Sleep and Breathing (2019) 23:865–871
https://doi.org/10.1007/s11325-018-01779-y

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

The association between obstructive sleep apnea during REM sleep and autonomic dysfunction as measured by heart rate variability

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Received: 20 September 2018 / Revised: 5 December 2018 / Accepted: 27 December 2018 / Published online: 26 January 2019

Abstract

Purpose To determine the effect of obstructive sleep apnea (OSA) during rapid eye movement (REM) sleep on autonomic dysfunction using heart rate variability (HRV) analysis.

Methods The medical records of adults who underwent nocturnal polysomnography at the Sleep and Chronobiology Center at Seoul National University Hospital were retrospectively reviewed. HRV parameters (mean RR interval, the standard deviation of all normal RR intervals [SDNN], square root of the mean squared differences of adjacent RR intervals [RMSSD], normalized low frequency [LF], normalized high frequency [HF], and the ratio of LF to HF [LF/HF]) were measured in 5-min electrocardiogram recordings obtained during W, N2, and R sleep stages. Comparisons were made among the control (apnea–hypopnea index (AHI < 15 and AHI during REM sleep (AHI_{REM}) < 15, $n = 27$), REM-associated OSA (AHI < 15 and $AHI_{REM} \geq 15$, $n = 27$), and OSA (AHI ≥ 15, $n = 27$) groups. The groups were matched for age, sex, and body mass index.

Results No significant differences were observed between the control and the REM-associated OSA groups for any of the HRV parameters. In contrast, compared with controls, the OSA group showed significantly lower normalized HF ($p = 0.031$) and higher LF/HF ($p = 0.018$) in stage W and a significantly shorter mean RR interval ($p = 0.046$) and lower RMSSD ($p = 0.034$) in stage N2.

Conclusions Our findings suggest that OSA during REM sleep is not a major contributor to autonomic dysfunction.

Keywords Sleep, REM · Sleep apnea, obstructive · Heart rate variability · Autonomic nervous system

Introduction

Obstructive sleep apnea (OSA) is a prevalent chronic sleep disorder [1] that is associated with increased risk of hypertension, coronary heart disease, and stroke [2–4]. The mechanisms underlying the OSA-associated increase in cardiovascular risk remain unclear; however, autonomic dysfunction induced by intermittent hypoxia and frequent arousal is thought to be a major contributor to cardiovascular risk [5].

Although obstructive respiratory events may occur in any stage of sleep, interest in the clinical implications of OSA during rapid eye movement (REM) sleep has grown in recent years. Upper airway collapsibility is thought to increase during REM sleep because muscle hypotonia, which induces obstructive respiratory events that last longer and cause greater oxygen desaturation than events during non-REM (NREM) sleep [6]. Moreover, REM sleep is associated with increased sympathetic activity in normal subjects [7]. Therefore, OSA during REM sleep may have a significant effect on cardiovascular risk, even when the apnea–hypopnea index (AHI) is low. Although some previous studies have shown an association of OSA during REM sleep with hypertension and nocturnal blood pressure non-dipping, a marker of cardiovascular risk [8, 9], others have found no effect on clinical features of OSA

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during REM sleep [10, 11]. Previous studies have focused on a single clinical outcome rather than investigating the physiological mechanisms underlying the increased cardiovascular risk associated with OSA during REM sleep.

Heart rate variability (HRV) is a validated noninvasive measure of autonomic dysfunction. A healthy heart has beat-to-beat fluctuations. Lower HRV reflects high sympathetic tone, low vagal tone, or both; by itself, it is associated with increased mortality and morbidity in patients with cardiovascular diseases associated with autonomic dysfunction, including heart failure, hypertension, diabetes mellitus, and coronary heart disease [12–15]. Previous studies have found reduced HRV in patients with OSA [16, 17]. These findings suggest that HRV is a valid measure of the effect of OSA during REM sleep on autonomic dysfunction and the associated cardiovascular risk.

Therefore, we measured HRV parameters during sleep in healthy control subjects, patients with REM-associated OSA who had obstructive respiratory events primarily confined to REM sleep, and patients with OSA to investigate the association between OSA during REM sleep and autonomic dysfunction.

Materials and methods

Participants

We retrospectively reviewed the medical records of adults (ages 18–64 years) who underwent nocturnal polysomnography (Profusion PSG3, Compumedics, Abbotsford, VIC, Australia) at the Sleep and Chronobiology Center at Seoul National University Hospital between November 2016 and December 2017. The healthy control group was defined by apnea–hypopnea index (AHI) < 15 events/h and AHI during REM sleep (AHI_{REM}) < 15 events/h, the REM-associated OSA group was defined by AHI < 15 events/h and $AHI_{REM} \geq 15$ events/h, and the OSA group was defined by AHI > 15 events/h. The exclusion criteria included (i) total sleep time < 4 h, duration of stage $R < 30$ min, or periodic limb movement index ≥ 15 events/h on polysomnography; (ii) presence of sleep disorders, including REM sleep behavior disorder, narcolepsy, and central sleep apnea diagnosed on polysomnography; (iii) medical conditions that may have affected autonomic activity, including arrhythmia, hypertension, coronary artery diseases, or diabetes mellitus [18]; (iv) treatments known to affect sympathetic activity, including beta-adrenergic blockers, calcium-channel blockers, and antiarrhythmic drugs [18]; (v) treatment for OSA, such as continuous positive airway pressure therapy, oral appliance, or surgical treatment for snoring; and (vi) major neurological or psychiatric disorders.

Twenty-seven subjects satisfied the criteria for REM-associated OSA. We selected 27 control and 27 OSA subjects matched with the REM-associated OSA subjects for age, sex, and body mass index (BMI) for participation in the study. The study was approved by the Institutional Review Board of Seoul National University Hospital.

Sleep recording

Nocturnal polysomnography consisted of electroencephalograms (electrodes at F3, F4, C3, C4, O1, and O2, with A1 and A2 as reference sites), bilateral electrooculograms, submental and bilateral tibialis anterior electromyograms, and a single-lead electrocardiogram; airflow was measured by a nasal pressure transducer and oronasal thermal sensor, a respiratory inductance plethysmography band was used to monitor chest and abdomen wall motion, and oxygen saturation was measured with a finger pulse oximeter. During polysomnography, the AHI, AHI_{REM}, periodic limb movement index, average blood oxygen saturation (SpO_2), minimum SpO_2, time in bed, total sleep time, sleep efficiency, wake after sleep onset, sleep latency, REM latency, and percentage of sleep in each stage were monitored. Polysomnography data were scored by experienced technicians and physicians in accordance with the American Academy of Sleep Medicine scoring manual version 2.4 [19]. The Epworth Sleepiness Scale (ESS), an eight-item self-report measure of daytime sleepiness [20], was administered to subjects before polysomnography to evaluate daytime sleepiness.

HRV measurement

The electrocardiogram was recorded simultaneously with polysomnography from lead II, and the signals were high-pass filtered at 3 Hz, then low-pass filtered at 30 Hz using fifth-order infinite impulse response Butterworth filters. R-peaks were detected using an automatic algorithm [21] and manually corrected. HRV parameters were extracted from the time and frequency domains. The time-domain parameters were the mean RR interval, the standard deviation of all normal RR intervals (SDNN), and the square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD). The frequency-domain parameters were the low-frequency (LF, 0.04–0.15 Hz) and high-frequency (HF, 0.15–0.4 Hz) components, and the LF/HF ratio (LF/HF). LF and HF were normalized by dividing each parameter by the value of their sum. We sought to obtain a 5-min epoch without any respiratory events, arousal, periodic limb movements, or excessive artifact in sleep stages W, N2, and R for each subject. R-peak detection and HRV parameter extraction were performed using MATLAB software (R2018a, MathWorks, Inc., Natick, MA, USA). If no suitable epoch

was found, the electrocardiogram recording of that stage was discarded. In total, ten control group electrocardiogram recordings for stage W were discarded, and nine stage W and two stage R REM-associated OSA group recordings were discarded. In the OSA group, eleven stage N3, two stage N2, and four stage R electrocardiogram recordings were discarded.

Statistical analysis

Descriptive statistics were used to summarize the demographic, polysomnographic, and HRV parameters. The HRV parameters were natural-log transformed to obtain a normal distribution. Differences among groups were assessed using an analysis of variance (ANOVA) followed by post hoc Bonferroni correction for normally distributed continuous variables, the Kruskal–Wallis test followed by post hoc Mann–Whitney *U* tests with the Bonferroni correction for non-normally distributed continuous variables, and the chi-square test for categorial variables. *P* values < 0.05 were considered to indicate statistical significance. All statistical tests were performed using the Statistical Package for the Social Sciences version 21.0 (SPSS, Inc., Chicago, IL, USA).

Results

Demographic and polysomnographic characteristics

The demographic and polysomnographic characteristics of the three groups are shown in Table 1. The ESS results for four control, one REM-associated OSA, and one OSA subjects were missing, and only complete ESS results were analyzed. The ESS scores of the REM-associated OSA and OSA groups were higher than those of the control group, but the differences did not reach statistical significance. As expected, the control group AHI (median [interquartile range], 3.8 [1.1–5.8]) and AHI_{REM} (4.7 [1.9–9.1] events/h) were lower than those in the REM-associated OSA (AHI: 9.6 [7.7–11.6], AHI_{REM}: 24.1 [17.8–28.5] events/h) and OSA (AHI: 24.1 [17.8–28.5], AHI_{REM}: 26.8 [10.5–41.1] events/h) groups ($p < 0.001$ for both comparisons). The REM-associated OSA group AHI was lower than that of the OSA group (9.6 [7.7–11.6] vs. 27.4 [17.4–33.4] events/h; $p < 0.001$); however, AHI_{REM} was not significantly different between groups. The minimum SpO2 was greatest in controls, followed by the REM-associated OSA and OSA groups (90.3 ± 3.2% vs. 86.2 ± 5.1% vs. 82.2 ± 7.1%, respectively; ANOVA, $p < 0.001$; with post hoc Bonferroni test: $p = 0.018$ for the control group vs. the REM-associated OSA group, $p < 0.001$ for the control group vs. the OSA group, and $p = 0.026$ for the REM-associated OSA group vs. the OSA group). With respect to sleep structure, the percentage of sleep spent in stage N1 was significantly greater in the OSA group (23.6 ± 11.4%) than in the control (16.3 ± 8.8%) and REM-associated OSA (15.7 ± 5.1%) groups (ANOVA, $p < 0.002$; with post hoc Bonferroni test: $p = 0.005$ for the control group vs. the OSA group, and $p = 0.010$ for the REM-associated OSA group vs. the OSA group). No other significant differences were observed among groups.

HRV comparisons among groups

The HRV parameters for the three groups are shown in Fig. 1. No significant differences were observed between the control and the REM-associated OSA groups for any of the HRV parameters. In contrast, the comparison between the control and OSA groups revealed that in the patients with OSA, normalized HF was significantly lower (−1.00 ± 0.30 vs. −1.44 ± 0.60, respectively; $p = 0.031$) and LF/HF was significantly higher (0.50 ± 0.47 vs. 1.09 ± 0.83, respectively; $p = 0.048$) in stage W and that the mean RR interval was shorter (6.90 ± 0.13 vs. 6.83 ± 0.12, respectively; $p = 0.046$) and the RMSSD was lower (3.55 ± 0.55 vs. 3.17 ± 0.46, respectively; $p = 0.034$) in stage N2. In other HRV parameters of stages W and N2, we observed consistent trends toward higher normalized LF and LF/HF, a shorter mean RR interval, lower SDNN and RMSSD, and normalized HF in the OSA group compared with controls, although not statistically significant. In stage R, the SDNN in the REM-associated OSA group was significantly higher than that in the OSA group (4.06 ± 0.27 vs. 3.75 ± 0.31, respectively; $p = 0.026$).

Discussion

Our cross-sectional study revealed no significant differences in time- or frequency-domain HRV parameters during sleep between healthy control subjects and patients with REM-associated OSA. In contrast, the LF component and LF/HF in stage W were significantly higher, and the mean RR interval and RMSSD in stage N2 were significantly lower, in patients with OSA compared with controls.

We found no evidence to suggest that OSA during REM sleep contributed significantly to autonomic dysfunction. The notion that OSA during REM sleep is clinically important is based, in part, on the association of REM sleep with high sympathetic tone and cardiovascular instability [7]. However, Somers et al. [22] found increased sympathetic activity during stages N2 and R sleep in patients with OSA. Ventilatory control instability is increased in the sleep state transition during NREM sleep [23]. Therefore, an irregular breathing pattern in patients with OSA, who experience frequent arousal, may increase during NREM sleep and contribute to autonomic dysfunction. Furthermore, because REM sleep normally occupies about 20% of total sleep time,

Table 1 Demographic and polysomnographic characteristics of groups

	Control (1) [a] $N = 27$	REM-associated OSA (2) [a] $N = 27$	OSA (3) [a] $N = 27$	p value	Post hoc
Age, years	44.4 ± 12.9	45.6 ± 11.8	46.0 ± 12.8	0.888	
Sex, female, %	9 (33.3)	7 (25.9)	8 (29.6)	0.837	
BMI, kg/m^2	24.3 ± 3.0	25.0 ± 2.6	25.0 ± 3.5	0.647	
ESS [c]	5.8 ± 3.3	7.1 ± 3.8	8.4 ± 5.1	0.105	
AHI, events/h	3.8 (1.1–5.8)	9.6 (7.7–11.6)	24.7 (17.4–33.4)	< 0.001	(1) vs. (2) $p < 0.001$ [b] (1) vs. (3) $p < 0.001$ [b] (2) vs. (3) $p < 0.001$ [b]
AHI_{REM}, events/h	4.7 (1.9–9.1)	24.1 (17.8–28.5)	26.8 (10.5–41.1)	< 0.001	(1) vs. (2) $p < 0.001$ [b] (1) vs. (3) $p < 0.001$ [b] (2) vs. (3) $p = 0.966$ [b]
PLMI, events/h	1.1 (0.0–6.4)	1.0 (0.0–7.6)	0.0 (0.0–5.9)	0.601	
Average SpO2, %	95.0 (94.0–96.0)	95.0 (95.0–96.0)	95.0 (93.0–95.0)	0.028	(1) vs. (2) $p = 0.625$ [b] (1) vs. (3) $p = 0.025$ [b] (2) vs. (3) $p = 0.019$ [b]
Minimum SpO2, %	90.3 ± 3.2	86.2 ± 5.1	82.2 ± 7.1	< 0.001	(1) vs. (2) $p = 0.018$ (1) vs. (3) $p < 0.001$ (2) vs. (3) $p = 0.026$
TIB, min	468.2 ± 33.4	483.1 ± 34.2	478.4 ± 30.3	0.448	
TST, min	408.1 ± 50.8	408.9 ± 43.2	420.6 ± 29.5	0.479	
Sleep efficiency, %	89.0 (85.8–93.3)	87.1 (80.1–91.3)	89.9 (82.6–92.4)	0.259	
WASO, min	38.5 (24.5–55.5)	48.5 (29.5–82.0)	39.5 (28.5–60.5)	0.395	
Sleep latency, min	7.5 (4.5–12.0)	9.0 (6.0–12.5)	5.0 (3.0–15.0)	0.300	
REM latency, min	86.0 (76.0–118.5)	91.0 (63.5–138.5)	90.5 (72.5–130.5)	0.882	
Stage N1, %	16.3 ± 8.8	15.7 ± 5.1	23.6 ± 11.4	0.002	(1) vs. (2) $p > 0.999$ (1) vs. (3) $p = 0.005$ (2) vs. (3) $p = 0.010$
Stage N2, %	54.0 ± 7.7	52.6 ± 7.7	49.4 ± 9.1	0.111	
Stage N3, %	7.6 ± 6.0	10.1 ± 9.5	7.4 ± 6.1	0.342	
Stage R, %	22.0 ± 6.5	21.5 ± 5.5	19.6 ± 5.2	0.271	

Data are presented as mean ± SD or median (25–75% interquartile range), or number (percentage)

REM rapid eye movement, *OSA* obstructive sleep apnea, *BMI* body mass index, *ESS* Epworth sleepiness scale, *AHI* apnea-hypopnea index, *PLMI* periodic limb movement index, *TIB* time in bed, *TST* total sleep time, *WASO* wake after sleep onset

[a] Control definition: overall AHI < 15, and $AHI_{REM} < 15$; REM-associated OSA definition: overall AHI < 15 and $AHI_{REM} \geq 15$, OSA definition: overall AHI > 15

[b] The Mann-Whitney U test with the Bonferroni's correction, with $p < 0.0167$ as statistically significant

[c] $N = 23$, 26, and 26 for control, REM-associated OSA, and OSA, respectively

obstructive respiratory events during REM sleep may have a relatively small effect on total sleep. We found that the severity of OSA during total sleep had a greater impact on autonomic dysfunction than that during REM sleep. In stage R, the SDNN in the REM-associated OSA group was unexpectedly higher than that in the control and OSA groups. The REM-associated OSA group had frequent obstructive respiratory events, arousal, movements, and sleep-stage shifts during REM sleep. Although we attempted to select electrocardiogram recordings without such confounding factors, adjacent events may have disturbed heart rate and increased transient beat-to-beat fluctuations.

Our findings support those of previous studies showing autonomic changes in patients with OSA. Reynolds et al. [17] used a short-term HRV analysis to assess frequency-domain parameters in patients with OSA and found increased LF and LF/HF in wakefulness, but not in stage N2 sleep, consistent with our findings. Moreover, we observed decreased HF in OSA patients during wakefulness. A nocturnal analysis of time-domain HRV parameters performed by Zhu et al. [24] revealed that the mean RR interval was decreased in patients with OSA. Furthermore, our analysis of each sleep stage revealed that the RMSSD in stage N2 was decreased in patients with OSA. HF is a marker of vagal tone, and LF is thought to represent sympathetic tone or a balance between sympathetic and vagal tones [25]. Our findings suggest that sympathetic tone is increased, and vagal tone is decreased in patients with OSA during the sleep and waking states.

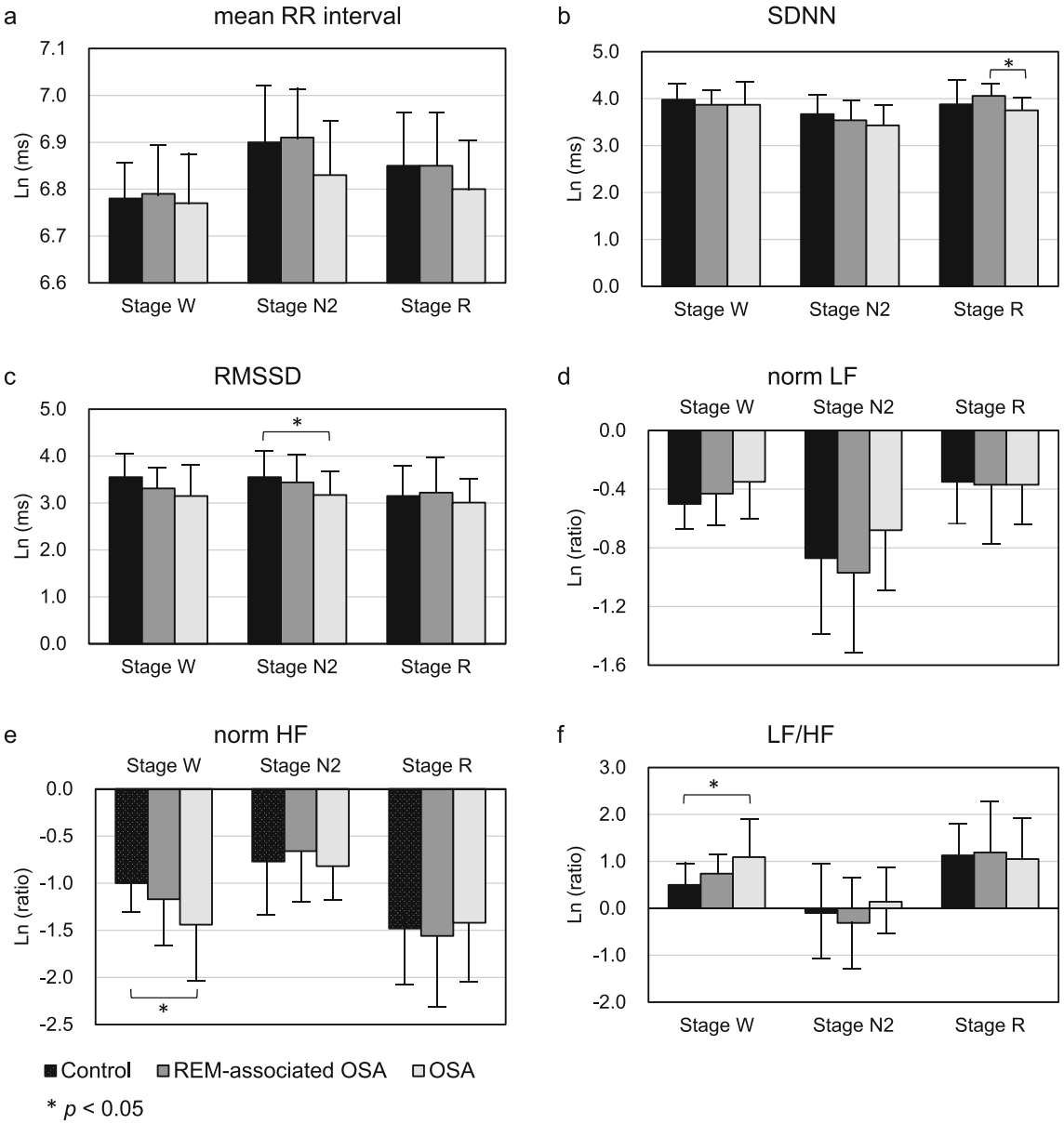

Fig. 1 Heart rate variability parameters were evaluated during 5-min periods without respiratory episodes in stage W ($N = 17$, 18, and 16 for control, REM-associated OSA, and OSA groups, respectively), stage N2 ($N = 27$, 27, and 25 for control, REM-associated OSA, and OSA groups, respectively), and stage R ($N = 27$, 25, and 23 for control, REM-associated OSA, and OSA groups, respectively). (a) There were no significant differences in the mean RR intervals among the three groups. (b) The OSA group had a significantly lower SDNN compare with the REM-associated OSA group in stage R (3.75 ± 0.31 vs. 4.06 ± 0.27 ln(ms), $p = 0.023$). (c) The OSA group had a significantly lower RMSSD compared with the control group in stage N2 (3.17 ± 0.46 vs. 3.55 ± 0.55 ln(ms), $p = 0.035$). (d) There were no significant differences in the norm LF among the three groups. (e) In stage W, the OSA group had significantly lower norm HF than the control group (-1.00 ± 0.30 vs. -1.44 ± 0.60 ln(ratio), $p = 0.028$) and (f) higher LF/HF than the control group (1.09 ± 0.83 vs. 0.50 ± 0.47 ln(ratio), $p = 0.044$). Mean RR interval and all HRV parameters are natural log transformed. *SDNN:* standard deviation of NN; *RMSSD:* root mean square of successive differences of NN; *norm LF:* normalized low-frequency (0.04–0.15 Hz); *norm HF:* normalized high-frequency (0.15–0.4 Hz)

The major strength of our study is the quantitative analysis of the effect of autonomic dysfunction, a potential mechanism underlying OSA, on cardiovascular risk in patients with REM-associated OSA. We controlled for factors that affect autonomic function, including periodic limb movements, age, sex, BMI, other sleep disorders, and major medical conditions. Nevertheless, our study has several limitations. First, the sample size was relatively small. Second, we excluded subjects with cardiovascular diseases or diabetes mellitus and those aged older than 64 years due to the potentially confounding effects of these conditions and age, respectively, on autonomic functioning [18]. However, this may have excluded individuals with severe REM-associated OSA or OSA, thereby attenuating autonomic dysfunction results for these

groups. Moreover, participants who developed OSA at a relatively young age may not have developed autonomic dysfunction by the time of their study participation. Thus, we cannot exclude the possibility that autonomic dysfunction may emerge in those with more advanced REM-associated OSA. Third, we used an AHI cutoff value of 15 events/h rather than 5 events/h to define REM-associated OSA and OSA, and this may have affected our results. Fourth, adjacent respiratory events, including arousal, movement, or sleep-stage shift may have affected the electrocardiogram recordings. Fifth, the definition of REM-associated OSA varies across studies and applying different criteria for REM-associated OSA may yield different results.

Our findings suggest that OSA during REM sleep is not a major contributor to autonomic dysfunction, which is associated with increased cardiovascular risk, although OSA was significantly associated with autonomic dysfunction. These findings help clarify the clinical importance of obstructive sleep apnea during REM sleep. Further study with large study population is needed to assess our findings.

Compliance with ethical standards

Ethical approval All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest All authors declare that they have no conflict of interest.

Informed consent The Institutional Review Board of Seoul National University Hospital approved this retrospective study (IRB number 1708-081-877) and waived the requirement for informed consent.

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