptoms and completed a brief physical examination and a self-reported questionnaire on sleep quality, sleepiness, and depressive symptoms. Also, in this study, no clinical scale to assess dysautonomia other than HRV, such as The Scale for Outcomes in Parkinson's Disease-Autonomic, was performed at baseline, so the association between RBD and dysautonomia actually experienced by patients could not be confirmed. SCOPA-AUT, a patient-reported questionnaire for evaluation of autonomic dysfunction in Parkinson's disease, has been widely translated and validated in other studies in PD (Visser M, Marinus J, Stiggelbout AM, et al. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov Disord 2004;19:1306-1312.), and could have been a good evaluation tool in our study. Finally, in the EMG analysis, the sensitivity of the RSWA measurement may have been reduced because data from the flexor digitorum superficialis/extensor digitorum brevis muscles could not be included in the analysis.

CONCLUSIONS

To conclude, we found a decline in cardiac autonomic function exhibiting parasympathetic dominance in patients with iRBD. HRV in patients with iRBD was associated with quantified tonic RSWA, which has been reported to be a possible predictor of phenoconversion. Additional prospective studies in a large population with assessment of HRV in patients with iRBD are required to determine whether a further decrease in HRV in fact triggers sympathetic dysfunction and ultimately an increase in the rate of conversion to α-synucleinopathies.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
AHI, apnea-hypopnea index
ECG, electrocardiogram
EMG, electromyogram
HF, high frequency
HRV, heart rate variability
iRBD, idiopathic rapid eye movement sleep behavior disorder
LF, low frequency
LMM, linear mixed model
N2, non-REM sleep stage N2
OSA, obstructive sleep apnea
PD, Parkinson disease
PLMI, periodic leg movement index
PSG, polysomnography
R, REM sleep stage
RBD, rapid eye movement sleep behavior disorder
REM, rapid eye movement
RMSSD, root mean square of successive RR-interval differences
RSWA, rapid eye movement sleep without atonia
SDNN, standard deviation of the R-R intervals
v-PSG, video polysomnography
W, awake

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at the Seoul National University Hospital, Seoul, Korea. The authors report no conflicts of interest.