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Electrophysiological Difference in Obstructive Sleep Apnea with and without REM sleep Behavior Disorder: Cardiopulmonary Coupling Analysis

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Abstract

Objectives: Although rapid eye movement behavior disorder (RBD) and obstructive sleep apnea syndrome (OSA) have different pathophysiology, RBD patients with OSA appeared to have more stable sleep compared to patients with OSA and to verify it by cardiopulmonary coupling (CPC) method.

Methods: The polysomnography (PSG) data of 138 subjects with OSA (AHI ≥ 15), RBD with OSA (AHI ≥ 15), RBD, normal control (N=32, 26, 29, 51, respectively) were collected. For conducting case control study between RBD with OSA and patients with OSA only, a total of 32 OSA controls, matched for age, AHI and BMI were recruited. CPC parameters were obtained using CPC analyzer in Rem Logic. Sleep spectrogram by CPC analyses revealed the percentage of stable tidal volume [high-frequency coupling (HFC), 0.1–0.4 Hz] and fluctuation tidal volume [low-frequency coupling (LFC), 0.01 Hz to 0.1 Hz)] during sleep.

Results: Although there was no significant Apnea-Hypopnea index (AHI) difference between RBD with OSA and OSA group (AHI 29.1 ± 15.6/hr *vs.* 34.1 ± 18.9, p=0.332), there was significant difference in CPC measurements. In RBD-OSA group showed lower LFC (35.9 ± 16.8 *vs.* 49.7 ± 21.3, p=0.010) than OSA group. Unlike higher AHI in RBD with OSA than RBD group (29.1 ± 15.6/hr *vs.* 3.2 ± 1.6, p<0.001), there was no significant difference in CPC study. Both OSA group and RBD with OSA group showed higher LFC (OSA *vs.* normal: 49.7 ± 21.3 *vs.* 28.4 ± 13.3, p<0.001, RBD with OSA *vs.* normal: 35.9 ± 16.8 *vs.* 28.4 ± 13.2 p=0.035) and lower HFC (OSA *vs.* normal: 37.5 ± 20.0 *vs.* 56.2 ± 16.2, p<0.001, RBD with OSA *vs.* normal: 46.8 ± 20.8 *vs.* 56.2 ± 16.2, p=0.031) when compared with normal control group, respectively.

Conclusions: In terms of autonomic-respiratory interaction, RBD with OSA showed similar CPC profile (higher LFC and lower HFC than normal) to OSA group but less severe than pure OSA group. It suggests that RBD may have a protective effect on OSA.

Keywords: Rapid eye movement behavior disorder; Obstructive sleep apnea syndrome; Cardiopulmonary coupling analysis

Introduction

Rapid eye movement sleep behavior disorder (RBD) is characterized by loss of normal skeletal muscle atonia during rapid eye movement (REM) sleep, in association with abnormal motor behavior while dreaming. Patients with RBD exhibit increased phasic or tonic muscle activity seen on electromyogram channels during polysomnography [1]. The prevalence of RBD has not been well researched yet, but previous epidemiological studies of RBD suggested that RBD is not rare in the elderly, with prevalence estimates of 0.38% to 2.01% in the elderly population [2,3]. However, these dream-enacting behaviors can also occur in other sleep disorders, a clinical situation termed as "pseudo-RBD" [4]. Abnormal sleep behavior can occur in patients with obstructive sleep apnea (OSA), Iranzo et al. described a group of 16 patients with severe OSA who reported harmful dream-enacting behaviors resembling RBD, but in whom PSG failed to demonstrate REM sleep without atonia [5]. OSA is a highly prevalent disease characterized by recurrent episodes of upper airway obstruction that result in recurrent arousals and episodic oxyhemoglobin desaturation during sleep. OSA and RBD have different pathophysiologic substrates. While RBD is thought to reflect dysfunction of the brainstem structures that modulate REM sleep, OSA is caused by various factors such as impaired upper airway anatomy and pharyngeal dilator muscle activity, neural control of the pharyngeal muscles, respiratory arousal threshold and stability of the respiratory control system [1,6,7]. There were several studies dealt with RBD and OSA, mostly severe OSA as a disguiser of pseudo-RBD [5,8]. But there were few studies to assess if the sum of conflicting reaction resulted in lower severity of OSA, considering the opposite action on muscle activity. Huang et al. reported that patients with RBD and OSA presented shorter duration of apneas and hypopneas during REM than NREM sleep [9]. Although the previous study revealed excessive EMG activity associated with RBD probably protected from long apneas shorter respiratory events and less REM sleep-related exacerbation, could not disclose the impact of RBD with OSA on overall sleep stability. Cardiopulmonary coupling (CPC) analysis is an uncomplicated and inexpensive method, which is ECG-based method to assess sleep stability and phenotype of sleep apnea based solely on the continuous electrocardiogram (ECG) [10]. Previous studies about sleep apnea [11], fibromyalgia [12], and

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depression [13] revealed the association between the CPC indices and the sleep quality. CPC signals are known have two basic patterns: high frequency coupling (HFC), representing breath-to breath stability of tidal volume or sinus arrhythmia; in contrary, low-frequency coupling (LFC) is known to associated with variation of fluctuating tidal volumes and heart rate [14].

In this study, we hypothesized that RBD with OSA is associated with better sleep quality relative to OSA in conditions with a similar degree of sleep-disordered breathing (apnea-hypopnea index). We tested this hypothesis by employing the CPC method to investigate and quantify physiologic sleep stability in each group.

Material and Method

Subjects

This study was conducted by retrospective review of subjects who performed PSG in university hospital from November, 2009 to October, 2014. We included the patients who visited sleep clinic with complaints of abnormal sleep behaviors. Diagnosis of RBD were based on the international classification of sleep disorder (ISCD) second or third edition, which included: 1) Presence of REM sleep without atonia on PSG; 2) sleep-related, injurious, potentially injurious, or disruptive behaviors by history (i.e., dream enactment behavior); 3) abnormal REM sleep behavior documented during polysomnographic monitoring [15]. We excluded subjects who had other sleep disorder (i.e., Parasomnia other than REM sleep behavior disorder), other neurologic disorder and acute medical illness which may affect PSG and CPC parameters. We also excluded pseudo-RBD; subjects who had severe OSA mimic the symptoms of RBD, after careful review of their sleep study. But in case of subject could be diagnosed both RBD and OSA, instead of excluding them, they were divided into two groups as RBD with OSA (n=26) or RBD only (n=29) group. All subjects were evaluated with overnight PSG and divided into two groups according to the apnea-hypopnea index (AHI). We designated patients with AHI lower than 5 as 'RBD only' group and with AHI higher than 15 as 'RBD with OSA (RBD-OSA)' group. Finally, fifty normal control subjects (AHI<5/h), without any specific sleep complaints and medical history, were also reviewed.

Case-control study

A case-control study was conducted to compare the characteristics of sleep-related respiratory events between RBD with OSA (RBD-OSA) and patients with OSA only (OSA controls). The inclusion criterion for RBD with OSA patients and OSA controls was apnea-hypopnea index (AHI) ≥ 15/h. Among fifty-five patients with RBD, 26 cases were designated as RBD-OSA and included for analysis. The total of 32 OSA control out of 236 OSA subjects, matched for age, AHI and BMI were recruited from patients who visited sleep clinic.

Overnight polysomnography

All patients underwent a PSG study by Embla N7000 & RemLogic (Embla Systems, Denver, CO, USA). The recordings included electroencephalogram (C3-A2, C4-A1, O1-A2, and O2-A1), bilateral electrooculograms and chin electromyogram to determine sleep stage and arousal events. Other devices included piezo bands to check chest and abdominal respiratory effort, finger pulse oximetry, singling lead electrocardiogram with the modified V2 lead, bilateral leg electromyograms, pre-tracheal microphone for snoring, and body position. Air-flow was monitored with thermistors and nasal-cannula pressure transducer. Sleep and arousal scoring were performed using standard criteria. The PSG were scored for sleep and sleep-disorders breathing events using the 2007 guidelines of the American Academy of Sleep Medicine [16-18]. RBD patients were closely monitored by technicians for any movement or vocalization. REM sleep without atonia (RSWA) was definded when following findings were detected. 1) sustained muscle activity in REM sleep with 50% of the epoch having increased chin EMG amplitude, and/or 2) excessive transient muscle activity, defined by the presence of 5 or more mini-epochs (a 30 second epoch is divided into ten 3-second mini-epochs) in an epoch having transient muscle activity lasting at least 0.5 seconds [17]. Other findings from PSG were amounts of each sleep stage, sleep latency, total sleep time (TST), sleep efficiency (SE), and wake after sleep onset (WASO).

Cardiopulmonary coupling analysis

Cardiopulmonary coupling analysis was performed with single-lead electrocardiography data extracted from the PSG by Rem Logic CPC analyzer. The analysis composed of five parameters: 1) high-frequency coupling (HFC, spectrogram peaks in the frequency range of 0.1 Hz to 0.5 Hz), which indicates stable sleep; 2) low-frequency coupling (LFC, spectrogram peaks in the frequency range of 0.01 Hz to 0.1 Hz), which indicates unstable sleep; 3) very-low-frequency coupling (VLFC, spectrogram peaks in the frequency range of 0.00391 Hz to 0.01 Hz), which indicates awake or REM sleep; 4) other (spectrogram peaks other than HFC, LFC, and VLFC, typically <1% to 2%); and 5) elevated low-frequency coupling (e-LFC, a subset of LFC with especially large low-frequency power), which is known to correlate with sleep fragmentation and sleep apnea [10,14].

Statistical analysis

Statistical analyses were performed with SPSS software (SPSS 18.0, SPSS Inc., Chicago, IL, USA). A p value of less than 0.05 was required for statistical significance. Independent t-test or Mann-Whitney U test was employed to compare the PSG characteristics and Apnea-related parameters between RBD-OSA patients and their OSA controls when Appropriate. Pearson's Chi-square test was used to compare categorical variables.. Between groups comparisons were performed with a one-way analysis of variance (ANOVA). Turkey's honest significant difference post hoc test was used to test the significance among groups. Partial Spearman correlations between CPC parameters and PSG data in each group were calculated after adjusting for age, BMI and AHI.

Results

Demographics

29 subjects were designated as RBD, 26 as RBD-OSA and 32 subjects as OSA control. Demographic data of subjects are presented in Table 1. There were no significant differences in age, sex and ESS score among those three groups. The proportion of males in each group was predominantly higher than female, but there was no significant difference between the groups. Each group had a similar degrees of neurodegenerative disease, diabetes and cerebrovascular accident prevalence rate, but the prevalence of hypertension was significantly higher in the OSA group (5/29(17.2%) *vs.* 4/26(15.4%) *vs.*16/32(50.0%) p=0.004 RBD only, RBD-OSA, OSA respectively). RBD group showed significant lower BMI compare to OSA group. (23.9 ± 2.5 *vs.* 25.4 ± 2.7 *vs.* 25.9 ± 3.5 p=0.042, RBD only, RBD-OSA, OSA respectively) RBD group and RBD-OSA group had higher periodic limb movement index (PLMI) than OSA group. (35.3 ± 50.4 *vs.* 20.2 ± 29.2 *vs.* 6.7 ± 10.1, p=0.006 RBD only, RBD-OSA, OSA respectively) Beck depression index (BDI) was reported higher in RBD-OSA as compared to OSA group (11.2 ± 7.6 *vs.* 14.4 ± 9.2 *vs.* 7.9 ± 7.5, p=0.019 RBD only, RBD-

Parameters	RBD (n=29)	RBD-OSA (n=26)	OSA (n=32)	*P* value
Demographic and clinical characteristics				
Age(years)	64.8 ± 8.5	64.9 ± 9.9	62.4 ± 9.7	0.51
Gender(male/female)	17-Dec	18-Aug	20-Dec	0.254†
BMI (kg/m^2)	23.9 ± 2.5 [a]	25.4 ± 2.7 [a,b]	25.9 ± 3.5 [b]	**0.042**
ESS score	7.7 ± 3.9	8.0 ± 6.1	7.7 ± 5.9	0.97
BDI	11.2 ± 7.6 [a,b]	14.4 ± 9.2 [a]	7.9 ± 7.5 [b]	**0.019**
Neurodegenerative disease, n (%)	2 (6.9)	3 (11.5)	1(3.1)	0.454†
	(Idiopathic Parkinson's disease:2)	(Idiopathic Parkinson's disease:1, Multiple systemic atrophy:1 Vascular dementia:1)	(Alzheimer dementia:1)	
Hypertension, n (%)	5 (17.2) [a]	4 (15.4) [a]	16 (50.0)	**0.004†**
Diabetes, n (%)	4 (13.8)	1 (3.8)	2(6.3)	0.358†
Cerebrovascular accident, n (%)	6 (20.7)	3 (11.5)	4 (12.5)	0.565†
Polysomnographic features				
Total sleep time(min)	356.0 ± 62.8	353.4 ± 63.9	343.2 ± 47.2	0.658
Sleep efficiency (%)	77.9 ± 12.2	78.0 ± 12.5	78.1 ± 10.6	0.998
Sleep latency(min)	19.8 ± 17.7	22.4 ± 42.7	12.0 ± 11.2	0.285
REM (%)	21.7 ± 8.3	18.6 ± 7.6	18.5 ± 8.1	0.22
Stage 1(%)	18.9 ± 10.8 [a]	25.5 ± 11.4 [a,b]	27.8 ± 15.5 [b]	0.026
Stage 2(%)	54.6 ± 6.6	52.6 ± 14.4	50.5 ± 12.4	0.397
Slow wave sleep (%)	4.8 ± 7.6	1.7 ± 2.4	3.2 ± 5.1	0.121
Total AHI (/hour)	3.2 ± 1.6	29.1 ± 15.6 [a]	34.1 ± 18.9 [a]	<0.001
PLM index (/hour)	35.3 ± 50.4 [a]	20.2 ± 29.2 [a,b]	6.7 ± 10.1 [b]	0.006
Arousal index (/hour)	19.0 ± 9.4 [a]	26.6 ± 11.5 [a,b]	31.0 ± 15.7 [b]	0.002
WASO (%)	18.8 ± 11.7	18.0 ± 10.5	19.9 ± 10.0	0.796

Analysis of variance (ANOVA) on the average abundance Values in the same column followed by the same letter are not significantly different from each other at the 95% confidence interval using Tukey's post-hoc Honestly Significant Difference (HSD) test.
BMI, body mass index; WASO, wake after sleep onset; AHI, apnea hypopnea index; ESS, Epworth sleepiness scale; BDI, Beck Depression Index; PLMS, periodic limb movements during sleep.
†Fisher exact test.

Table 1: Sample characteristics of RBD, RBD-OSA and OSA controls.

OSA, OSA respectively). OSA and RBD-OSA group showed higher arousal index in comparison with RBD group (19.0 ± 9.4 *vs.* 26.6 ± 11.5 *vs.* 31.0 ± 15.7, p=0.002 RBD only, RBD-OSA, OSA respectively).

Comparison of respiratory-related and CPC parameters between RBD-OSA, OSA control

Table 2 depicts the comparison of OSA severity variables. Although the basal SpO_2 levels were similar (96.0 ± 0.9 *vs.* 95.1 ± 2.1, p=0.154), RBD-OSA group demonstrated higher nadir SpO_2 during sleep (85.6 ± 5.2 *vs.* 80.9 ± 7.2, p=0.003) shorter maximum apnea duration (34.4 ± 22.2 *vs.* 48.8 ± 28.5, p=0.028) and mean apnea duration (18.4 ± 8.5 *vs.* 23.7 ± 11.8, p=0.023) than OSA controls. The comparison of CPC parameters of both OSA-RBD and OSA control groups are presented in Table 3. Although there was no significant Apnea-Hypopnea index (AHI) difference between RBD-OSA and OSA group (AHI 29.1 ± 15.6/hr *vs.* 34.1 ± 18.9, p=0.332), there was significant difference in CPC measurements. In RBD-OSA group showed lower LFC (35.9 ± 16.8 *vs.* 49.7 ± 21.3 p=0.010) than OSA group. RBD-OSA group showed higher HFC than OSA group (46.7 ± 20.8 *vs.* 37.5 ± 20.0, p=0.069), but this difference was not statistically significant. Unlike higher AHI in RBD-OSA than RBD group (29.1 ± 15.6/hr *vs.* 3.2 ± 1.6, p<0.001), there was no significant difference in CPC study. RBD-OSA group showed higher LFC values than RBD group (35.9±16.8 *vs.* 28.5±18.8, p=0.086), but statistically insignificant. Both OSA group and RBD-OSA group showed higher LFC (OSA *vs.* normal: 49.7 ± 21.3 *vs.* 28.4 ± 13.3, p<0.001, RBD-OSA *vs.* normal: 35.9 ± 16.8 *vs.* 28.4 ± 13.2, p=0.035) and lower HFC (OSA *vs.* normal: 37.5 ± 20.0 *vs.* 56.2 ± 16.2, p<0.001, RBD with OSA vs. normal: 46.8 ± 20.8 *vs.* 56.2 ± 16.2, p=0.031) when compared with normal control group, respectively. Table 4 demonstrated comparison of demographic, PSG parameters and CPC parameters of RBD *vs.*

Parameters	RBD-OSA (N=26)	OSA control (N=32)	*P* value‡
Total AHI	29.1 ± 15.6	34.1 ± 18.9	0.332
REM AHI	27.4 ± 15.1	33.0 ± 19.3	0.303
NREM AHI	28.1 ± 17.2	30.7 ± 19.5	0.415
Basal SpO_2 (%)	96.0 ± 0.9	95.1 ± 2.1	0.154
lowest SpO_2 during sleep (%)	85.6 ± 5.2	80.9 ± 7.2	**0.003**
O_2 desaturation index	24.7 ± 15.1	31.2 ± 18.8	0.226
Mean apnea duration(sec)	18.4 ± 8.5	23.7 ± 11.8	**0.023**
Maximum apnea duration(sec)	34.4 ± 22.2	48.8 ± 28.5	**0.028**
Mean hypopnea duration(sec)	26.8 ± 7.3	28.8±6.1	0.159
Maximum hypopnea duration(sec)	63.1±17.2	71.9 ± 26.2	0.179
Obstructive Apnea index	8.5 ± 13.4	8.4 ± 11.2	0.057
Central Apnea index	0.1 ± 0.2	0.2 ± 0.6	0.095
Mixed Apnea index	1.9 ± 4.2	4.0 ± 6.0	0.166
F hypopnea	71.6 ± 26.3	63.6 ± 27.2	0.663

AHI: Apnea Hypopnea Index; SpO_2 Oxygen Saturation Measured by Pulse Oximeter;
F hypopnea: Fraction of Events that were Hypopneas.
‡ Mann-Whitney U test.

Table 2: Comparison of respiratory-related parameters between RBD-OSA and OSA.

Parameters	RBD-OSA	OSA	*P* value‡
HFC duration (%)	46.7 ± 20.8	37.5 ± 20.0	0.069
LFC duration (%)	35.9 ± 16.8	49.7 ± 21.3	**0.01**
vLFC duration (%)	15.9 ± 7.1	12.3 ± 5.7	0.084
eLFC	18.0 ± 16.5	30.9 ± 18.6	**0.012**

HFC: High Frequency Coupling; LFC: Low Frequency Coupling; vLFC: Very Low Frequency Coupling; eLFC.
‡ Mann-Whitney U test.

Table 3: CPC characteristics of RBD-OSA *vs.* OSA controls.

Parameters	RBD (n=29)	Normal control (n=51)	*P* value
Demographic and clinical characteristics			
Age (years)	64.8 ± 8.5	47.9 ± 5.9	**<0.001**
Gender (male/female)	17-Dec	24/27	0.320†
BMI (kg/m^2)	23.9 ± 2.5	22.6 ± 1.8	**0.005**
ESS score	7.7 ± 3.9	6.9 ± 4.1	0.412
BDI	11.2 ± 7.6	7.1 ± 6.3	**0.019**
Polysomnographic features			
Total sleep time(min)	356.0 ± 62.8	388.7 ± 47.5	**0.019**
Sleep efficiency (%)	77.9 ± 12.2	90.1 ± 11.1	**<0.001**
Sleep latency (min)	19.8 ± 17.7	8.4 ± 6.8	**0.002**
REM (%)	21.7 ± 8.3	22.8 ± 5.0	0.525
Stage1 (%)	18.9 ± 10.8	13.5 ± 4.9	**0.016**
Stage 2(%)	54.6 ± 6.6	58.0 ± 6.2	**0.025**
Slow wave sleep (%)	4.8 ± 7.6	5.7 ± 5.6	0.538
Total AHI (/hour)	3.2 ± 1.6	2.2 ± 2.2	**0.027**
PLM index (/hour)	35.3 ± 50.4	4.8 ± 8.6	**0.003**
Arousal index (/hour)	19.0 ± 9.4	14.6 ± 6.0	**0.027**
WASO (%)	18.8 ± 11.7	9.8 ± 6.8	**<0.001**

BMI: Body Mass Index; WASO: Wake After Sleep Onset; AHI: Apnea Hypopnea Index; ESS: Epworth Sleepiness Scale; BDI: Beck Depression Index; PLMS: Periodic Limb Movements during Sleep.
†Fisher exact test.

Table 4: Sample characteristics of RBD and normal controls.

normal control. RBD group was significantly older than normal control (64.8 ± 8.5 *vs.* 47.9 ± 5.9, p<0.001) and showed higher BMI (23.9 ± 2.5 *vs.* 22.6 ± 1.8, p=0.005) and BDI score (11.2 ± 7.6 *vs.* 7.1 ± 6.3, p=0.019). PSG parameter showed poor sleep efficiency (77.9 ± 12.2 *vs.* 90.1 ± 11.1, p<0.001), delayed sleep latency (19.8 ± 17.7 *vs.* 8.4 ± 6.8, p=0.002), increased PLMI (35.3 ± 50.4 *vs.* 4.8 ± 8.6, p=0.003), higher arousal index (19.0 ± 9.4 *vs.* 14.6 ± 6.0, p=0.027) and longer wakefulness after sleep onset (WASO) (18.8 ± 11.7 *vs.* 9.8 ± 6.8, p<0.001) in RBD compared to normal control. Overall, these results suggested that normal control had better PSG parameters than those of RBD group, but there was no significant difference in CPC parameters (Table 5).

Correlation analysis between PSG parameters and CPC parameters

In OSA group, the correlations between PSG parameters and CPC parameters analyzed by Spearman's correlation analysis model, was presented in Table 6. HFC was negatively correlated with AI, AHI (rho=-0.626, p<0.001, rho=-0.633, p<0.001), positively correlated lowest SaO_2 (rho=0.504, p=0.003) and did not show significant correlation with TST, sleep latency, SE, WASO and PLM index. LFC and e-LFC showed positive correlation with AI, AHI (rho=0.635, p<0.001 and rho=0.651, p<0.001 in LFC, rho=0.60, p<0.001 and rho=0.587, p<0.001 in e-LFC), and negative correlation with lowest O_2 saturation (rho=-0.507, p=0.003 and rho=-0.462, p=0.003). LFC and e-LFC did not show significant correlation with TST, sleep latency, SE, WASO and PLM index, either. VLFC did not show correlation with all PSG parameters. Unlike PSG

Parameters	RBD	Normal	*P* value‡
HFC duration (%)	52.3 ± 23.0	56.2 ± 16.2	0.545
LFC duration (%)	28.5 ± 18.8	28.4 ± 13.3	0.535
vLFC duration (%)	17.5 ± 8.1	14.8 ± 5.3	0.104
eLFC	13.6 ± 14.8	13.7 ± 10.1	0.426

HFC: High Frequency Coupling; LFC: Low Frequency Coupling; vLFC: Very Low Frequency Coupling; eLFC.
‡ Mann-Whitney U test.

Table 5: Sample characteristics of RBD and normal controls.

parameters showed good correlation with CPC parameters in OSA group, RBD-OSA group demonstrated positive correlation between HFC and lowest O_2 saturation (rho=0.507, p=0.008) and weak positive correlation with HFC and sleep latency (rho=0.49, p=0.033) (Table 7). LFC showed weak negative correlation with lowest O_2 saturation (rho=-0.414, p=0.035). Other than that, there was no significant correlation with TST, SE, WASO and PLM index.

Discussion

The key findings of this study, based on the CPC analysis, include the followings:

1) Despite a similar degree of AHI, reduced unstable sleep was found in RBD-OSA group compared with OSA controls.

2) In spite of the findings suggesting poor sleep quality in polysomnography, there was no significant difference in CPC results between RBD group and normal control group.

Quality sleep is defined as normal sleep architecture with lack of fragmentation and an absence of sleep disordered breathing. The CPC analysis is an automated measure of sleep physiology and complements traditional sleep-scoring system used to assess sleep stability/quality because it objectively contains features of physiological dynamics not accounted by EEG-based techniques [13]. Among the CPC parameters, the HFC is a physiologic marker of stable and consolidated sleep. On the other hand, the LFC is related to breath-to-breath fluctuation of tidal volumes and cyclic variations in a heart rate, reflecting unstable and fragmented sleep [14]. The VLFC is associated with wake or rapid eye movement (REM) period, and elevated LFC (e-LFC) is associated with probable apneas or hypopneas [14].

Several previous CPC studies consistently demonstrated that decreased HFC and increased LFC in OSA [14,19-21]. The same results were obtained in this study, both RBD-OSA and OSA group showed higher HFC and lower LFC than normal control. The tendency in CPC feature of obstructive sleep apnea was maintained, but RBD-OSA group had lesser unstable sleep than OSA group. In the previous study, increased muscle activities during REM sleep, apnea related parameters such as nadir SpO_2, maximum oxygen desaturation duration and apnea/hypopnea duration were less severe in RBD-OSA patients than their OSA controls [9]. The study provided the evidence to support that hypothesis quantitatively, by measuring REM-related EMG activity (REMREEA), suggested that increased REMREEA was associated with lower severity of OSA in RBD patients [9]. As shown in the previous study, our study also demonstrated that RBD-OSA group had higher nadir SpO_2, shorter maximum and mean apnea duration during sleep than OSA controls. According to recent various insights into sleep apnea pathogenesis, the neural control of muscles also contributing to OSA phathogenesis [7]. In the transcranial magnetic stimulation (TMS) studies in OSA, decreased moter excitatory potential (MEP) suggesting enhanced depression of the cortical motor neuron activity

Parameters	TST	SL	SE	AI	AHI	Lowest SpO_2	WASO (%)	PLMI
HFC	0.081	0.31	-0.096	-0.626**	-0.633**	0.504**	0.013	-0.068
LFC	-0.023	-0.249	0.149	0.635**	0.651**	-0.507**	-0.066	0.039
vLFC	-0.14	-0.104	-0.217	-0.107	-0.192	0.163	0.185	0.207
e-LFC	-0.014	-0.3	0.153	0.600**	0.587**	-0.462**	-0.059	0.126

TST: Total Sleep Time; SL, Sleep Latency; SE: Sleep Efficiency; AI: Arousal Index; AHI: Apnea-Hypopnea Index; WASO: Wakefulness After Sleep Onset; PLMI: Periodic Limb Movement Index; HFC: High Frequency Coupling; LFC: Low Frequency Coupling; vLFC: Very Low Frequency Coupling; eLFC.
Spearmans rho values are presented. * p<0.05 **p<0.01

Table 6: Partial Spearman correlation analysis between PSG parameters and CPC parameters after adjustment of age, gender and BMI in patients of OSA only (n=32).

Parameters	TST	SL	SE	AI	AHI	Lowest SpO_2	WASO	PLMI
HFC	-0.036	0.419*	-0.077	-0.197	-0.091	0.507**	-0.02	0.07
LFC	0.046	-0.264	0.022	0.334	0.271	-0.414*	0.094	-0.233
vLFC	-0.016	-0.376	0.081	-0.239	-0.302	-0.343	-0.087	0.154
e-LFC	0.139	-0.163	0.078	0.265	0.266	-0.233	0.016	-0.226

TST: Total Sleep Time; SL, Sleep Latency; SE: Sleep Efficiency; AI: Arousal Index; AHI: Apnea-Hypopnea Index; WASO: Wakefulness After Sleep Onset; PLMI: Periodic Limb Movement Index; HFC: High Frequency Coupling; LFC: Low Frequency Coupling; vLFC: Very Low Frequency Coupling; eLFC.
Spearmans rho values are presented. * p<0.05 **p<0.01

Table 7: Partial Spearman correlation analysis between PSG parameters and CPC parameters after adjustment of age, gender and BMI in patients of RBD with OSA (n=26).

was observed. Those abnormality were outside of the pharyngeal district which means wide spread dysfunction of the cortical-spinal system in OSA [22]. The pathogenesis of RBD is assumed that involvement of several brainstem structures, such as cholinergic pedunculopontine nucleus (PPN) which activates the muscle tone inhibitory system [23]. The dysfunction of GABAergic basal ganglia output which controls postural muscle tone by modulating PPN neuron may contribute to muscular atonia of REM sleep [24]. In terms of dysfunctional neural control of both diseases, it is possible that modulation of neural activity to increased muscular tone for lowering the severity of OSA. There was one case report of resolved OSA after implanting subthalamic nucleus deep brain stimulation [25]. Other non-anatomical traits, such as a low respiratory arousal threshold (awaken easily), is also important for many patients [7]. Premature awakening may prevent accumulation of respiratory stimuli to upper-airway dilator muscle activation as well as the resulting stabilization of sleep and breathing [26]. Sommerauer et al. reported that cortical arousability in response to respiratory and motor event is significantly attenuated in Parkinson's disease (PD) patients. They suggested that loss of multiple arousal promoting nuclei, such as the PPN, the locus coeruleus(LC) and the dorsal raphe neucleus, was responsible for the low arousability in PD [27]. Given that RBD also related to PPN and LC lesions, increased arousal threshold might also have contributed to reduce unstable sleep in RBD-OSA group. PSG and CPC parameters showed HFC, LFC had significant correlation with AI, AHI and nadir SpO_2 during sleep in OSA group, which was consistent with previous study [21]. But RBD-OSA group showed no correlation between PSG and CPC parameters except for lowest Oxygen saturation during sleep and HFC. One possible explanation for this discrepancy is that CPC showed a closer relationship with CAP/non-CAP rather than conventional NREM-stage scoring [10]. CPC is not a sleep-stage or respiratory event detector but does provide a dynamic measure of cardiopulmonary coupling during sleep. Therefore, tight correlations with visually scored sleep states would not be expected [10]. Those explanations also could be applied to the discrepancy between PSG and CPC parameters in RBD *vs.* normal control. In spite RBD group showed poor sleep quality indicators including lower SE, higher AI, PLMI and WASO, CPC revealed that there was no significant difference to normal control. Regarding the CPC finding of RBD and RBD-OSA, LFC was higher in RBD-OSA without statistical significance. Although AHI was higher in the group of RBD-OSA, both groups had poor sleep quality with lower sleep efficiency and higher arousal index on PSG and it might reduce the effect of sleep-disordered breathing on CPC profiles.

There were several findings which reflect the characteristics of each group. In this study, there were more males in all groups. OSA [28] and RBD [2,29,30] both are male and elderly predominant disorder and thought to be naturally reflected in our study. In RBD group showed high PLMI which is very common in idiopathic RBD, occurring in all stages of sleep, especially during REM sleep [31]. Another intriguing finding was that RBD-OSA patients showed significantly higher BDI score than OSA controls. Considering greater prevalence of depression in patients with RBD when compared to those without in early PD patient [32], they might share common pathophysiology. It perhaps explained by the proximity of the serotoninergic raphe and other brainstem nuclei to the nuclei implemented in the pathophysiology of RBD [33]. Several strengths worth to note in this study. To our knowledge, this is the first study investigating CPC analysis in RBD patient. In addition, we investigate CPC in four well-characterized group which were RBD only, RBD with OSA, OSA only and normal control. By comparing those four groups in terms of demographics, PSG parameters and CPC parameters, this study provided new evidence of protective effect of RBD on OSA. We confirmed our initial findings of the correlation study that RBD patients had less severe apnea-related parameters by case-control study. Lastly, as previous study revealed that decreased heart rate variability in patients with RBD [34], simultaneous incorporating both cardiac interbeat(R-R) and ECG-derived respiration (EDR) investigation of this study minimized the limitation in cardiopulmonary coupling analysis of possible autonomic dysfunction subjects.

However, several limitations should also be noted in this study. First, separated CPC analysis according to REM *vs.* NREM sleep was not available. Since the time window of assessment of CPC is 8 minutes, unlike 30 seconds in PSG. This study showed RBD with OSA had more stable sleep than OSA control group. But we did not reveal the mechanism of the effect of RBD on OSA. Further studies with documentation of various factors developing OSA such as anatomical change, neuromuscular aspect and respiratory arousal threshold in each group are warranted to confirm our findings.

Another limitation was significant age difference between normal group and the other groups (RBD, RBD-OSA, and OSA). Aging itself is

associated with changes in sleep architecture, decreased sleep efficiency and increased arousal. The prevalence of sleep disorders increases with age (e.g. Insomnia, RBD, and OSA) [35]. Also coexistent illness or medication use which might effect on sleep is very common among elderly people. We had difficulty with recruit normal control of similar age with RBD and OSA group for those reasons.

Lastly, RBD is known to a precursor of PD or dementia and also related to cognitive impairment even in idiopathic RBD [23]. Since OSA is also known to cause cognitive dysfunction [36,37], measuring objective score related to neurodegeneration might help us understating various aspects of those two diseases. Since pure RBD showed similar profile to normal control in terms of CPC analysis, it could be used as screening test for patients with RBD whether pure RBD or other complicating sleep disorder which require further investigation. If RBD patient showed poor quality of sleep measured by CPC, concomitant disease (e.g. insomnia, depression, fibromyalgia) or pseudo-RBD should be considered. In this regard, our study suggested that the differences of the CPC between RBD and OSA could also help differentiate the ambiguous cases.

Conclusion

In conclusions, our study demonstrated that OSA patients with RBD showed more stable sleep than patients with OSA without RBD patients, which was proven by CPC parameters. It suggests that RBD probably has a positive impact on OSA, and this raises the need for further study to investigate the mechanism of RBD and OSA.

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