Journal of
Health Science and Alternative Medicine

Original Article Open Access

Arterial Stiffness and Cardiac Autonomic Function in Severe Obstructive Sleep Apnea Patients without Continuous Positive Airway Pressure

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Received July 22, 2020
Accepted December 10, 2020
Published December 23, 2020

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder and contributes to increased morbidity and poor cardiovascular outcomes. It is one of the risk factors for cardiovascular disease. **Objective:** This study aimed to determine the associations between sleep apnea parameters and arterial stiffness, cardiac autonomic function, and evaluate changes in arterial stiffness and cardiac autonomic function in patients with severe OSA without continuous positive airway pressure (CPAP) treatment. **Methods:** Twenty severe OSA patients without CPAP treatment were recruited for this study. All participants underwent arterial stiffness evaluation by carotid-femoral pulse wave velocity (PWV) using a SphygmoCor device, and cardiac autonomic function by heart rate variability (HRV) measurement using LabChart-7. All participants were measured using these medical instruments at baseline on day 0, day 90, and day 180. Associations between sleep apnea parameters and HRV parameters were observed during the supine and tilt positions. The significance levels were set at $\alpha = 0.050$ and 0.001, respectively. **Results:** There was no significant association between sleep apnea parameters and PWV. HRV showed significant changes at day 90 (p-value < 0.001) and day 180 (p-value < 0.001). PWV increased significantly after day 180 without CPAP treatment. **Conclusions:** This study revealed that sleep apnea indices are associated with cardiac autonomic function. OSA patients without CPAP treatment have deteriorated cardiac autonomic function in the supine and tilt positions and increased arterial stiffness after day 180.

Keywords: *Obstructive sleep apnea; Arterial stiffness; Heart rate variability*

Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder and contributes to increased morbidity and poor cardiovascular outcomes [1]. OSA has been recognized as a major public health issue, as it has a significant influence on the incidence and prognosis of cardiovascular diseases [2]. Pathologic cardiovascular changes are associated with OSA along with many other factors. Repetitive obstructive events during sleep cause intermittent hypoxia (IH), resulting in the activation of oxygen free radicals and oxidative stress response. The concurrent presence of inflammation is linked to damage to the vascular endothelium, leading to atheroma formation, vascular events, [3] and increased sympathetic nervous system (SNS) [4]. Therefore, the adverse effects of OSA could develop a serious health challenge.

The cardiometabolic biomarkers commonly used to assess changes in vascular events and cardiac autonomic function, with two parameters are: i) carotid-femoral pulse wave velocity (cfPWV), and ii) heart rate variability (HRV). The cfPWV is the gold standard for assessing large artery stiffening because it reflects vessel status predominantly in the central aorta and proximal elastic arteries [5]. HRV is used for cardiac autonomic function, which is a noninvasive method [4]. However, there is limited information available on the associations between arterial stiffness, cardiac autonomic function, and sleep apnea severity.

Currently, continuous positive airway pressure (CPAP) therapy in the OSA patients is accepted as the 'gold standard' treatment for the management of OSA, globally. It can reduce symptoms and improve the quality of life of patients [6]. Although several clinical studies have demonstrated the effective outcome of CPAP on various biomarkers [7], there are still questions on the results. Regarding cfPWV and HRV, CPAP is associated with a deterioration of 1.21 m/s in cfPWV. HRV is calculated by the low-frequency power (LF), high-frequency power (HF), or the square root of the mean of the sum of the squares of the differences between adjacent NN intervals (RMSSD) and LF/HF representing SNS, and sympathovagal

balance, respectively. In patients with OSA, LF and LF/HF ratio is higher, while it is lower when compared with those of healthy subjects, and LF is greater while HF and LF/HF ratio are not different after non-CPAP treatments [8–10].

It is not clear whether there is any change in autonomic function and arterial stiffness in patients with severe OSA without CPAP treatment. This study aimed to determine the association between autonomic function and arterial stiffness and sleep apnea parameters, and to determine the changes in autonomic function and arterial stiffness in patients with severe OSA without CPAP treatment.

Methods

Study participants and characteristics

This study was a non-randomized, open-label design. Twenty patients with severe OSA were recruited into the study; nine males and 11 females, aged 30 years or older. Patients with a history of smoking, cardiovascular, neuromuscular, or pulmonary disease, severe microvascular diabetic complications, diabetes mellitus, hypertension (blood pressure ≥ 140/90 mmHg), arthritis, and patients who chose CPAP treatment were excluded from the study. The purpose, benefits, and possible risks associated with the study were explained to the participants before obtaining informed consent on a voluntary basis. The study protocol and all procedures used in the study were approved by the Khon Kaen University Ethics Committee for Human Research (IRB No. HE591202).

Research procedure

All OSA patients who were newly diagnosed by medical specialists using polysomnography (PSG) within the month preceding the beginning of the study were recruited from the Sleep Disorder Clinic at Srinagarind Hospital, Khon Kaen, and Thailand. OSA patients had an apnea-hypopnea index (AHI) of at least 30 events per hour and no history of treatment for OSA with CPAP or oral devices, tracheostomy, or the use of oxygen therapy at home. The choice of being treated on a non-CPAP treatment was based on individual reasons such as financial problems. All participants were screened by a physician. Patients received a general health care treatment program for OSA, including nasal spray for nasal allergies and sleep hygiene education, which comprises a variety of methods to obtain good sleep quality, such as avoiding caffeine and strenuous work towards bedtime, preparing a good sleep environment, exposure to natural light, etc.

After recruitment, all participants were asked to provide genetic information such as age, gender, smoking, epworth sleepiness scale (ESS), and medical history. Physical examination was performed to obtain information on height, weight, and body mass index (BMI). Peripheral blood pressure and heart rate were measured using a blood pressure monitor (Omrom, Japan) at rest on the left upper arm three times consecutively, and the average value was used for the study. Participants

Arterial stiffness was assessed using the SphygmoCor device to determine the carotid-femoral pulse wave velocity (PWV). Heart rate variability (HRV) was measured using LabChart 7 to determine cardiac autonomic function. All measurements were performed at baseline and repeated at day 90 and day 180.

Outcome measures

a) Polysomnography

OSA patients underwent full-night PSG using a digital system at the Sleep Disorder Clinic, Faculty of Medicine (Srinagarind Hospital, Khon Kaen University). PSG was performed using a previously described procedure [8]. Briefly, apnea was defined as a decrease in the amplitude of airflow of at least 90.0% for at least 10 seconds and continued respiratory effort. Similarly, hypopnea was defined as a reduction in airflow of at least 30.0%, which coincided with a decrease in oxygen desaturation of at least 3.0% [9].

b) Arterial stiffness measurement

Before cfPWV, participants were asked to rest until the vital signs were normal. The central arterial blood pressure and cfPWV were assessed non-invasively in all participants using the SphygmoCor device (AtCor Medical, West Ryde, and Australia). The cfPWV was performed using a procedure described previously [10] and assessed by sequential recordings of the arterial pressure waveforms at the left carotid artery and left femoral artery. The distance between the two arterial sites was measured. The pulse transit time was the average of 10 consecutive beats. The cfPWV was calculated as the ratio of the distance in meters to the transit time in seconds.

c) HRV measurement

Before HRV, the participants were asked to rest until the vital signs were normal. HRV was measured by an autoregressive power spectral analysis of RR electrocardiographic interval acquisition (LapChart 7, Power Lab 26TADINSTRUMENTS, and Australia). HRV was performed using a previously described procedure [11]. In summary, the test involved lying quietly on a bed (V.S. ENGINEERING, US.) for 10 min, tilted at an angle of 70° for a period of 10 min while electrocardiogram (EKG) was being monitored. HRV was analyzed during the 5-min period just before tilting during supine rest and during the 5-min period immediately after the tilt.

Statistical Analyses

Statistical analyses were performed using STATA version 13.0 (StataCorp, College Station, TX, USA). Data are expressed as the mean and standard deviation (SD). The Shapiro-Wilk test was used to

screen the data. A repeated-measures analysis of variance (Repeated ANOVA) was used to compare arterial stiffness and heart rate variability parameters between days 0, 90, and 180. The Bonferroni post-hoc test was used to detect the significant pairs. Pearson correlation (r) analysis was used to assess the correlations between variables, and at a significance level of $\alpha = 0.050$.

Results

The mean age of the 20-OSA patients was 44.4 years (± 11.9) (Table 1); 9 males and 11 females. All patients were diagnosed with severe OSA, in which the information was supported by the AHI indexes: respiratory effort-related arousals, respiratory disturbance index, arousal index, apnea index, and lowest SpO_2.

In the supine position, AHI was found to be positively correlated with LF (r = 0.38; p-value < 0.050) and LF/HF ratio (r = 0.37; p-value < 0.050), but had a negative correlation with HF (r = -0.37; p-value < 0.050). The arousal index was found to be positively correlated with LF (r = 0.38; p-value < 0.050) and LF/HF ratio (r = 0.36; p-value < 0.050), but negatively correlated with HF (r = -0.40; p-value < 0.050). Apnea index was found to be positively correlated with LF (r = 0.35; p-value < 0.050) and LF/HF ratio (r = 0.32; p-value < 0.050), but had a negative correlation with HF (r = -0.38; p-value < 0.050). The lowest SpO_2 was found to be negatively correlated with LF (r = -0.39; p-value < 0.050) and LF/HF ratio (r = -0.33; p-value < 0.050) but showed a positive correlation with HF (r = 43; p-value < 0.010). In the tilt position, LF was found to be positively correlated with AHI, arousal index, and apnea index (r = 0.62, 0.64, and 0.61, respectively; p-value < 0.010), but had a negative correlation with the lowest SpO_2 (r = -0.42; p-value < 0.05). The LF/HF ratio was found to be positively correlated with AHI,

Table 1. Baseline demographic and polysomnographic data in OSA patients.

Demographic data	**OSA patients** (n = 20)
Age (years)	44.4 ± 11.9
Gender (M/F)	9/11
Height (cm)	165.2 ± 3.4
Weight (kg)	68.0 ± 7.8
BMI (kg/m^2)	25.9 ± 3.7
Neck circumference (cm)	32.9 ± 1.4
Waist circumference (cm)	86.3 ± 6.5
Hip circumference (cm)	93.9 ± 1.7
Epworth sleepiness scale	16.2 ± 1.5
Heart rate (/min)	88.7 ± 11.1
Systolic BP (mm Hg)	129.0 ± 8.7
Diastolic BP (mm Hg)	85.4 ± 11.0
MAP (mm Hg)	99.0 ± 11.6
Polysomnographic data (day-0)	
Apnea hypopnea index (/h)	38.9 ± 4.1
Respiratory effort related arousals (/h)	43.2 ± 11.4
Respiratory disturbance index (/h)	63.7 ± 13.8
Arousal index (/h)	53.6 ± 11.0
Apnea index (/h)	19.4 ± 8.5
Lowest SpO_2 (%)	82.7 ± 3.1

Data are expressed as mean ± SD. OSA: obstructive sleep apnea; airway pressure; M: male; F: female; BMI: body mass index; BP: blood pressure MAP: mean arterial pressure.

arousal index, and apnea index (r = 0.56, 0.57, and 0.54; p-value < 0.010), but showed a negative correlation with the lowest SpO_2 (r = -0.33; p-value < 0.050). There were no statistically significant correlations between sleep severity indices and arterial stiffness parameters (Table 2).

Among patients without CPAP therapy, the significant deterioration of the SDNN, LF, HF, LF/HF ratio, and RMSSD markers after day 90 (p-value < 0.010) and after the day 180 (p-value < 0.001), statistically significant differences were detected. Moreover, the SDNN (p-value < 0.001), HF (p-value < 0.001), RMSSD (p-value < 0.01), LF (p-value < 0.010), and LF/HF ratio (p-value < 0.001) were significantly impaired when compared with the values between day 180 and day 90 (Table 3). Nevertheless, in patients without CPAP therapy, the deterioration of SDNN (p-value < 0.010), LF (p -value < 0.010), and LF/HF ratio (p-value < 0.010) after day 180 were statistically significant differences. However, the SDNN (p-value < 0.050), LF (p-value < 0.010), and LF/HF ratio (p-value < 0.050) were significantly impaired when comparing between day 180 and at day 90 (Table 3).

Discussion

In summary, the main findings of this study were as follows: (I) sleep apnea indices were associated with heart rate variability, (II) OSA patients without CPAP treatment had deteriorated cardiac autonomic function in the supine and tilt positions, and (III) arterial stiffness was significantly increased after the day 180 in patients with severe OSA without CPAP treatment.

According to the associations between sleep apnea indices and cardiac autonomic function, it was consistent with some previous studies [12, 13], while cardiac autonomic function was assessed by the assessment of HRV. In the analysis of HRV, the LF component was mainly correlated with sympathetic efferent activity and vagal activity or parasympathetic activity. The LF/HF ratio served as the specific index of sympathovagal balance [14, 15]. The severity of sleep apnea parameters was correlated with several directions of the makers: increases in LF, decrease in HF, and increase in LF/HF ratio. The correlation between indices of sleep apnea severity and sympathetic activity may be due to increased ventilatory effort during sleep. This is the result of obstructed breathing in apneic or hypopneas episodes, that could contribute to frequent arousals and increased sympathetic activity [16]. A previous study demonstrated that the OSA measurement of HRV in postural supine to tilt testing was a significant cause for different indexes: decreased LF, decreased LF/HF rate, increased SNS, and decreased in both HF and PNS. Furthermore, OSA patients without CPAP treatment showed deterioration of the cardiac autonomic function in the supine and tilt positions, and an increase in the arterial stiffness parameter. In this study, sympathetic activity increased, but vagal activity was reduced in OSA patients without CPAP treatment. Moreover, it seems that patients with OSA have a higher arousal index and a higher degree of hypoxemia, which triggers sympathetic overactivity. Without CPAP

Table 2 Associations between heart rate variability, arterial stiffness parameters and sleep severity in OSA patients

		OSA patients (n=20)	**Correlation coefficient** (r)			
			AHI	Arousal index	Apnea index	Lowest SpO_2
Heart rate variability						
Supine position	SDNN (ms)	49.2 (2.3)	-0.11	-0.19	-0.23	0.16
	RMSSD (ms)	37.2 (13.8)	0.03	0.04	0.05	-0.10
	LF (n.u.)	53.9 (15.8)	0.38*	0.38*	0.35*	-0.39*
	HF (n.u.)	41.2 (11.9)	-0.37 *	-0.40*	-0.38*	0.43**
	LF/HF ratio	1.6 (0.9)	0.37*	0.36*	0.32*	-0.35*
Tilt position	SDNN (ms)	41.3 (12.4)	-0.01	-0.08	-0.11	0.00
	RMSSD (ms)	27.3 (10.9)	-0.09	-0.17	-0.21	0.08
	LF (n.u.)	67.5 (14.5)	0.62**	0.64**	0.61**	-0.42*
	HF (n.u.)	28.2 (7.4)	-0.18	-0.18	-0.17	0.01
	LF/HF ratio	2.6 (1.0)	0.56**	0.57**	0.54**	-0.33*
Arterial stiffness						
	Pulse wave velocity (m/s)	7.9 (0.6)	-0.07	-0.01	0.02	0.22

Data are expressed as mean (SD). SpO_2: oxygen saturation; AHI: Apnea hypopnea index; SDNN: The standard deviation of NN intervals; RMSSD: Root mean square of successive differences; LF: Low frequency; HF: High frequency. * p-value < 0.050, ** p-value < 0.010.

Table 3 Heart rate variability and arterial stiffness parameters in OSA patients

		Outcome at		
		Day-0	Day-90	Day-180
Heart rate variability				
Supine position	SDNN (ms)	49.2 (2.3)	59.0 (2.7)§§§	64.9 (3.0)$^{ɣɣɣ, ββ}$
	RMSSD (ms)	37.2 (13.8)	33.5 (12.5)§§	26.8 (10.0)$^{ɣɣɣ, ββ}$
	LF (n.u.)	53.9 (15.8)	64.7 (18.9)§§§	71.2 (20.8)$^{ɣɣɣ, ββ}$
	HF (n.u.)	41.2 (11.9)	37.0 (10.7)§§§	29.6 (8.6)$^{ɣɣɣ, βββ}$
	LF/HF ratio	1.6 (0.9)	2.1 (1.2)§§§	2.8 (1.7)$^{ɣɣɣ, ββ}$
Tilt position	SDNN (ms)	41.3 (12.4)	50.7 (17.6)	63.4 (22.0)$^{ɣɣɣ, β}$
	RMSSD (ms)	27.3 (10.9)	31.4 (13.9)	28.2 (12.5)
	LF (n.u.)	67.5 (14.5)	74.1 (20.0)	92.6 (25.0)$^{ɣɣɣ, ββ}$
	HF (n.u.)	28.2 (7.4)	29.2 (10.0)	26.3 (9.0)
	LF/HF ratio	2.6 (1.0)	3.0 (1.7)	4.1 (2.3)$^{ɣɣ, β}$
Arterial stiffness				
Pulse wave velocity (m/s)		7.9 (0.6)	8.1 (0.4)	8.4 (0.5)^{ɣ}

Data are expressed as mean (SD): §§ p-value < 0.010, §§§ p-value < 0.001 day 0 vs. day 90; ^{ɣ} p-value < 0.050, ^{ɣɣ} p-value < 0.010, ^{ɣɣɣ} p-value < 0.001 day 0 vs. day 180; ^{β} p-value < 0.050, ^{ββ} p-value < 0.010, ^{βββ} p-value < 0.001, day 90 vs. day 180

treatment, it may promote severe damage caused by sympathetic overactivity in OSA patients.

In this study, the tilted position registered no statistically significant correlation between arterial stiffness and sleep apnea severity. However, it presented a significant increase in PWV after the 180 day without CPAP treatment in severe OSA patients. The study also found that the PWV was significantly higher in patients with OSA while comparing to healthy Thais [10]. The mechanism of the increase in pulse wave velocity could be explained by intermittent hypoxia resulting from activated oxygen free radicals and oxidative stress response. A concurrent study on inflammation has reported that damage to the vascular endothelium leads to atheroma formation and vascular events [3], which consequently leads to arterial stiffness. A previous study demonstrated that the LF/HF ratio was positively correlated with changes in brachial-ankle PWV [17]. The occurrence of changes in the sympathovagal balance might be correlated with the increase in arterial stiffness of the central to middle-sized arteries in patients with OSA.

This study clarified the associations among many markers in severe OSA patients without CPAP treatment: autonomic function, arterial stiffness, and sleep apnea parameters and changes in autonomic function and arterial stiffness. This study also found that OSA patients without CPAP treatment could have worsened cardiac autonomic function and increased arterial stiffness.

This study has some limitations. First, this study did not record the dietary and sleep diaries of OSA patients. Second, to ensure the associations between markers, it needs the longitudinal study particularly in assessing the changes in autonomic function and arterial stiffness in severe OSA patients without CPAP treatment. Finally, in further studies, it should determine the changes in sleep duration or dietary affect arterial stiffness, and the effect of optional OSA treatment programs such as lifestyle modification or oral devices on cardiac autonomic and arterial stiffness in OSA patients. In clinical application, this study provided information about the disadvantage of non-CPAP treatment on cardiac autonomic and arterial stiffness in OSA patients.

Conclusions

The present study shows that sleep apnea indices are associated with cardiac autonomic function. OSA patients without CPAP treatment have a deterioration in cardiac autonomic function in the supine and tilt positions and increase arterial stiffness after day 180.

Acknowledgement

The author would like to thank the OSA patients who participated in the study and the nurses who are working at the Chest Unit, Srinakarind Hospital, Faculty of Medicine, and Khon Kaen University. Special thank to Ms. Arunrat Srithawong for her helped in arterial stiffness evaluation.

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