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Original Article

Comparison of cardiac autonomic activity between positional and nonpositional obstructive sleep apnea using heart rate variability

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ABSTRACT

Objectives: Patients with obstructive sleep apnea (OSA) experience sympathetic hyperactivation during sleep, which is associated with increased cardiovascular risk factors. However, the difference in cardiac autonomic activity in OSA patients according to position dependency has not been evaluated. This study aimed to evaluate the differences between positional OSA (pOSA) and nonpositional OSA (npOSA) using heart rate variability (HRV) analysis.

Methods: This was a single-center cross-sectional study. Twenty-eight patients with npOSA and 28 age-, sex-, and AHI-matched patients with pOSA underwent standard polysomnography. A five-minute R-R interval from stable waking conditions before bedtime was collected from each subject and analyzed for HRV.

Results: Patients with pOSA had lower body-mass index (BMI, 25.8 ± 2.9 vs 28.9 ± 3.7 kg/m^2, p = 0.001), shorter apnea duration (24.1 ± 7.1 vs 30.3 ± 12.7 s, p = 0.028) and higher minimum oxygen saturation (78.2 ± 7.1 vs 71.5 ± 11.4%, p = 0.011) than those with npOSA. HRV analysis showed higher parasympathetic activity in pOSA patients than in npOSA patients, including a higher square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD, 31.3 ± 29.0 vs 18.6 ± 9.2, p = 0.032), percentage of pairs of adjacent NN intervals that differ by more than 50 ms (pNN50%, 10.7 ± 17.1 vs 3.3 ± 6.5, p = 0.024), and high-frequency (HF) power (534.7 ± 986.8 vs 146.7 ± 150.5, p = 0.026). The group difference was insignificant after adjusting for age and BMI. The log-transformed supine/nonsupine AHI ratio was the sole independent predictor of HRV parameters.

Conclusion: The waking HRV was higher in pOSA patients than in npOSA patients due to the lower BMI of pOSA patients. The difference was especially apparent in parasympathetic indices. Higher parasympathetic activity in pOSA may suggest a lower risk for cardiovascular morbidity and mortality.

1. Introduction

Position during sleep has a substantial effect on the frequency and severity of respiratory disturbances in patients with obstructive sleep apnea (OSA). Respiratory disturbances occur more frequently and are more severe in the supine position [1]. The suggested mechanism for worse disturbance in the supine position is unfavorable airway geometry with increased collapsibility and reduced lung volume [2]. Supine-dominant positional OSA is indicated if the frequency of respiratory disturbances is twice as high in the supine position than in the nonsupine position [2,3]. More than half of patients with OSA have supine-dominant positional OSA, and the frequency of this type of OSA is even higher in the Asian population, ranging from 67–75% [4–6].

Patients with moderate to severe OSA are well known to be associated with a multitude of cardiovascular diseases, including hypertension, congestive heart failure, stroke, coronary artery disease and metabolic syndrome [7,8]. Different cardiovascular outcomes between positional OSA (pOSA) and nonpositional OSA (npOSA) have been reported. The proportion of patients with hypertension [9] and diabetes [10] is higher in npOSA than in pOSA. Among patients with mild to moderate OSA, mortality and morbidity

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were higher for npOSA than for pOSA. However, among patients with severe OSA, pOSA showed higher mortality than npOSA [11]. Sympathetic and parasympathetic control of the heart rate was reported to be unstable in patients with OSA, which may be linked to its increased risk of cardiovascular morbidity and mortality [12]. The difference in cardiovascular outcomes may be due to distinct autonomic function between patients with pOSA and npOSA.

Measurement of changes in heart rate (HR) over time (heart rate variability, HRV) provides information about autonomic function. The HRV is a well-accepted noninvasive tool to evaluate cardiac autonomic function [13]. HRV is defined as the variation in the beat-to-beat time interval, which is mediated by underlying sympathetic and parasympathetic activities. Both domain parameters—the time domain parameters, which are simple measurements of HRV present in an ECG, and the frequency domain parameters, which provide information on sympathetic and parasympathetic function—can be derived [14]. HRV analysis showed increased sympathetic activity and decreased parasympathetic activity in patients with OSA [15]. The HRV parameters were associated with excessive daytime sleepiness [16], arousal index [17], AHI [15,17–19], and nocturnal oxygen desaturation [17,20]. Treatment of OSA with continuous positive airway pressure (CPAP) ameliorated the changes in HRV parameters [19,21]. To date, only one study has analyzed HRV in pOSA patients, but this study did not include controls [22]. Differences in HRV between pOSA and npOSA patients have not been evaluated.

To clarify the reason for the distinct cardiovascular outcome between pOSA and npOSA, we compared HRV indices between pOSA and npOSA patients. Moreover, we investigated factors that can affect HRV in OSA patients, including position dependency.

2. Methods

2.1. Patients

This was a cross-sectional single-center study performed at Kyung Hee University Hospital at Gangdong. Patients who underwent polysomnography (PSG) and were diagnosed with moderate to severe OSA (AHI > 15/hr) between April 2011 and December 2017 were reviewed. Consecutive patients with npOSA and age-, sex-, and AHI-matched patients with pOSA were enrolled. pOSA and npOSA were defined according to previous criteria [2,3]: (1) npOSA: supine AHI <2 times the nonsupine AHI and (2) pOSA: supine AHI >2 times the nonsupine AHI, with nonsupine AHI <5. To accurately diagnose pOSA, only patients with supine and nonsupine sleeping times of 30 min or more were included. Individuals with cardiac disease (eg, angina pectoris, myocardial infarction, or atrial fibrillation), comorbidities (eg, diabetes, or stroke), other sleep disorders (eg, rapid eye movement sleep behavior disorder, narcolepsy, or restless legs syndrome) or taking medications (eg, beta-blockers or antiarrhythmics) that could affect the autonomic nervous system were excluded. Patients with poor-quality electrocardiography (ECG) data were also excluded from this study.

This study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong. Informed consent to participate was obtained from the enrolled patients.

2.2. Procedures

The results of sleep questionnaires and PSG for each patient were reviewed. The sleep questionnaires were performed prior to PSG, including the Pittsburgh Sleep Quality Index (PSQI) [23], Epworth Sleepiness Scale (ESS) [24]; Insomnia Severity Index (ISI) [25], and Beck Depression Inventory (BDI)-II [26]. The PSQI measures the quality and patterns of sleep over a four-week period, the ESS is an 8-item self-reported questionnaire evaluating the level of daytime sleepiness, the ISI is a 7-item questionnaire measuring the patient's perception of insomnia, and the BDI-II measures depression with 21 multiple-choice questions, each of which can be scored from 0 to 3.

The PSG was performed using a digital polygraph system (Grass-Telefactor twin version 2.6, West Warwick, RI, USA) according to standard protocols. The data were manually scored according to the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events, Version 2.0 [27]. Taking medications that can affect sleep, caffeine intake, and smoking were discouraged on the day of polysomnography.

2.3. Heart rate variability

The lead II ECG was recorded (sampling rate 400 Hz) in the supine position. Five-minute stable waking electrocardiogram (ECG) before lights-off time (21:00–24:00) was selected from routine PSG data and converted into consecutive R-R intervals for the heart rate variability (HRV) analysis using Kubios Premium ver. 3.0.2 [28]. Because it was difficult to obtain stable apnea-free 5-minute ECG samples for severe OSA patients, we used stable waking ECG data acquired before bedtime. Standard linear HRV, including time and frequency domains, was analyzed according to the HRV Task Force Guidelines [14]. The time domain of HRV features included the mean R-R interval, standard deviation of NN intervals (SDNN), square root of the mean of the sum of the squares of the difference between adjacent NN intervals (RMSSD), and percentage of differences between adjacent NN intervals that are longer than 50 ms (pNN50). The frequency domain of HRV was analyzed using fast Fourier transformation (FFT) with Welch's periodogram method (256 s window width and 50% overlap window) [29], which included very-low-frequency (VLF, 0.01–0.04 Hz), low-frequency (LF, 0.04–0.15 Hz), and high-frequency (HF, 0.15–0.4 Hz) band power, total power and the LF/HF ratio.

2.4. Statistical analysis

Continuous data were tested for normal distribution with the Kolmogorow Smirnov test and are presented as the mean ± SD. Because cardiac autonomic measures were not distributed normally, the nonparametric Mann–Whitney U test was used to compare the continuous variables between the groups. Categorical variables were compared using the chi-square test. Logistic linear regression analysis, adjusted for possible confounders of autonomic function (age and BMI), was then performed to test the group differences of all HRV parameters. To identify factors that are associated with the HRV, the initial univariate linear regression was used, and the results are expressed as Pearson correlation coefficients. Next, a multivariate regression analysis with a stepwise method was performed to identify factors independently associated with HRV parameters. Anticipated factors included age, body-mass index (BMI), ESS, arousal index, AHI, minimum oxygen saturation, and supine/nonsupine AHI ratio. Age and factors with p-values < 0.10 were entered into a multiple regression model. The supine/nonsupine AHI ratio was log transformed owing to its skewed distribution. The level of significance was set at $p < 0.05$. All statistical comparisons were performed with SPSS (Version 22.0, Chicago, IL, USA).

3. Results

3.1. Clinical features and demographics

A total of 28 patients with npOSA and 28 age-, sex-, and AHI-matched pOSA patients were enrolled. The height, weight, and

neck circumference were similar between the two groups; however, BMI was lower for the pOSA patients than for npOSA patients (25.8 ± 2.9 vs. 28.9 ± 3.7, p = 0.001). There was no difference in the questionnaire score regarding sleep-related symptoms and depression. Comorbidities and medications at the time of PSG are listed in Supplementary Table 1.

Total sleep time, sleep structures, sleep-onset latency, and sleep efficacy were similar between the two groups. Respiratory indices, including total apnea-hypopnea, apnea, hypopnea, and flow limitation, were also comparable between the pOSA and npOSA patients. As expected, the AHI in the nonsupine position was lower (1.3 ± 1.5 vs. 32.5 ± 12.3, p < 0.001) in pOSA patients than in npOSA patients, but the AHI in the supine position was comparable between the two groups. Apnea duration was shorter (24.1 ± 7.1 vs. 30.3 ± 12.7, p = 0.028), and nadir saturation was higher (78.2 ± 7.1 vs. 71.5 ± 11.4, p = 0.011) in patients with pOSA than patients with npOSA (Table 1).

3.2. Heart rate variability measures between the groups

Time domain HRV analysis showed higher SDNN (32.7 ± 28.0 vs 21.5 ± 11.2, p = 0.049), triangular index (7.5 ± 4.6 vs 5.3 ± 2.1, p = 0.025), RMSSD (31.3 ± 29.0 vs 18.6 ± 9.2, p = 0.032) and pNN50 (10.7 ± 17.1 vs 3.3 ± 6.5, p = 0.024) in pOSA patients than in npOSA patients. Frequency domain analysis showed increased HF power (534.7 ± 986.8 vs. 146.7 ± 150.5, p = 0.026) and a tendency toward increases in LF and total power (p = 0.080 and 0.059, respectively) in pOSA patients. However, the VLF power, LF and HF normalized units, and LF/HF ratio were similar between the two groups (Table 2). The logistic regression model adjusted for age and BMI showed no significant differences in the HRV parameters between the two groups, with consistent significance found only in BMI.

3.3. Association between heart rate variability measures and clinical features

In the initial linear regression analysis, BMI was negatively correlated with HRV parameters, including SDNN (r = −0.347, p = 0.009), triangular index (r = −0.266, p = 0.047), RMSSD (r = −2.355, p = 0.022), pNN50% (r = −0.303, p = 0.023), and HF power (r = −0.275, p = 0.04). The log-transformed supine/nonsupine AHI ratio was positively correlated with SDNN (r = 0.33, p = 0.013), triangular index (r = 0.354, p = 0.007), RMSSD (r = 0.376, p = 0.004), and pNN50% (r = 0.366, p = 0.006) (Fig. 1). Age correlated with only the triangular index (r = −0.306, p = 0.022), and minimum saturation correlated with only pNN50% (r = 0.269, p = 0.045). Stepwise multivariate linear regression analysis showed an independent positive correlation between the log supine/nonsupine AHI ratio and triangular index (β = 0.316, p = 0.014), RMSSD (β = 0.361, p = 0.006), pNN50% (r = 0.350, p = 0.008), and HF power (r = 0.283, p = 0.035). An independent negative correlation was found between BMI and SDNN (β = −0.347, P = 0.009) and between age and the triangular index (β = −0.278, P = 0.029) (Table 3).

4. Discussion

We compared 5-min HRV during awake periods between pOSA and npOSA patients. The HRV was higher in pOSA patients than in npOSA patients, especially in parasympathetic indices including RMSSD, pNN50%, and HF. Although the patients enrolled in this study were matched for age, sex, and AHI, those with pOSA had lower BMI, shorter apnea duration, and higher minimum oxygen saturation than those with npOSA. After adjusting for age and BMI, no difference in HRV was found between the two groups. However, the log-transformed supine/nonsupine AHI ratio was the sole

Table 1
Demographic and polysomnographic results.

	Nonpositional OSA	Positional OSA	p-value
	n = 28	n = 28	
Age	51.9 ± 11.4	50.2 ± 10.8	0.557
Sex (male)	19 (67.9)	23 (82.1)	0.217
Neck circumference (cm)	38.9 ± 4.1	37.7 ± 2.8	0.225
Height	164.8 ± 9.0	167.7 ± 9.0	0.239
Weight	78.9 ± 14.2	72.9 ± 11.4	0.084
BMI (kg/m^2)	28.9 ± 3.7	25.8 ± 2.9	0.001
Questionnaire			
PSQI	7.7 ± 3.5	8.7 ± 4.9	0.432
ESS	7.4 ± 4.1	7.1 ± 2.6	0.726
ISI	10.6 ± 5.8	12.5 ± 6.5	0.273
BDI-II	8.9 ± 6.5	11.5 ± 10.0	0.254
Polysomnography			
TST	293.0 ± 56.5	294.3 ± 40.0	0.921
N1%	30.2 ± 12.8	28.3 ± 12.1	0.563
N2%	40.9 ± 14.0	41.6 ± 8.9	0.806
N3%	14.6 ± 12.5	15.4 ± 6.4	0.771
REM%	14.3 ± 7.4	14.6 ± 8.9	0.860
WASO%	21.4 ± 11.4	19.2 ± 12.9	0.499
Supine time	191.0 ± 86.3	223.8 ± 45.7	0.086
Nonsupine time	94.5 ± 67.4	70.0 ± 32.9	0.091
Arousal index	55.2 ± 14.1	56.7 ± 14.0	0.689
SL	13.7 ± 19.7	6.8 ± 7.2	0.085
SE%	77.4 ± 12.7	81.7 ± 9.0	0.150
Apnea index	26.1 ± 17.9	20.2 ± 10.2	0.137
Hypopnea index	15.6 ± 13.0	16.6 ± 10.5	0.746
Flow limitation	8.7 ± 8.1	11.3 ± 11.0	0.326
AHI	41.7 ± 13.4	37.0 ± 7.4	0.113
Supine AHI	46.4 ± 16.7	49.5 ± 13.8	0.463
Nonsupine AHI	32.5 ± 12.3	1.3 ± 1.5	<0.001
Supine/nonsupine ratio	1.5 ± 0.3	36.6 ± 19.1	<0.001
RDI	50.4 ± 12.9	48.3 ± 11.8	0.528
Apnea duration	30.3 ± 12.7	24.1 ± 7.1	0.028
Hypopnea duration	31.6 ± 14.2	27.8 ± 6.0	0.196
Min sat%	71.5 ± 11.4	78.2 ± 7.1	0.011

Data are expressed as the means ± standard deviations or numbers (percentages).
Abbreviations: OSA; Obstructive sleep apnea, BMI; body-mass index; PSQI; Pittsburgh Sleep Quality Index, ISI; Insomnia severity index, ESS; Epworth sleepiness scale, BDI-II; Beck Depression Inventory-II, TST; total sleep time, WASO; wake after sleep onset, SL; sleep latency, SE; sleep efficacy, AI; arousal index, AHI; apnea-hypopnea index, RDI; respiratory distress index, PLMAI; periodic limb movement arousal index, PLMI; periodic limb movement index; na, not available.

Table 2
HRV parameters between positional and nonpositional OSA.

	Nonpositional OSA	Positional OSA	p-value
	n = 28	n = 28	
Mean R-R interval	885.1 ± 116.5	876.1 ± 158.4	0.706
SDNN	21.5 ± 11.2	32.7 ± 28.0	0.049
Triangular index	5.3 ± 2.1	7.5 ± 4.6	0.025
RMSSD	18.6 ± 9.2	31.3 ± 29.0	0.032
pNN50%	3.3 ± 6.5	10.7 ± 17.1	0.024
VLF	57.9 ± 90.0	85.3 ± 123.9	0.441
LF	262.7 ± 368.0	477.7 ± 554.1	0.080
HF	146.7 ± 150.5	534.7 ± 986.8	0.026
Total power	467.5 ± 536.5	1098.3 ± 1555.5	0.059
LFnu	56.5 ± 19.8	54.0 ± 16.9	0.706
HFnu	43.4 ± 19.7	45.9 ± 16.9	0.694
LF/HF ratio	1.98 ± 1.77	1.75 ± 2.10	0.694

Data are expressed as the means ± standard deviations.
Abbreviations: R-R, interbeat; SDNN, standard deviation of R-R intervals; RMSSD, Root Mean Square of the Successive Differences; pNN50, percentage of the number of pairs of adjacent R-R intervals differing by more than 50 ms; VLF, very-low-frequency power; LF, low-frequency power; HF, high-frequency power; LFnu, low-frequency normalized units (LF/total power-VLF)x100; HFnu, high-frequency normalized units (HF/total power-VLF)x100.

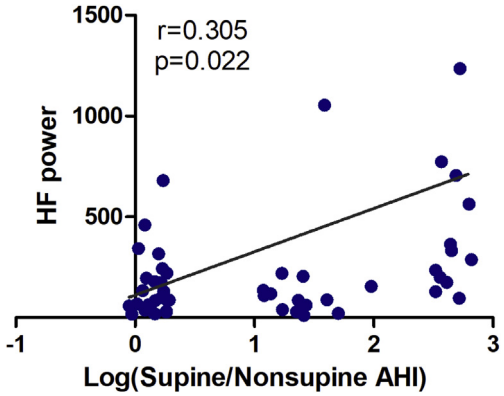

Fig. 1. The relationship between high-frequency power and the log-transformed supine/nonsupine AHI. Abbreviations: HF; high frequency, AHI; apnea-hypopnea index.

independent factor associated with the HRV parameters, including triangular index, RMSSD, pNN50%, and HF, even after adjusting for age and BMI. Higher parasympathetic activity in pOSA may lead to lower cardiovascular morbidity and mortality.

pOSA is considered a milder form of OSA than npOSA [30,31]. Generally, pOSA patients have a lower BMI and AHI and show higher minimum oxygen saturation than npOSA patients [6,30–33]. Our patients with pOSA had lower BMI, shorter apnea duration, and higher minimum saturation even after matching age, sex, and total AHI. Low BMI is well known as a predictor for pOSA [34]. A recent population-based cohort study showed that a lower BMI was an independent factor associated with pOSA [35]. Weight gain may increase lateral pharyngeal wall soft tissue volume and is strongly associated with the progression or worsening of sleep apnea. pOSA patients who had significant weight gain developed npOSA and npOSA patients who had significant weight loss developed pOSA at the follow-up [36]. Low BMI may be a crucial factor associated with the pathogenesis of pOSA.

Table 3
Univariate and multivariate linear regression analysis results.

HRV parameter	Characteristics	Univariate		Multivariable Stepwise		
		r	*p*-value	R2	Beta	*p*
SDNN	Age	−0.188	0.164	0.121		
	BMI	−0.347	0.009		−0.347	0.009
	ESS	−0.083	0.542			
	Arousal index	−0.112	0.413			
	min Sat%	0.217	0.108			
	AHI	−0.197	0.146			
	Log AHI ratio	0.33	0.013			
Triangular index	**Age**	−0.306	0.022	0.205	−0.278	0.027
	BMI	−0.266	0.047			
	ESS	−0.079	0.564			
	Arousal index	−0.018	0.895			
	min Sat%	0.196	0.148			
	AHI	−0.204	0.132			
	Log AHI ratio	0.358	0.007		0.335	0.009
RMSSD	Age	−0.215	0.111	0.135		
	BMI	−2.355	0.022			
	ESS	−0.002	0.988			
	Arousal index	0.020	0.884			
	min Sat%	1.734	0.089			
	AHI	−0.243	0.071			
	Log AHI ratio	0.376	0.005		0.367	0.005
pNN50%	Age	−0.262	0.051	0.125		
	BMI	−0.303	0.023			
	ESS	−0.037	0.784			
	Arousal index	−0.050	0.716			
	min Sat%	0.269	0.045			
	AHI	−0.202	0.136			
	Log AHI ratio	0.354	0.007		0.354	0.007
HF	Age	−0.137	0.314	0.093		
	BMI	−0.275	0.04			
	ESS	0.036	0.792			
	Arousal index	0.093	0.497			
	min Sat%	0.203	0.134			
	AHI	−0.177	0.192			
	Log AHI ratio	0.305	0.022		0.305	0.022

Abbreviations: SDNN, standard deviation of R-R intervals; RMSSD, Root Mean Square of the Successive Differences; pNN50, percentage of the number of pairs of adjacent R-R intervals differing by more than 50 ms; HF, high-frequency power; BMI; body-mass index; ESS; Epworth sleepiness scale, min Sat%; minimum oxygen saturation, AHI; apnea-hypopnea index, Log AHI ratio; log transformed supine AHI/nonsupine AHI ratio.

The results of HRV analysis in our study suggested that patients with pOSA have higher parasympathetic activity than npOSA patients. The patients with pOSA had higher RMSSD, pNN50, and HF power than those with npOSA. The RMSSD, the square root of the mean squared differences of successive R–R intervals, reflects vagus nerve-mediated autonomic control of the heart. The percentage of adjacent NN intervals that differ by more than 50 ms (pNN50) is another parameter for parasympathetic activity and correlates with the RMSSD. HF power corresponds to the HRV related to the respiratory cycle and indicates parasympathetic tone. Moreover, increased HF power with similar VLF and LF power indicates activation of parasympathetic rather than sympathetic activity [13,37]. The difference in HRV between positional and nonpositional OSA may be due to the lower BMI of pOSA patients. Overweight and obese individuals have reduced HRV [38]. This result is consistent with a previous study that suggested favorable cardiovascular outcomes in pOSA because of lower BMI and AHI [2].

The log-transformed ratio of supine/nonsupine AHI had an independent positive correlation with the parasympathetic HRV parameters. The number and severity of apnea events are worse in the supine position than in the lateral position [1]. The AHI during the supine position was similar between pOSA and npOSA patients; however, nonsupine AHI was 32.5/hr in npOSA, compared to 1.3/hr in pOSA patients. Moreover, patients with npOSA had more prolonged apnea and lower minimum saturation than patients with pOSA. Although apnea duration does not affect autonomic modulation during sleep, the hypoxia process can enhance sympathetic activation in response to apneas/hypopneas [39]. The results of our study suggest that the parasympathetic activity during awake periods in OSA patients can be affected by position dependency itself. These findings are in line with a previous study that showed an independent association between positional dependency and the prevalence of hypertension after adjusting for age, BMI, and AHI [9].

Changes in HRV parameters are associated with mortality and sudden death [38,40]. Reduced SDNN in npOSA patients was associated with higher cardiac mortality in patients with chronic heart failure [41]. A reduction in RMSSD was also reported to be associated with a high risk for sudden unexpected death in epilepsy [42]. One study reported a worse mortality rate in mild to moderate npOSA patients than in severe pOSA patients [11]; however, that study used only supine AHI to determine pOSA severity. Increased autonomic function, including SDNN and RMSSD, in moderate to severe pOSA in our study, may suggest a lower risk for mortality than that in pOSA patients with a similar total AHI.

Although this study was a single-center study, it is the first to evaluate the differences in autonomic fluctuations between pOSA and npOSA. The number of patients was small, and we did not include healthy controls. However, we strictly included pOSA patients who had both supine and nonsupine sleeping times of 30 min or more. We only analyzed HRV during the awake time before bedtime, not during sleep. Moreover, other autonomic parameters, such as muscle sympathetic nerve activity or serum catecholamine levels, were not measured.

5. Conclusion

An analysis of cardiac autonomic function during awake periods revealed higher heart rate variability, especially in parasympathetic indices, in patients with pOSA than in those with npOSA. Positional dependency was the sole independent predictor of parasympathetic activity. A more extensive study with long-term follow-up might help to clarify the relationship between cardiac autonomic dysfunction and cardiovascular outcomes in OSA patients according to their position dependency.

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None.

Conflict 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.2019.06.021.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.06.021.

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