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Original Article

Effect of arousal on sympathetic overactivity in patients with obstructive sleep apnea

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) is associated with sympathetic overactivity. Intermittent hypoxemia and repetitive arousals are the proposed mechanisms; however, the main contributing factor for sympathetic overactivity remains to be determined. We therefore investigated the independent effect of apnea or arousal on sympathetic activity in a large cohort of OSA patients using heart rate variability analysis.

Methods: Frequency domain heart rate variability parameters were measured and compared between 782 patients with OSA (198 mild, 259 moderate, 325 severe) and 119 non-OSA controls. Univariate analysis was performed to identify associations between clinical and polysomnographic variables and heart rate variability measurements. Multivariate analysis was further performed to determine the potential contributing factors for sympathetic overactivity.

Results: Patients with OSA exhibited overall alterations in heart rate variability measures indicating sympathetic overactivity compared to controls, and this tendency was more pronounced in those with severe OSA. Univariate analysis showed that both apnea-hypopnea and arousal indices correlated with increased sympathetic activity and decreased parasympathetic activity. In multivariate analysis, arousal index was found to be more closely associated with sympathetic overactivity than apnea-hypopnea index.

Conclusion: The present study showed that arousal may be a more potent contributing factor than apnea for sympathetic overactivity in OSA patients. Our results suggest that arousal index, rather than apnea-hypopnea index, could be considered as a surrogate marker for sympathetic overactivity in OSA. Further longitudinal studies should elucidate causal relationship between arousals and sympathetic overactivity in patients with OSA.

1. Introduction

Obstructive sleep apnea (OSA) is the most common breathing disorder of sleep and is characterized by repetitive episodes of upper airway obstruction [1]. Based on cohort studies from Western countries, the prevalence of OSA is approximately 9–15% in adult women and 19–24% in adult men [2,3]. It is generally accepted that OSA increases the risk of cardiovascular diseases such as hypertension, cardiac arrhythmia, congestive heart failure, acute myocardial infarction, and stroke [4–7]. Although the underlying pathogenetic mechanisms are not fully understood, alterations in autonomic function are implicated in the development of these cardiovascular diseases in patients with OSA [8–11].

Heart rate is modulated by the interaction between the sympathetic and parasympathetic nervous systems, and heart rate variability (HRV) has been widely used as a noninvasive tool to evaluate the function of the autonomic nervous system [12,13]. Previous studies analyzing HRV have consistently shown alterations of autonomic nervous system activity in patients with OSA [14–21]. A vast majority of those studies showed a higher low-frequency power (LF) and a higher LF to high-frequency power (HF) ratio in OSA patients than in healthy controls, suggesting a shift in the sympathovagal balance toward sympathetic overactivity [15,17–19,21].

The pathophysiological mechanisms underlying sympathetic overactivity in OSA are still largely unknown. Repetitive exposure to apnea-induced hypoxemia and hypercapnia has been proposed

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as a possible mechanism for sympathetic overactivity in patients with OSA [22]. In support of this premise, previous investigations showed an increase in sympathetic activity in relation to the increasing apnea-hypopnea index (AHI) in patients with OSA [18,19]. In addition to the chemical factors (ie, apnea-induced hypoxemia and hypercapnia), it is hypothesized that mechanical factors such as decreased intrathoracic pressure during the apneic period could cause sympathetic overactivity [8]. Moreover, recurrent arousal has also been considered as a cause of sympathetic overactivity [23,24]. Gaining a better understanding of the mechanisms underlying sympathetic overactivity in OSA may provide insight into the development of cardiovascular consequences. However, the main contributing factor for sympathetic overactivity in OSA remains to be determined.

To our knowledge, there has been a dearth of available studies that explored the major risk factors for sympathetic overactivity in patients with OSA [25]. Herein, we aimed to investigate the independent effect of apnea or arousal on sympathetic activity in a large cohort of OSA patients, controlling for possible confounders. We hypothesized that not only AHI reflecting the severity of apnea-induced hypoxemia but also arousal would independently contribute to sympathetic overactivity in OSA.

2. Methods

2.1. Subjects

We retrospectively studied 1334 subjects who underwent overnight polysomnography (PSG) at the Korea University Guro Hospital from 2011 to 2016. Subjects referred to the sleep disorders clinic for snoring or suspected OSA were included in this study. Patients with OSA were categorized into mild ($5 \leq$ AHI < 15), moderate ($15 \leq$ AHI < 30), and severe (AHI ≥ 30) groups. Subjects who did not meet the criteria for OSA (AHI < 5) were served as a non-OSA control group. Subjects with a history of angina pectoris, myocardial infarction, atrial fibrillation, or stroke were excluded. Subjects with other sleep disorders potentially affecting the autonomic nervous system [23] were further excluded, including rapid eye movement (REM) sleep behavior disorder, narcolepsy, or restless legs syndrome. The local ethics committee approved the study protocol.

2.2. Polysomnography

An overnight PSG recording was performed with Embla N7000 system (Natus Medical Inc., Pleasanton, CA, USA) and RemLogic software (Version 2.0; Embla Co., Broomfield, USA). Electroencephalography was monitored using four leads (C3-A2, C4-A1, O1-A2, and O2-A1), and two pairs of electro-oculographic leads were used. Electromyographic leads were applied on the submentalis and the tibialis anterior muscles. Airflow was continuously measured using a thermistor and a nasal pressure cannula. Respiratory movements were monitored using respiratory inductive plethysmographic belts around the chest and abdomen. Oxygen saturation was measured by using a pulse oximeter.

Sleep stages and events were scored according to the American Academy of Sleep Medicine (AASM) manual [26]. The following parameters related to sleep architecture were measured: time in bed, total sleep time, wake after sleep onset, sleep latency, sleep efficiency, stage 1 sleep, stage 2 sleep, slow-wave sleep, REM sleep, and arousal. Arousal was defined as an abrupt shift of electroencephalographic frequency including alpha, theta and/or frequencies greater than 16 Hz (but not spindles) that lasts at least 3 s, with at least 10 s of stable sleep preceding the change. Scoring of arousal during REM requires a concurrent increase in submental EMG lasting at least 1 s [26]. The arousal index (AI) was defined as the number of arousals per hour, and calculated as the sum of apnea-hypopnea AI, periodic limb movement AI, and spontaneous AI. The oxygen desaturation index (ODI) was defined as the number of events per hour in which oxygen saturation decreased by 4% or more. Apnea was defined as a drop $\geq$90% of baseline in airflow for at least 10 s, and hypopnea was defined as a reduction $\geq$30% of baseline in airflow for at least 10 s in association with either $\geq$3% oxygen desaturation or an arousal [27]. The AHI was calculated by dividing the total number of apnea and hypopnea events by the number of hours of actual sleep.

2.3. Heart rate variability

The electrocardiography data extracted from the entire overnight PSG recording were visually inspected for accuracy and quality, and used for HRV analysis. Ectopic beats and artifacts were eliminated, and only normal-to-normal beats were selected for analysis [28]. Time domain and frequency domain measurements are used for the assessment of HRV. As time domain HRV parameters, which quantify the amount of variability in beat-to-beat intervals, are influenced by both sympathetic and parasympathetic activities, these parameters cannot discriminate the contributions to autonomic nervous system functions between sympathetic and parasympathetic activity [12]. The frequency domain parameters of HRV are obtained using the fast Fourier transform and categorized into frequency ranges and their spectral powers, which can provide information about specific changes in sympathetic and parasympathetic activity [12]. Therefore, we focused on frequency domain parameters of HRV in the present study to better investigate alterations in autonomic nervous system function by separating sympathetic and parasympathetic activity. The following frequency domain parameters were automatically calculated for spectral analysis implemented in RemLogic software: (1) total power spectrum (TP); (2) very low-frequency band power (VLF; 0.0033–0.04 Hz); (3) low-frequency band power (LF; 0.04–0.15 Hz); and (4) high-frequency band power (HF; 0.15–0.40 Hz). HF and LF are considered to represent vagal activity and baroreflex-mediated sympathetic activity, respectively [28]. The LF/HF ratio is considered as the representative index of sympathetic to parasympathetic (sympathovagal) balance with a higher LF/HF indicating a predominance of sympathetic activity [29]. In order to represent the activity of two branches of the autonomic nervous system (ie, sympathetic and parasympathetic) with minimizing the effects of the changes in TP on the values of LF and HF, normalized units of LF (LFnu) and HF (HFnu) were calculated by the formulas, LF/(TP-VLF) $\times$ 100 and HF/(TP-VLF) $\times$ 100, respectively [28,30]. The frequency domain HRV parameters are described in detail in Table 1.

2.4. Statistical analysis

Group comparisons of clinical variables, PSG data, and HRV parameters were performed using chi-square test (significant at $p < 0.05$) or analysis of variance with post-hoc Bonferroni correction (significant at $p < 0.008$), where appropriate. Univariate analysis was carried out to identify the effects of clinical and PSG variables on frequency domain HRV parameters (ie, LFnu, HFnu, and LF/HF ratio) using a simple linear regression. Variables found to be possible predictors of each frequency domain parameter with statistical significance ($p < 0.05$) in univariate analysis entered into a multivariate analysis. Multivariate analysis was conducted using a hierarchical linear regression to determine factors independently contributing to the LFnu, HFnu, and LF/HF ratio: Model 1 adjusted for age, sex, and clinical variables (eg, body mass index [BMI], hypertension, and diabetes mellitus); Model 2 adjusted for Model 1 variables + AHI; and Model 3 adjusted for Model 2 variables + AI (ie, the sum of apnea-hypopnea AI, periodic limb movement AI, and

Table 1
Frequency domain parameters of heart rate variability.

Parameters		Description
TP (ms^2)	Total power over measured period	Reflects total HRV
VLF (ms^2)	Spectral power in the very low frequency band (<0.04 Hz)	Reflects vagal and renin-angiotensin system effects on HR
LF (ms^2)	Spectral power in the low-frequency band (0.04–0.15 Hz)	Reflects combination of SNS and PNS influences. Captures baroreflex rhythms
HF (ms^2)	Spectral power in the high-frequency band (0.15–0.40 Hz)	Under normal circumstances reflects vagal activity
LFnu (%)	[LF/(TP − VLF)] × 100 for the measured period	Purported to reflect SNS activity
HFnu (%)	[HF/(TP − VLF)] × 100 for the measured period	Purported to reflect PNS activity
LF/HF ratio	LF-to-HF (LF/HF) ratio of HRV	Purported to reflect SNS/PNS balance

Abbreviations: HF, high-frequency power; HFnu, normalized HF; HR, heart rate; HRV, heart rate variability; LF, low-frequency power; LFnu, normalized LF; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; TP, total power; VLF, very low-frequency power.

spontaneous AI). The effect of multicollinearity between the variables was assessed using variance inflation factors (VIFs). Only variables for which the VIF was less than 5 entered into multivariate analyses as independent variables. Statistical significance was set to $p < 0.05$. Statistical analyses were performed with the Statistical Package for the Social Sciences software (Version 21.0; IBM Corp., Armonk, New York, USA).

3. Results

A total of 782 patients with OSA (198 mild, 259 moderate, 325 severe) and 119 non-OSA controls were finally selected for the statistical analysis. Demographics and clinical characteristics as well as PSG parameters are detailed in Table 2. Compared with controls, OSA patients were more likely to be older, male, and hypertensive (all $p < 0.001$). Epworth sleepiness scale (ESS) score was higher in the severe OSA group than in the mild OSA group ($p = 0.001$). BMI, AHI, ODI, and AI were higher in the severe OSA group than in the control, mild, and moderate OSA groups (all $p < 0.001$). AHI and ODI were higher in the moderate OSA group than in the control and mild OSA groups (all $p < 0.001$). BMI, AHI, and ODI were higher in the mild OSA group than in the control group (all $p < 0.001$).

Details of the frequency domain HRV parameters and statistical results are presented in Table 3. TP was higher in the severe OSA group than in the control and mild OSA groups (both $p < 0.001$). VLF was higher in the severe OSA group than in the control ($p < 0.001$), mild OSA ($p < 0.001$), and moderate OSA groups ($p = 0.003$). LF was higher in the severe OSA group than in the control group ($p < 0.001$). There was no difference in HF among the four groups (all $p > 0.008$). LFnu was higher in the severe OSA group than in the control and mild OSA groups (both $p < 0.001$). HFnu was lower in the severe OSA group than in the control, mild, and moderate OSA groups (all $p < 0.001$). The LF/HF ratio was higher in the severe OSA group than in the control and mild OSA groups (both $p < 0.001$). ESS score did not correlate with LFnu, HFnu, or LF/HF ratio (all $p > 0.008$).

Results of univariate analyses are summarized in Table 4. Male sex ($p < 0.001$), increasing BMI ($p = 0.044$), increasing AHI ($p < 0.001$), and increasing AI ($p < 0.001$) were associated with an increase in LFnu. Increasing age ($p = 0.001$), male sex ($p < 0.001$), increasing BMI ($p = 0.028$), diabetes mellitus ($p = 0.025$), increasing AHI ($p < 0.001$), and increasing AI ($p < 0.001$) were associated with a decrease in HFnu. Increasing age ($p = 0.012$), male sex ($p < 0.001$), hypertension ($p = 0.035$), increasing AHI ($p < 0.001$), and increasing AI ($p < 0.001$) were associated with an increase in LF/HF ratio.

Results of multivariate analyses are summarized in Table 5. Male sex ($p < 0.001$) and AI ($p < 0.001$) independently contributed to an increase in LFnu. Age ($p < 0.001$), male sex ($p < 0.001$), AHI ($p = 0.011$), and AI ($p < 0.001$) independently contributed to a decrease in HFnu. Age ($p = 0.004$), male sex ($p < 0.001$), AHI

Table 2
Baseline characteristics and polysomnographic parameters.

	Control (n = 119)	Mild OSA (n = 198)	Moderate OSA (n = 259)	Severe OSA (n = 325)	*p*
Baseline characteristics					
Age, years	44.7 ± 14.5	49.7 ± 14.7[a]	52.1 ± 12.3[a]	52.4 ± 12.5[a]	<0.001
Male, n (%)	42 (35.3)	136 (68.7)	186 (71.8)	284 (87.4)	<0.001
BMI (kg/m^2)	23.0 ± 2.9	25.1 ± 3.4[a]	26.2 ± 3.8[a]	27.6 ± 4.3[a,b,c]	<0.001
Hypertension, n (%)	16 (13.4)	69 (34.8)	105 (40.5)	178 (54.8)	<0.001
Diabetes mellitus, n (%)	8 (6.7)	17 (8.6)	22 (8.5)	43 (13.2)	0.026
ESS score	7.5 ± 5.1	6.8 ± 4.2	7.7 ± 4.6	8.4 ± 4.8[b]	0.002
PSG parameters					
Total sleep time (min)	323.1 ± 84.8	334.8 ± 59.6	340.1 ± 63.2	321.7 ± 70.4[c]	0.006
Sleep latency (min)	29.6 ± 46.0	21.1 ± 30.2[a]	13.8 ± 19.4[a,b]	12.6 ± 20.1[a,b]	<0.001
Sleep efficiency (%)	76.2 ± 20.2	81.0 ± 14.4	83.7 ± 13.5[a]	81.4 ± 13.6[a]	<0.001
WASO (%)	19.0 ± 18.8	15.2 ± 12.9	13.7 ± 12.6[a]	16.1 ± 12.9	0.006
N1 (%)	25.7 ± 13.2	25.2 ± 10.6	26.6 ± 12.7	40.3 ± 16.5[a,b,c]	<0.001
N2 (%)	37.2 ± 12.1	39.7 ± 12.3	40.3 ± 25.8	31.7 ± 14.6[b,c]	<0.001
N3 (%)	10.3 ± 9.8	7.4 ± 9.0	7.4 ± 9.3	4.2 ± 6.5[a,b,c]	<0.001
REM (%)	26.9 ± 9.2	27.7 ± 9.2	26.9 ± 8.7	24.2 ± 10.0[b,c]	<0.001
AHI	2.1 ± 1.5	10.3 ± 2.9[a]	21.9 ± 4.6[a,b]	54.0 ± 20.0[a,b,c]	<0.001
ODI	2.6 ± 8.4	8.2 ± 3.1[a]	17.4 ± 5.7[a,b]	46.9 ± 20.9[a,b,c]	<0.001
AI	29.1 ± 19.2	29.6 ± 14.6	33.9 ± 18.0	51.1 ± 20.3[a,b,c]	<0.001

Values are presented as number (%) or mean ± standard deviation.
Group comparisons were performed using chi-square test or analysis of variance, where appropriate.
Abbreviations: AHI, apnea-hypopnea index; AI, arousal index; BMI, body mass index; ESS, Epworth sleepiness scale; N1/N2/N3, non-REM sleep stages 1/2/slow-wave sleep; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; REM, rapid eye movement; WASO, wake after sleep onset.
[a] *p*-value < 0.008 compared with control group.
[b] *p*-value < 0.008 compared with mild OSA group.
[c] *p*-value < 0.008 compared with moderate OSA group.

Table 3
Heart rate variability parameters between the groups.

	Control (n = 119)	Mild OSA (n = 198)	Moderate OSA (n = 259)	Severe OSA (n = 325)	*p*
TP (ms^2)	29,481 ± 13,347	34,045 ± 16,526	36,612 ± 18,450	41,678 ± 26483[a,b]	<0.001
VLF (ms^2)	13,783 ± 8189	16,158 ± 9828	18,493 ± 11,308	22,296 ± 17278[a,b,c]	<0.001
LF (ms^2)	8920 ± 5002	10,805 ± 6445	11,368 ± 7074	13,013 ± 9436[a]	<0.001
HF (ms^2)	5839 ± 2467	6272 ± 3378	5971 ± 3531	5462 ± 3139	0.039
LFnu (%)	55.0 ± 11.5	57.6 ± 15.2	60.2 ± 14.7	63.6 ± 14.8[a,b]	<0.001
HFnu (%)	38.0 ± 9.8	36.2 ± 13.2	33.9 ± 13.3	29.7 ± 11.7[a,b,c]	<0.001
LF/HF ratio	1.7 ± 1.4	2.1 ± 1.7	2.4 ± 1.9	2.9 ± 2.8[a,b]	<0.001

Values are presented as mean ± standard deviation.
Abbreviations: HF, high-frequency power; HFnu, normalized HF; LF, low-frequency power; LFnu, normalized LF; OSA, obstructive sleep apnea; TP, total power; VLF, very low-frequency power.
[a] *p*-value < 0.008 compared with control group.
[b] *p*-value < 0.008 compared with mild OSA group.
[c] *p*-value < 0.008 compared with moderate OSA group.

Table 4
Results of univariate analyses.

Variables	LFnu		HFnu		LF/HF ratio	
	β	*p*	*β*	*p*	*β*	*p*
Age	0.032	0.333	−0.110	0.001	0.084	0.012
Male sex	0.239	<0.001	−0.240	<0.001	0.179	<0.001
BMI	0.067	0.044	−0.073	0.028	0.031	0.346
Hypertension	0.019	0.569	−0.056	0.095	0.070	0.035
Diabetes mellitus	0.034	0.310	−0.075	0.025	0.022	0.514
ESS	0.014	0.692	0.005	0.888	−0.015	0.670
AHI	0.234	<0.001	−0.295	<0.001	0.250	<0.001
AI	0.266	<0.001	−0.301	<0.001	0.247	<0.001

Abbreviations: AHI, apnea-hypopnea index; AI, arousal index; BMI, body mass index; ESS, Epworth sleepiness scale; HF, high-frequency power; HFnu, normalized HF; LF, low-frequency power; LFnu, normalized LF.

($p = 0.021$), and AI ($p < 0.001$) independently contributed to an increase in LF/HF ratio. ODI was omitted in the regression analysis due to a multicollinearity with AHI (VIF = 17.795).

4. Discussion

We confirmed that patients with OSA had overall alterations in HRV measures indicating sympathetic overactivity, and this tendency was more pronounced in those with severe OSA. Both AHI and AI correlated well with increased sympathetic activity and decreased parasympathetic activity. It is of note that AI was found to be a more potent contributing factor than AHI for sympathetic overactivity in OSA patients.

Our finding of increasing sympathetic activity in relation to increasing apnea severity accords well with previous studies showing a significant correlation between the LF/HF ratio and AHI, implicating a role of apnea severity in the sympathetic overactivity in patients with OSA [18,19,31–33]. We also observed that AHI independently contributed to a shift in the sympathovagal balance toward sympathetic overactivity. Although the mechanisms underlying sympathetic overactivity in OSA are unclear, the majority of previous observations suggest that repeated exposure to hypoxemia and hypercapnia may trigger acute sympathetic activation [18,19,31]. This premise could be supported by previous studies demonstrating an increase in the release of urinary catecholamines in patients with OSA compared with healthy controls [34,35]. Chronic exposure to intermittent hypoxia augmented chemoreflex-stimulated sympathetic outflow, and increased production of catecholamines and blood pressure in animals [36,37]. Furthermore, surgical denervation of peripheral chemoreceptors as well as chemical denervation of the peripheral sympathetic nervous system prevented the observed increase in blood pressure [36]. Collectively, repetitive hypoxemia could be a cause of systemic hypertension in OSA, and sympathetic overactivity may be the proposed underlying mechanism.

Repetitive arousals have also been supposed to increase sympathetic activity in OSA [23,24]. To our knowledge, there are very few studies investigating the relationship between sleep fragmentation and sympathetic activity in patients with OSA [25,38]. The sleep fragmentation index was found to strongly correlate with the LF/HF ratio and VLF in patients with various sleep disorders including OSA, supporting the hypothesis that sleep fragmentation could cause sympathetic overactivity [38]. A population-based study observed that sleep fragmentation was associated with elevated systolic blood pressure and higher risk of hypertension in healthy elderly volunteers, suggesting a role of repetitive arousals

Table 5
Results of multivariate analyses.

Variables	LFnu			HFnu			LF/HF ratio		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Age				−0.160***	−0.116***	−0.123***	0.113**	0.094**	0.097**
Male sex	0.237***	0.191***	0.200***	−0.263***	−0.198***	−0.209***	0.205***	0.143***	0.151***
BMI	NS	NS	NS	NS	NS	NS			
Hypertension							NS	NS	NS
Diabetes mellitus				NS	NS	NS			
AHI		NS	NS		−0.243***	−0.110*		0.200***	0.098*
AI			0.207***			−0.208***			0.165***

Values represent the regression coefficient (*β*).
Abbreviations: AHI, apnea-hypopnea index; AI, arousal index; BMI, body mass index; HF, high-frequency power; HFnu, normalized HF; LF, low-frequency power; LFnu, normalized LF; NS, not significant.
Hierarchical linear regression analysis: Model 1 adjusted for age, sex, BMI, hypertension, and diabetes mellitus; Model 2 adjusted for Model 1 variables + AHI; Model 3 adjusted for Model 2 variables + AI.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

during sleep in sympathetic overactivity and cardiovascular comorbidity [39]. The LF/HF ratio and VLF independently contributed to the increased microarousal index in OSA patients [25]. In line with above-mentioned studies, we found that increasing AI was strongly associated with an increase in sympathetic activity and a decrease in parasympathetic activity. Furthermore, multivariate analysis revealed that AI was more closely related to sympathetic predominance than AHI, suggesting that arousal is an important contributing factor for sympathetic overactivity in OSA. In support of our findings, an experimental study performed on healthy volunteers demonstrated rapid parasympathetic withdrawal and sympathetic overactivity after arousal in both normoxia and hypoxia conditions [40]. No difference was observed in cardiovascular responses to arousal between hypoxia and normoxia conditions [40], implying that arousal per se could be an important determinant in sympathetic overactivity. Moreover, sleep fragmentation resulted in daytime systolic hypertension in healthy adult subjects free of sleep-disordered breathing even after controlling confounders [39,41]. Taken together, we speculate that repetitive arousals during sleep could induce sympathetic overactivity, which may in turn give rise to daytime hypertension in OSA population. Further studies incorporating a longitudinal design would provide a hint to disentangle causal relations between arousals and sympathetic overactivity as well as cardiovascular complications in OSA.

The mechanisms that underlies sympathetic overactivity caused by sleep fragmentation are not well understood. Given that the neuroanatomical correlates of the autonomic nervous system and the sleep-wake system lie in close proximity in the hypothalamus and upper brainstem, both systems may interact through common afferent and efferent pathways for regulating homeostatic functions [23]. Specifically, the locus coeruleus (LC), a dense cluster of norepinephrine neurons, is a major nucleus involved in the neural pathways controlling both arousal and autonomic function [42]. The LC increases sympathetic activity via the activation of α1-adrenoceptors on preganglionic sympathetic neurons, and reduces parasympathetic activity via the activation of α2-adrenoceptors on preganglionic parasympathetic neurons [42]. Meanwhile, the LC is a well-known major wakefulness-promoting nucleus [43], where the activity of the LC closely correlates with the level of arousal [44]. In addition, the neurotransmitters involved in the regulation of sleep-wake cycle also control autonomic functions [23]. For instance, norepinephrine, released from the nerve terminals of postsynaptic sympathetic neurons in the locus coeruleus, leads to sympathetic overactivity and an increase in blood pressure in response to stress-related and psychostimulant-induced arousals [45]. Acetylcholine, released from the cholinergic neurons located in the pedunculopontine tegmentum and laterodorsal tegmentum, modulates the balance between sympathetic and parasympathetic activity and plays a role in awakening in sleep-wake cycle [23,43].

Several potential limitations of the present study should be taken into consideration in the interpretation of our results. First, only subjects who were referred to a university-affiliated hospital were included, and thus, the generalizability of our findings to the entire OSA population is limited. Second, this is a cross-sectional study, and thus, the directionality of the relationships and their causality remains uncertain. Third, we cannot exclude the first-night effect which assumes a decrease in parasympathetic and an increase in sympathetic activity owing to reduced slow-wave sleep and increased arousals. However, PSG was conducted under identical conditions for all subjects, and thus, it is unlikely that the first-night effect has affected comparisons in HRV indices between the groups [46]. Lastly, OSA patients and non-OSA controls were not matched for age and sex. However, both covariates were included in the multivariate model to eliminate the confounding effect of age [47] and sex [48] on HRV parameters. Moreover, non-OSA control group consisted of subjects who did not meet the criteria for OSA (AHI < 5); therefore, this group does not necessarily represent healthy control group. Although patients with restless legs syndrome, narcolepsy, and REM sleep behavior disorder were excluded based on the sleep complaints and sleep questionnaires as well as PSG findings, inclusion of insomniacs in the non-OSA control group could not be entirely ruled out.

We have shown that AI is strongly associated with HRV changes indicating sympathetic predominance and that AI is a more potent contributing factor than AHI for sympathetic overactivity in OSA patients. Our findings suggest that arousal, rather than apnea, might be considered as a surrogate marker for sympathetic overactivity and prediction of risk for cardiovascular complications in OSA. Future prospective studies are required to determine whether therapeutic interventions (eg, continuous positive airway pressure) mitigate sympathetic overactivity, and consequently, reduce cardiovascular morbidity such as hypertension in patients with OSA.

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Conflict of interest

All authors declare that they have no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.01.044

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