DOI: 10.5665/SLEEP.1126

Amelioration of Obstructive Sleep Apnea in REM Sleep Behavior Disorder: Implications for the Neuromuscular Control of OSA

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Objectives: The relationship between REM sleep behavior disorder (RBD) and obstructive sleep apnea (OSA) remains unclear. We aimed to (1) explore the association of REM-related EMG activity (REMREEA) with OSA in RBD patients; (2) compare the severity of OSA between RBD patients with OSA (RBD-OSA) and their age-, sex-, AHI-, and BMI- matched OSA controls.
Design: a. Correlation study in consecutive RBD subjects and b. case-control study
Setting: Sleep laboratory
Participants: 71 RBD patients in the correlation study and 55 subjects (28 RBD-OSA cases and 27 OSA controls) in the case-control study.
Intervention: N/A
Methods: Polysomnographic assessment to document the sleep architecture, sleep apnea related parameters, and REMREEA.
Results: (1) In the correlation study, increased REMREEA was associated with lower severity of OSA in RBD patients, including total AHI (r = −0.263), NREM AHI (r = −0.242), obstructive AHI (r = −0.265), and mean apnea duration (r = −0.353) (P < 0.05).
(2) In the case-control study, RBD-OSA patients had lesser severity of sleep apnea parameters than OSA controls in terms of higher nadir SpO_2 (85.7% ± 4.9% vs 80.8% ± 5.9%, P < 0.01), shorter maximum hypopnea duration (53.8 ± 16.7 vs 69.4 ± 22.4 seconds, P < 0.05), and maximum (45.8 ± 20.5 vs 60.8 ± 19.6 sec, P < 0.01) and mean apnea duration (22.3 ± 8.1 vs 26.3 ± 5.8 sec, P < 0.05). Significant interaction effects indicated that the usual REM sleep exacerbation of sleep apneas was seen only in OSA controls but not in RBD subjects.
Conclusions: This study demonstrated that excessive EMG activity in RBD might protect patients against severe OSA and suggests this may be a naturalistic model for understanding neuromuscular control of OSA.
Keywords: REM sleep behavior disorder; obstructive sleep apnea; REM-related EMG activity
Citation: Huang J; Zhang J; Lam SP; Li SX; Ho CKW; Lam V; Yu MWM; Wing YK. Amelioration of obstructive sleep apnea in REM sleep behavior disorder: implications for the neuromuscular control of OSA. *SLEEP* 2011;34(7):909-915.

INTRODUCTION

REM sleep behavior disorder (RBD) is a parasomnia characterized by a loss of REM sleep related normal skeletal muscle atonia with prominent motor activities and dream enactment behaviors.[1,2] Epidemiological studies of RBD suggested that RBD is not an uncommon disorder, with prevalence estimates of 0.38% to 0.5% in the elderly population.[3,4] The typical electrophysiological characteristic of RBD is increased electromyographic (EMG) tone during REM sleep.[1] Several clinical series have documented that majority (87.3% to 100%) of RBD patients had excessive tonic and/or phasic EMG activities during REM sleep across different populations.[2,5-7]

Obstructive sleep apnea (OSA) is a common sleep disorder[8,9] that is associated with pervasive cardiovascular, neurocognitive and metabolic consequences.[9-11] It has been suggested that decreased muscle tone of pharyngeal airway dilator muscles plays a critical role in the pathogenesis of OSA.[12] Tonic and phasic EMG activities of pharyngeal airway dilator muscles gradually decrease from wakefulness, NREM to REM sleep in both animal models and human subjects.[12-14] The reduction of upper airway dilator muscle EMG activity at sleep onset[15] may cause an individual, who has a more collapsible airway, to develop an obstructive respiratory event. The further reduction of genioglossus activity would explain the increased severity of OSA during normal REM sleep.[14] Furthermore, peak and tonic EMG activity in genioglossus has been shown to be associated with stable breathing.[14] Strychnine, an antagonist of glycine, has been found to increase upper airway muscles activity with consequent reduction of the duration and oxygen desaturation of apneas in OSA patients.[16] As early as the 1990s, Schenck and Mahowald proposed that RBD (related to its REM sleep without atonia [RSWA]) might protect against obstructive sleep apnea.[17] Nonetheless, it remains unclear on how excessive EMG activities may modulate the severity of OSA in RBD patients. In this study, we hypothesized that persistence of REM-related EMG activity (REMREEA) could ameliorate the severity of OSA in RBD patients. We aimed to (1) explore the associations of tonic and phasic EMG activities with sleep apnea-related variables in RBD patients; (2) compare the severity of OSA between RBD-OSA patients and their OSA controls matched for age, sex, apnea-hypopnea index (AHI) and body mass index (BMI).

Submitted for publication October, 2010
Submitted in final revised form January, 2011
Accepted for publication January, 2011
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METHODS

Subjects

Correlation study of the cohort series

The present study was conducted by a retrospective review of the case notes and baseline polysomnographic (PSG)

features of our consecutive series of RBD patients.[18] The diagnostic criteria of RBD were based on the International Classification of Sleep Disorder (ISCD) first or second edition, which included: (1) a history of problematic sleep behaviors that were harmful or potentially harmful, or disruptive of sleep continuity or disturbing to self and/or sleep partner; (2) PSG abnormality of excessive augmentation of chin EMG tone or excessive chin or limb EMG twitching during REM sleep; (3) identifiable motor activities related to dream enactment during REM sleep by video recordings (not related to PLMS or respiratory events).[1,19] Among 84 available patients, 13 patients' PSG data were excluded from the current study in view of the early paper recordings. Final analysis included 71 RBD patients with computerized PSG monitoring.

Case-control study

A case-control study was conducted to compare the characteristics of sleep-related respiratory events between RBD-OSA and patients with OSA only (OSA controls). The inclusion criterion for RBD-OSA patients and OSA controls was apnea-hypopnea index (AHI) > 10/h. Those subjects who were on benzodiazepine treatments were excluded in view of benzodiazepine effect on both muscle tone and OSA severity.[20,21] Among 71 patients with RBD, 28 cases were included for analysis. A total of 27 OSA controls, matched for age, gender, AHI, and BMI were recruited from community elderly population.[22] These control subjects were not recruited by their presence of OSA symptoms.

Polysomnographic (PSG) Measures

All patients underwent an overnight video-PSG study with a CNS 1000P polygraph (CNS, Inc, Chanhassen, Minnesota, USA). As reported in our previous study, a single night video-PSG was reliable and adequate to diagnose RBD and to document the semi-quantitative EMG activities.[7] For those with ≥ 2 PSG studies, first night data (without any concomitant CPAP treatment) was analyzed. The basic recordings included standard electroencephalogram (C3-A2, C4-A1), electrooculogram (LE-A2, RE-A1), chin electromyogram (EMG), bilateral leg EMG (anterior tibialis muscles), electrocardiogram, nasal-oral pressure transducer airflow, thoracic and abdominal respiratory efforts, oxyhemoglobin saturation, breathing sound, and body position. The sleep studies for RBD patients were simultaneously videotaped and closely observed by a technician for any movement or vocalization. All computerized sleep data were further manually scored by experienced PSG technologists and clinicians according to standard criteria.[23] Sleep stages were scored according to Rechtschaffen and Kales criteria,[24] using 30-sec epochs, with modifications to allow the persistence of EMG tone during epochs that were otherwise clearly REM sleep (i.e., epochs showing mixed-frequency low-amplitude EEG waveforms with absence of sleep spindles or K complexes, accompanied by presence of rapid eye movements).[25] Arousals were scored according to standard criteria.[23]

Sleep Apnea-Related Parameters

Apnea was defined as an absence of airflow lasting ≥ 10 sec, irrespective of changes in oxygen saturation. Hypopnea was defined as a reduction of ≥ 50% in the amplitude of the airflow signal and was only quantified if lasting ≥ 10 sec and accompanied by oxygen desaturation ≥ 3% and/or arousal. Apnea and hypopnea were further divided as obstructive, mixed, and central types according to the respiratory effort. AHI was calculated as the total number of apnea-hypopnea episodes per hour of sleep (total sleep, REM sleep, and NREM sleep, respectively). The duration of apnea and hypopnea episodes (mean and maximum) were also measured. Oxygen desaturation episode was defined as a dip in pulse oximeter oxygen saturation ≥ 3%. Oxygen desaturation index was calculated as the total number of desaturation episodes divided by total sleep time. Mean oxygen desaturation duration was the average period of all desaturation events during sleep. Nadir SpO_2 was defined as the lowest SpO_2 level during the sleep period.

REMREEA scoring method

Excessive EMG activities during REM sleep (REMREEA) were scored according to the method developed by Lapierre and Montplaisir[25] and further validated by Consens et al.[26] The EMG analysis was extracted from chin EMG channel. Details about the REMREEA were described in our previous study.[7] In brief, excessive EMG activities during REM sleep were divided into phasic and tonic activities. The phasic EMG events were defined as any burst of EMG activity lasting 0.1 to 5 sec with amplitude > 4 times the background EMG activity.[25,26] Short EMG bursts (< 100 msec) were not counted. The result was represented as the percentage of 3-sec mini-epochs with phasic EMG activity. Regarding tonic EMG activity, each 30-sec epoch was scored as tonic or atonic depending on whether tonic chin EMG activity was present for more or less than 50% of the epoch. REMREEA was calculated as the percentage of tonic and phasic EMG activities during REM sleep.

Statistical Analysis

Descriptive statistics were given as means ± standard deviations as well as frequencies (percentage). In the correlation study, Spearman correlation was used to test the correlation between EMG activities (tonic and phasic) during REM sleep and apnea-related parameters (Table 2). In the case-control study, 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. Fisher exact test was used to test the rate differences in major medical diseases between RBD-OSA patients and their OSA controls. Two-way ANOVA was used to explore the potential interaction between REM-NREM sleep and RBD-OSA on sleep apnea related parameters. P-value < 0.05 was considered statistically significant. SPSS 16.0 (Chicago, IL) for Windows was used for all statistical analysis.

RESULTS

Correlation Study

Demographic, clinical, and polysomnographic characteristics of 71 RBD patients are shown in Table 1. The average AHI was 23.7 ± 24.0/h; 60.6% of the patients had an AHI > 10/h. The average EMG activity was 23.4% ± 24.1%, 9.7% ± 6.9%, and 33.1% ± 24.8% for tonic, phasic, and tonic + phasic EMGs (REMREEA), respectively.

Table 2 shows that the percentage of tonic EMG activity during REM sleep in RBD patients was negatively associated with total AHI ($r = -0.31$, $P < 0.05$), NREM AHI ($r = -0.29$, $P < 0.05$), and obstructive AHI ($r = -0.31$, $P < 0.05$), but not REM AHI ($P > 0.05$). In addition, tonic EMG activity (%) was negatively correlated with mean apnea duration ($r = -0.35$, $P < 0.01$), while phasic EMG activity (%) was negatively correlated with mean hypopnea duration ($r = -0.32$, $P < 0.01$) and mean oxygen desaturation duration ($r = -0.30$, $P < 0.05$). There was also a trend that tonic EMG activity (%) was negatively correlated with maximum apnea duration, maximum and mean oxygen desaturation duration ($P < 0.10$). Overall, REMREEA was significantly and negatively correlated with several apnea-related parameters, including total AHI ($r = -0.26$, $P < 0.05$), NREM AHI ($r = -0.24$, $P < 0.05$), obstructive AHI ($r = -0.26$, $P < 0.05$), and mean apnea duration ($r = -0.35$, $P < 0.01$).

Table 1—Characteristics of REM sleep behavior disorder (RBD) cohort series

	RBD (n = 71)
Age (years ± SD)	67.0 ± 10.5 (23-84)
Gender (male/female)	58 (81.7%)/13 (18.3%)
BMI (kg/m^2)	24.3 ± 3.1 (17.4-31.0)
Diabetes (n, %)	7 (9.9%)
Hypertension (n, %)	18 (25.4%)
Neurodegenerative diseases (n, %)	10 (14.1%)
Benzodiazepine treatment (n, %)	24 (33.8%)
AHI	23.7 ± 24.0 (0.80-95.1)
AHI > 10/h (n, %)	43 (60.6%)
Tonic EMG activity (%)	23.4 ± 24.1
Phasic EMG activity (%)	9.7 ± 6.9
Tonic +phasic EMG activity (REMREEA) (%)	33.1 ± 24.8

BMI, body mass index; AHI, apnea-hypopnea index; REMREEA, REM-related EMG activity.

Case-Control Study

Table 3 depicts the sample characteristics of RBD-OSA patients and their age-, sex-, BMI-, and AHI-matched OSA controls. Overall, these results suggested that the clinical features in these 2 groups were similar, except that RBD-OSA patients were slightly sleepier than OSA controls as measured by Epworth Sleepiness Scale. Although RBD-OSA patients seemed to have more diabetes and hypertension, the differences were not statistically significant. No significant differences were found in PSG characteristics between these 2 groups ($P > 0.05$), except that both tonic and phasic EMG activities during REM sleep were significantly higher in RBD-OSA patients (18.3% ± 22.3% vs 0.4% ± 1.1%, and 9.3% ± 5.3% vs 2.1% ± 1.3%, respectively) than in OSA controls.

Table 2—Correlations between sleep apnea and hypopnea parameters and EMG activity during REM sleep in RBD subjects

	%of tonic EMG activity	%of phasic EMG activity	REMREEA
AHI	-0.31*	0.034	-0.26*
REM AHI	-0.15	0.018	-0.13
NREM AHI	-0.29*	0.026	-0.24*
Obstructive AHI	-0.31*	0.025	-0.27*
Central AHI	-0.16	-0.21	-0.19
Mixed AHI	-0.19	-0.16	-0.22
Mean apnea duration# (n = 61)	-0.35**	-0.14	-0.35**
Maximum apnea duration# (n = 61)	-0.25†	-0.18	-0.26†
Mean hypopnea duration# (n = 63)	-0.011	-0.32**	-0.073
Maximum hypopnea duration# (n = 63)	-0.12	-0.24†	-0.134
O_2 desaturation index	-0.20	-0.072	-0.18
Nadir SpO_2 during sleep	-0.11	-0.18	-0.14
Maximum O_2 desaturation duration# (n = 59)	-0.22†	-0.14	-0.24†
Mean O_2 desaturation duration# (n = 52)	-0.26†	-0.30*	-0.32

REMREEA, REM-related EMG activity; AHI, apnea-hypopnea index; SpO_2, oxygen saturation measured by pulse oximeter. Spearman correlation test (n = 71). *P < 0.05; **P < 0.01; †P < 0.10. #Subjects with at least one corresponding event were recruited into analysis.

The comparison of OSA severity variables is presented in Table 4. Although the basal SpO_2 levels were similar (94.8% ± 1.6% vs 94.2% ± 1.5%, $P > 0.05$), RBD-OSA patients had lower severity of oxygen desaturation than OSA controls, including higher nadir SpO_2 (85.7% ± 4.9% vs 80.8% ± 5.9%, $P < 0.01$), shorter maximum desaturation duration, and lower desaturation indices ($P < 0.05$). RBD-OSA patients had shorter maximum apnea duration (45.8 ± 20.5 vs 60.8 ± 19.6 sec, $P < 0.01$), mean apnea duration (22.3 ± 8.1 vs 26.3 ± 5.8 sec, $P < 0.05$), and maximum hypopnea duration (53.8 ± 16.7 vs 69.4 ± 22.4 sec, $P < 0.05$) than OSA controls. The differences in mean oxygen desaturation duration and mean hypopnea duration did not reach statistical significance. RBD-OSA patients had slightly less mixed AHI but similar obstructive and central AHI as compared to OSA controls.

As respiratory events were more likely to occur during REM sleep in OSA patients, we further investigated whether there were differences in sleep stage-related respiratory events between RBD-OSA patients and OSA controls. Significant interaction effects by 2-way ANOVA were found in mean and maximum apnea duration, which indicated that REM sleep exerted different effects on these parameters in RBD-OSA patients and OSA controls. For instance, mean apnea duration decreased from NREM to REM sleep in RBD-OSA patients but increased in OSA patients (interaction $P = 0.015$). There was also a trend of interaction in nadir SpO_2 which decreased from NREM to REM sleep in OSA controls but remained stable in RBD-OSA subjects (interaction $P = 0.081$).

DISCUSSION

In view of the typical feature of persistent EMG activity during REM sleep, RBD has been proposed to be protective against OSA since the 1990s.[17] Our results, for the first time, provided evidence to support this hypothesis quantitatively. Nonetheless,

Table 3—Sample characteristics of RBD subjects with OSA (RBD-OSA) and OSA controls

	RBD-OSA (n = 28)	OSA Controls (n = 27)	P Value
Demographic and clinical characteristics			
Age (years)	66.8 (12.0)	65.3 (13.1)	0.66
Gender (male), n (%)	24 (85.7)	24 (88.9)	0.72
BMI (kg/m^2)	24.2 (3.3)	25.4 (3.7)	0.22
Neurodegenerative diseases n/N (%)	3/28 (10.7%)	0/27 (0%)	0.24†
Hypertensions n/N (%)	6/28 (21.4%)	2/27 (7.4%)	0.25†
Diabetes n/N (%)	4/28 (7.3%)	0/27 (0%)	0.11†
ESS score	10.4 (5.1)	7.4 (4.7)	0.028*
Polysomnographic features			
Time in bed (min)	538.6 (83.8)	490.6 (63.4)	0.051#
Total sleep time (min)	383.0 (91.3)	358.1 (88.1)	0.59#
Sleep efficiency (%)	71.1 (12.0)	72.7 (13.4)	0.56#
WASO (min)	134.3 (64.2)	120.2 (63.8)	0.38#
REM sleep latency (min)	110.2 (78.0)	113.6 (74.1)	0.96#
Sleep latency (min)	21.4 (18.0)	12.4 (5.4)	0.21#
REM (%)	19.3 (8.2)	19.8 (7.6)	0.79
Stage 1(%)	21.2 (9.2)	19.0 (8.5)	0.38
Stage 2(%)	58.4 (9.7)	60.8 (8.5)	0.34
Slow wave sleep (%)	1.17 (2.62)	0.36 (0.81)	0.23#
AHI#	34.2 (22.6)	36.9 (16.5)	0.25
PLMS index@	8.7 (10.2)	22.3 (30.4)	0.76#
Tonic EMG activity (%)	18.3 (22.3)	0.4 (1.1)	< 0.001#
Phasic EMG activity (%)	9.3 (5.3)	2.1 (1.3)	< 0.001#
REMREEA (%)	27.6 (23.0)	2.4 (2.0)	< 0.001#

BMI, body mass index; WASO, wake after sleep onset; AHI, apnea hypopnea index; ESS, Epworth Sleepiness Scale; PLMS, periodic limb movements during sleep; REMREEA, REM-related EMG activity. #Mann-Whitney U; †Fisher exact test; @50% of RBD-OSA patients had PLMS.

Table 4—Comparison of respiratory-related parameters between RBD-OSA patients and OSA controls

	RBD-OSA (n = 28)	OSA Controls (n = 27)	P Value#
Basal SpO_2 during sleep (%)	94.8 (1.6)	94.2 (1.5)	0.18
Nadir SpO_2 during sleep (%)	85.7 (4.9)	80.8 (5.9)	< 0.01
Maximum O_2 desaturation duration (sec)	102.0 (43.0)	158.4 (125.0)	< 0.01
Mean O_2 desaturation duration (sec)	42.8 (11.7)	45.3 (12.0)	0.38
O_2 desaturation index	14.1 (18.6)	20.1 (12.8)	< 0.05
< 90% O_2 saturation index	5.8 (10.9)	11.0 (9.6)	< 0.01
< 80% O_2 saturation index	0.05 (0.16)	0.40 (0.89)	< 0.05
Mean apnea duration (sec)	22.3 (8.1)	26.3 (5.8)	< 0.05
Maximum apnea duration (sec)	45.8 (20.5)	60.8 (19.6)	< 0.01
Mean hypopnea duration (sec)	24.1 (5.1)	26.2 (6.0)	0.23
Maximum hypopnea duration (sec)	53.8 (16.7)	69.4 (24.4)	< 0.05
Obstructive AHI	29.9 (20.3)	33.1 (15.9)	0.35
Central AHI	1.5 (3.4)	1.3 (2.2)	0.68
Mixed AHI	1.9 (3.5)	2.6 (2.7)	< 0.05

SpO_2, oxygen saturation measured by pulse oximeter; AHI, apnea hypopnea index. #Mann-Whitney U test.

OSA, defined as AHI > 10/h, has been reported to be highly prevalent in RBD patients with a prevalence rate of 34% and 61% in case series from the US[5] and Hong Kong,[18] respectively. This seems to contradict our hypothesis that excessive EMG activity could alleviate the severity of OSA. We speculated that a few explanations might account for the apparently high rate of OSA in our RBD patients. First, OSA is a male predominant disorder increasing with age.[8,27,28] The rate of OSA as defined by AHI ≥ 10/h in the elderly ranges from 24% to 62% across various studies.[8,27,28] Second, a high rate of OSA in RBD patients might be due to sampling bias, as all RBD patients in this study were recruited from clinical rather than community settings. Third, other determinants of OSA, such as anatomical and mechanical factors were not investigated in this study. Thus, we further conducted a case-control study to explore the detail differences of respiratory events between RBD cases to that of carefully matched OSA controls. By controlling the frequency of apneas and hypopneas, our case-control study allowed us to investigate how the excessive EMG activity could modulate the respiratory events in more detail. Accompanied by substantially higher EMG activities (both tonic and phasic) during REM sleep, RBD-OSA subjects were less severe in various apnea related parameters such as nadir SpO_2, maximum oxygen desaturation duration, oxygen desaturation index, mean and maximum apnea duration, and maximum hypopnea duration than their OSA controls. In other words, our case-control study demonstrated that RBD had shorter duration of respiratory events with consequently lesser oxygen desaturation. As the active critical closing pressure (active P_{crit}) of the upper airway, which is partially determined by EMG activity during sleep, plays a core role in the termination of sleep-related respiratory events,[29] we speculated that shortened duration of respiratory events might be accounted by enhanced active P_{crit} in the RBD patients. In addition, dilator muscle recruitment, which is modified by basic EMG tone in RBD patients might also affect active P_{crit}.[30] Further studies regarding the mechanism underlying the relationship between RBD and OSA should specifically focus on the neuromuscular control and P_{crit} of the upper airway.

Similarly, a recent study found that patients with Parkinson disease, which was also accompanied by increased muscle tone during sleep, had lower severity of OSA than controls.[30] On the other hand, Iranzo and Santamaria reported that severe OSA could mimic the symptoms of RBD and these apparent RBD symptoms could be eliminated by CPAP treatment.[31] In this regard, our study suggested that the differences of the semi-quantitative EMG (REMREEA) between RBD and OSA could also help differentiate the ambiguous cases.

Table 5—Comparison of respiratory-related parameters during REM and NREM sleep between RBD-OSA patients and OSA controls

	RBD-OSA (n = 28)		OSA Controls (n = 27)		P1	P2	P3
	REM	NREM	REM	NREM			
AI	21.2 (22.9)	22.8 (22.5)	31.3 (20.8)	24.3 (16.0)	0.15	0.50	0.28
HI	12.9 (10.6)	10.7 (6.6)	11.4 (10.5)	11.2 (5.9)	0.76	0.46	0.56
AHI	34.2 (23.0)	33.9 (23.8)	42.7 (21.8)	35.2 (17.9)	0.24	0.34	0.39
Nadir SpO_2 during sleep (%)	87.7 (5.0)	87.6 (4.0)	82.2 (6.3)	85.6 (4.7)	< 0.001**	0.095	0.081
Mean O_2 desaturation duration (sec)	48.8 (30.1)	36.7 (12.6)	50.8 (13.8)	41.6 (15.9)	0.37	0.006**	0.71
Mean apnea duration (sec)	21.3 (8.8)	24.0 (6.8)	29.7 (9.7)	24.9 (5.1)	0.003**	0.51	0.015*
Maximum apnea duration (sec)	36.6 (19.2)	46.3 (18.2)	57.2 (20.9)	53.0 (17.3)	< 0.001**	0.46	0.063
Mean hypopnea duration (sec)	23.6 (5.4)	24.1 (5.6)	28.2 (10.4)	25.4 (5.7)	0.045*	0.42	0.24
Maximum hypopnea duration (sec)	40.2 (12.8)	51.4 (17.9)	53.6 (28.1)	62.8 (20.8)	0.002**	0.012*	0.81

P1, group effect; P2, REM-NREM sleep effect; P3, interaction effect; AI, apnea index; HI, hypopnea index; AHI, apnea-hypopnea index; SpO_2, oxygen saturation measured by pulse oximeter. *P < 0.05; **P < 0.01.

An unexpected but interesting finding was that REMREEA was more likely to be associated with a decrease in NREM-related AHI rather than REM-related AHI in our study. By using the phasic electromyographic metric (PEM), Bliwise et al. reported that EMG activity actually increased during both REM and NREM sleep in RBD patients when compared with normal controls.[32] Thus, enhanced EMG activity in RBD patients during both REM and NREM sleep might account for the decrease in OSA severity in NREM sleep. The reason for the lack of correlation between REM-related AHI and REMREEA is uncertain. Even in this group of bona fide RBD patients, only one-third of time was associated with excessive EMG activity during REM sleep (Table 1). In other words, REMREEA might be able to modulate the severity but could not completely abolish OSA that occurred during REM sleep in RBD patients (please see below for further elaboration). Nonetheless, future studies with a larger sample size with varying degrees of REMREEA and investigation of other determinants of OSA, such as anatomical and mechanical factors, will be needed.

Another interesting finding was the differences in the severity of several apnea-related parameters (especially mean apnea duration) across REM and NREM sleep between RBD-OSA patients and OSA controls. In normal situation, REM sleep is associated with more severe apneic attacks in OSA.[33] However, it was not the case in our RBD subjects who had shorter duration of apneas and hypopneas during REM than NREM sleep (Table 5). Taking the findings altogether from the correlation and case-control studies, the excessive EMG activity in RBD ameliorated the severity of OSA resulting in shorter respiratory events, less REM sleep-related exacerbation, and probably a lower frequency of apneas and hypopneas.

Another intriguing finding was that RBD-OSA patients were slightly sleepier than OSA controls. Two possible reasons might account for the apparent increase in sleepiness in RBD-OSA. As RBD may be a precursor of Parkinson disease, this neurodegenerative disease was highly correlated with sleepiness.[34] The other reason may be related to the origins of the subjects at which clinical subjects (RBD) tended to be sleepier than the community subjects (OSA), even with same severity of OSA.[35] Although RBD-OSA patients seemed to have more diabetes and hypertension than OSA controls, these differences were not statistically significant (Table 3). Nonetheless, the potential selection bias of the subjects (clinical vs community) might have affected concomitant clinical features.

Although RBD has been suggested as a precursor of synucleinopathy-related neurodegeneration, we could not find any difference in the central AHI between RBD-OSA patients and OSA controls. These results indicated that the damage related to RBD might not include the central respiratory center. Nonetheless, further neuroimaging studies should be done to delineate the brainstem involvement of RBD with respect to respiratory involvement.

Clinical Implications

OSA is a highly prevalent sleep disorder worldwide with considerable morbidity and mortality.[9-11] Although continuous positive airway pressure (CPAP) treatment is the first-line treatment, it is not tolerated by a significant number of patients because of frequent side effects, such as mask leak, pressure intolerance, insomnia, and headache.[36] Compliance with CPAP treatment is alarmingly low, with rates ranging from 17% to 54%.[37] Hence, other alternative treatments, such as surgical therapy, pharmacological respiratory stimuli, electrical stimulation, and dental appliance have been developed. Among these alternative therapies, selective intramuscular and hypoglossal nerve stimulation by electrical device has shown some promising results in improving upper airway collapsibility and OSA severity.[38,39] In this regard, our study provided complementary evidence to demonstrate that the loss of atonia in skeletal muscle in RBD patients could lead to lower severity of OSA with shorter apneas and hypopneas. The shorter respiratory events could also result in less oxygen desaturation, which has been suggested to be an even better predictor of cardiovascular and metabolic outcomes than AHI.[9,40-42] Our study also suggested that drugs that might increase muscle activity could also benefit OSA in terms of both AHI and duration of sleep apnea. Previous studies found that serotonergic enhancers such as paroxetine,[43] mirtazapine[44] and glycinergic antagonists[16] could alleviate the severity of OSA via increasing EMG activity. However, the long-term safety, for example, precipitation of serotonergic drug related REM parasomnia in vulnerable subjects[45,46] and efficacy of these modulatory drugs are still unclear.

Strengths and Limitations

Several strengths are worthy to note in this study. To our knowledge, this is the first study systematically investigating the relationship between REM sleep-related EMG activities and respiratory events in RBD patients. The semi-quantification of EMG activities during REM sleep as scored by validated method provided a reliable assessment of the EMG activities. Second, the employment of a case-control study confirmed our initial findings of the correlation study that RBD patients had less severe apnea-related parameters. However, several limitations should also be noted in this study. First, the recording of EMG activity was based on surface EMG rather than upper airway dilator muscle EMG, which might not be accurate enough to reflect the total airway muscle response. Furthermore, we did not score EMG activity during NREM sleep in this study. Further studies with documentation of EMG activities of pharyngeal airway dilator muscles and Pcrit are warranted to confirm our findings. Since epoch-based scoring method could lead to both "overestimation" (tonic epoch with brief period of normal amplitude EMG) and "underestimation" (atonic epoch with brief period of abnormal EMG) issues, a more precise scoring method might be needed to improve the prediction of REMREEA on the severity of sleep apnea. Two recently developed automatic scoring methods, the PEM method[46] and suprathreshold REM EMG activity metric (STREAM),[48] based on mini-epochs of 2.5-3 seconds might improve sensitivity and accuracy of measuring EMG activities. The pathogenesis of OSA is determined by a series of complex etiologies in addition to muscular control. Other determinants of OSA, such as anatomical, mechanical and neural factors should also be taken into account in evaluating OSA in RBD patients. Future studies should also investigate whether RBD-OSA patients might be protected against the usual cardiovascular and metabolic complications that frequently affect OSA patients. Finally, the different origins of RBD-OSA (clinical) and OSA subjects (community) in the case-control study might lead to potential selection bias. Nonetheless, both groups were well-matched in terms of age, sex, AHI, and BMI; and the scoring of REMREEA in both groups further strengthened the negative association of EMG activities and apnea severity.

CONCLUSIONS

Our study demonstrated that excessive EMG activities in RBD patients might ameliorate the severity of OSA. In this regard, RBD is probably a good naturalistic model for further understanding of the neuromuscular control as well as potential treatment of OSA by activating upper airway dilator muscle activity.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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