Original Research

The Severity of Obstructive Sleep Apnea Increases the Risk of Arteriosclerosis

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Abstract

Background: Obstructive sleep apnea (OSA) is a common disorder worldwide. It is associated with myocardial remodeling and arteriosclerosis in patients with hypertension. Our study investigated the relationship between OSA severity and arteriosclerosis and blood pressure in an Asian population. **Methods**: We enrolled 365 subjects from July 2018 to December 2020 at Ruijin Hospital. We recorded data from the medical history and collected blood samples from all participants. We performed 24-hour ambulatory Blood Pressure (BP) monitoring and Carotid-femoral pulse wave velocity (cf-PWV) measurements. Overnight polysomnography (PSG) was performed using Respironics Alice PDxSleepware. **Results**: PSG was performed in a total of 365 subjects; mean age of 49.1 ± 12.8 years and Body Mass Index (BMI) 28.1 ± 3.8 kg/m^2. The majority (89.3%) were male. The office systolic BP was significantly higher in the moderate to severe group than mild OSA group (148 ± 21 mmHg vs 139 ± 19 mmHg, $p < 0.01$). The subjects with moderate to severe OSA presented higher cf-PWV values than those in the mild group (10.03 ± 3.67 m/s vs 7.62 ± 1.48 m/s, $p < 0.01$). BMI was significantly higher in the moderate to severe than the mild OSA groups (28.3 ± 4.0 kg/m^2 vs 27.5 ± 3.2 kg/m^2, $p < 0.05$). The Pearson correlation showed that the apnea-hypopnea index (AHI) was significantly and positively correlated with cf-PWV ($r = 0.217$, $p < 0.01$), Age ($r = 0.148$, $p < 0.01$), BMI ($r = 0.228$, $p < 0.01$) and HbA1c ($r = 0.172$, $p < 0.01$). After adjusting for age, BMI, low density lipoprotein cholesterin (LDL-c), FGB, AHI, estimated Glomerular Filtration Rate (eGFR), Night BP, office diastolic BP and Day BP in Logistic regression model, AHI (OR = 1.03, 95% CI: 1.01–1.05) and office diastolic pressure (OR = 1.04, 95% CI: 1.00–1.08) and age (OR = 1.12, 95% CI: 1.06–1.19) were independent risk factors for arteriosclerosis. **Conclusions**: The severity of OSA was positively correlated with pulse wave velocity. AHI, office BP and age were independent risk factors for arteriosclerosis.

Keywords: obstructive sleep apnea; pulse wave velocity; arterial stiffness

1. Introduction

Obstructive sleep apnea (OSA) is a condition characterized by intermittent hypoxia, awakening, excessive respiratory effort, and excessive negative intrathoracic pressure fluctuations, resulting in increased sympathetic activity, oxidative stress, inflammation, endothelial dysfunction, vascular stiffness and insulin resistance [1–3]. Although apnea occurs only during sleep, the pathophysiological consequences of recurrent apnea do not subside upon awakening [4]. Each episode of apnea usually lasts a minute or less, but when repeated night after night, and for years or decades, the resulting hemodynamic and inflammatory disturbances can have long-term consequences for OSA patients. More evidence suggests that OSA is associated with increased cardiovascular events, such as myocardial infarction [5] and stroke [6]. We have also gradually recognized the relationship between OSA and cardiovascular disease, and tried to carry out early intervention (such as non-invasive positive airway pressure ventilation) to reduce the risk of subsequent cardiovascular disease. The current problem is how to early detect the cardiovascular risk of OSA patients and give early intervention according to possible targets. One study has shown that OSA is associated with myocardial remodeling and arteriosclerosis in patients with hypertension [7]. There are few studies on the relationship between OSA severity and arteriosclerosis and blood pressure in the Asian population. Whether this is an early assessment and intervention target is unknown. Carotid-femoral pulse wave velocity (cf-PWV) is a noninvasive and well-validated technique to assess arterial stiffness, which is a major factor determining arteriosclerosis due to degenerative medical changes in the arterial wall. OSA is a common disorder worldwide and is associated with myocardial remodeling and arteriosclerosis in patients with hypertension. Our study investigated the relationship between OSA severity and arteriosclerosis (measured by cf-PWV) and blood pressure in an Asian population. We hope to explore the early assessment and intervention targets of cardiovascular disease risk in patients with OSA.

2. Materials and Methods

2.1 Study Participants

The study was a cross-sectional analysis of 365 subjects from July 2018 to December 2020 at Ruijin Hospital. We collected data from the medical history (including past medical history, a smoking and alcohol intake history) and anthropometric measurements, including hip circumference, waist circumference, and body mass index (BMI). Blood samples were obtained in all participants. Inclusion criteria: (1) Age $\geq$18 years old; (2) All the participants performed overnight polysomnography and 24-hour ambulatory blood pressure monitoring; (3) Arterial stiffness was measured by Carotid-femoral pulse wave velocity; (4) Agreement for participation in this study and provide written and signed informed consent. Exclusion criteria: Patients with (1) valvular disease and cardiomyopathy; (2) atrial fibrillation, atrioventricular and intraventricular block; (3) cardiovascular or cerebrovascular disease in the past 3 months; (4) Myocardial infarction, chronic heart failure in the past 3 months; (5) cancer diagnosis. All subjects provided written informed consent. The study was approved by the Ethics Committee of Ruijin Hospital, Shanghai, approved the study protocol (2017(1)-1), and written informed consent was provided by all participants. Correlation sample size calculation: Total sample size = N = $[(Z_\alpha + Z_\beta)/C]^2 + 3 = 234$ ($r = 0.217$) (https://sample-size.net/correlation-sample-size/).

2.2 Arterial Stiffness

Carotid-femoral pulse wave velocity (cf-PWV) was measured by means of arterial pulse detection with applanation tonometry with a Millar transducer and SphygmoCor software (AtCor Medical, Sydney, Australia). cf-PWV measurement was doneby sequential registration of the femoral and carotid artery pulse and measuring the pulse transit time in relation to the R wave ofr the ECG signal. Pulse travel distance was measured from the suprasternal notch to the femoral and carotid artery sites and the subtraction distance method was used to determine cf-PWV from the foot-to-foot pulse transit time between the carotid and femoral pulses.

2.3 Ambulatory BP Monitoring

We performed 24-hour ambulatory Blood Pressure (BP) monitoring (Mobil-O-Graph PWA, IEM, Stolberg, Germany). BP was measured every 20 minutes during the day and every 30 minutes during the night with an appropriate cuff placed on the dominant arm. Daytime values of systolic and diastolic BPs <135 mmHg and <85 mmHg and nighttime values <120 mmHg and <70 mmHg respectively were considered normal [8].

2.4 Polysomnography

Overnight polysomnography (PSG) (n = 365 subjects) was performed using Respironics Alice PDxSleepware (Respironics, Inc., Murraysville, PA, USA, CN1043844) digital equipment. Obstructive apnea was defined as a flat or nearly flat amplitude of the nasal pressure signal (from peak to trough) for >10 seconds, accompanied by respiratory effort on a thoracoabdominal sensing volume tracing band. Subjects with apnea-hypopnea index (AHI) $\geq$5 were defined as OSA. Sleep apnea was categorized by the following AHI categories: <5 (unaffected); $\geq$5 to <15 (mild), $\geq$15 to <30 (moderate), and $\geq$30 (severe) [9].

2.5 Definition of Hypertension and Diabetes

Hypertension was defined as in the absence of antihypertensive drugs, blood pressure $\geq$140/90 mmHg was measured in the clinic three times on different days, or currently on antihypertensive medication [10]. Diabetes was defined as having a fasting plasma glucose (FPG) $\geq$126 mg/dL (7.0 mmol/L), or 2-h plasma glucose (PG) $\geq$200 mg/dL (11.1 mmol/L) [11], or currently on treatment for diabetes.

2.6 Statistical Analysis

Continuous variables are presented as mean $\pm$ SD. The correlation between normally distributed univariate variables and cf-PWV was evaluated by the Pearson test. A two-sided p value less than 0.05 was considered statistically significant. The association of AHI categories with cf-PWV was assessed by linear regression. The risk factors of arteriosclerosis were analyzed by binary regression analysis. Statistical analyses were performed using SPSS (version 23.0, SPSS, Chicago, IL, USA).

3. Results

PSG was performed in a total of 365 subjects. The clinical characteristics of the study subjects are shown in (Table 1). A total of 365 subjects were studied with a mean age of 49.1 $\pm$ 12.8 years and a BMI of 28.1 $\pm$ 3.8 kg/m^2. The majority (89.3%) were male; 79.7% had hypertension, and 20.8% had diabetes mellitus.

The subjects were divided into two groups base on AHI severity. The office systolic BP was significantly higher in the group with moderate to severe than mild OSA subjects (148 $\pm$ 21 mmHg vs 139 $\pm$ 19 mmHg, $p < 0.01$). But office diastolic BP, 24 h systolic BP, 24 h diastolic BP, day and night BP were not different between the two groups (Table 2).

The subjects with moderate to severe OSA had significantly higher cf-PWV values than the mild group (10.03 $\pm$ 3.67 m/s vs 7.62 $\pm$ 1.48 m/s, $p < 0.01$). BMI was significantly higher in the moderate to severe OSA group than the mild group (28.3 $\pm$ 4.0 kg/m^2 vs 27.5 $\pm$ 3.2 kg/m^2, $p < 0.05$). The severe OSA subjects were older (50.9 $\pm$ 12.8 years vs 44.6 $\pm$ 11.8 years, $p < 0.01$), and more likely to have hypertension (216 vs 75, $p < 0.01$) or diabetes mellitus s (65 vs 10, $p < 0.01$). Subjects with moderate to severe OSA group were more likely to be smokers (94 vs 28, $p < 0.01$) (Table 2) (Fig. 1).

Table 1. Demographic characteristics of the population.

Parameter	Mean ± SD
Age (years)	49.1 ± 12.8
BMI (kg/m^2)	28.1 ± 3.8
WHR	1.0 ± 0.1
Sex	
Male (%)	326 (89.3%)
Female (%)	39 (10.7%)
HR (bpm)	78 ± 14
IMT (mm)	0.7 ± 0.2
LDL-c (mmol/L)	3.3 ± 1.8
FPG (mmol/L)	5.9 ± 2.0
HbA1C (%)	6.1 ± 1.1
eGFR (mL/min/1.73 m^2)	93.1 ± 16.4
LVMI (g/m^2)	124.1 ± 28.3
cf-PWV (m/s)	9.5 ± 3.2
Smoking (%)	122 (33.4%)
Drink (%)	94 (25.8%)
Diabetes	75 (20.5%)
Hypertension	291 (79.7%)

BMI, Body Mass Index; WHR, Waist-Hip ratio; HR, Heart Rate; IMT, intima-media thickness; eGFR, estimated Glomerular Filtration Rate; LVMI, PWV, pulse wave velocity; Left Ventricular Mass index; FPG, fasting plasma glucose; LDL-c, low-density lipoprotein cholesterol.
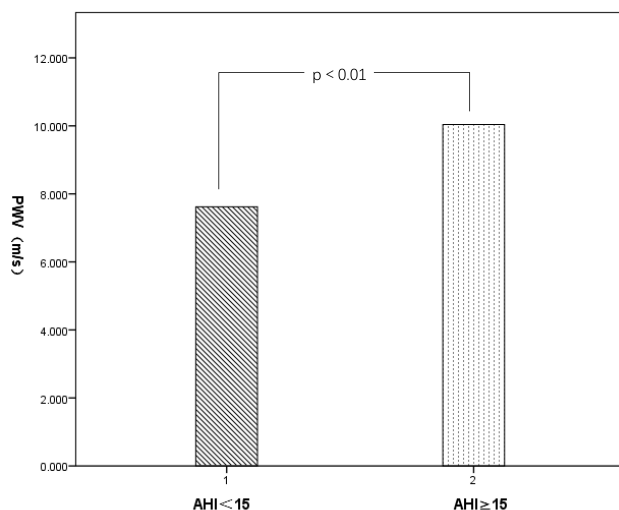

Fig. 1. The comparison of PWV grouped by AHI. The subjects with AHI ≥15 had significantly higher cf-PWV than those with AHI <15 (10.03 ± 3.67 m/s vs 7.62 ± 1.48 m/s, $p < 0.01$).

The subjects with moderate to severe OSA presented higher c-fPWV values than those in the mild group (10.03 ± 3.67 m/s vs 7.62 ± 1.48 m/s, $p < 0.01$). The Pearson correlation showed AHI was significantly and positively correlated with cf-PWV ($r = 0.217$, $p < 0.01$), Age ($r = 0.148$, $p < 0.01$), BMI ($r = 0.228$, $p < 0.01$) and HbA1c ($r = 0.172$, $p < 0.01$) (Table 3).

After adjusting for age, BMI, LDL-c, FGB, AHI, eGFR, Night BP, office diastolic BP and Day BP in Logistic regression model, AHI (OR = 1.03, 95% CI: 1.01–1.05) and office diastolic pressure (OR = 1.04, 95% CI: 1.00–1.08) and age (OR = 1.12, 95% CI: 1.06–1.19) were independent risk factors for arteriosclerosis (Table 4).

4. Discussion

OSA is a common disorder worldwide. It is associated with increased cardiovascular morbidity and mortality. cf-PWV is a potent cardio-vascular risk marker for arterial stiffness. Higher cf-PWV has been shown to be associated with worse clinical outcomes [12]. This cross-sectional study analyzed the relationship between OSA and arterial stiffness in a Chinese population. Our study shows that cf-PWV was significantly higher in moderate to severe compared to mild OSA patients. AHI was significantly and positively correlated with cf-PWV, and was an independent risk factor for arteriosclerosis.

Our study found that cf-PWV was significantly higher in moderate to severe compared to mild OSA patients. Many studies have confirmed that OSA is related to impaired vascular function. For example, a recent meta-analysis showed that cf-PWV or AIx of OSA patients was significantly higher than that of healthy people [13]. Compared with a control group, patients with OSA without known cardiovascular disease have increased PWV [14]. Compared to a control group, OSA patients also have higher intima-media thickness and carotid diameter, similar to those in patients with hypertension [15]. Intermittent hypoxemia and oxidative stress may be the cause of impaired vascular function caused by OSA [16]. Intermittent hypoxia can lead to increase of inflammatory markers such as endothelin-1 (ET-1), interleukin-6 (IL-6), C-reactive protein (CRP) and nitric oxide (NO). These factors associated with inflammation can affect vascular endothelial function as well as promoting arteriosclerosis and inflammatory vascular remodelingarteriosclerosis [17].

In addition, the impact of day and night differences in certain influencing factors on PWV needs to be considered. For example, intermittent hypoxemia at night may lead to activation of inflammatory pathways, increased sympathetic tone and impaired endothelium-dependent vasodilation [18]. Patients who suffer from sleepiness during the day have more severe OSA and greater improvement in arterial stiffness after treatment with continuous positive airway pressure (CPAP). This may be because daytime sleepiness is related to the severity of inflammation associated with sleep disruption (wakefulness and sleep fragmentation) and decreased saturation at night [19]. Short-term (8 weeks) CPAP treatment has been shown to significantly improve central systolic blood pressure, aortic pulse wave velocity, aortic augmentation index in patients

Table 2. The comparison of parameters grouped by AHI.

Parameter	AHI <15 (n = 108)	AHI ≥15 (n = 257)	p value
Age (year)	44.6 ± 11.8	50.9 ± 12.8	<0.01
BMI (kg/m^2)	27.5 ± 3.2	28.3 ± 4.0	<0.05
HR (beat per minuite)	82 ± 12	77 ± 14	<0.01
WHR	0.99 ± 0.08	0.98 ± 0.06	0.312
cf-PWV (m/s)	7.62 ± 1.48	10.03 ± 3.67	<0.01
AHI	7.3 ± 4.0	38.7 ± 10.2	<0.01
SpO$_2$%	84 ± 6	76 ± 10	<0.01
LDL-c (mmol/L)	3.10 ± 1.09	3.33 ± 2.03	0.32
FPG (mmol/L)	5.43 ± 0.77	0.69 ± 2.25	<0.01
HbA1C	5.80 ± 0.73	6.16 ± 1.21	<0.05
IMT (mm)	0.72 ± 0.15	0.72 ± 0.16	0.949
LVMI (g/m^2)	122.86 ± 25.43	124.54 ± 29.36	0.644
eGFR (mL/min/1.73 m^2)	95.9 ± 16.1	91.8 ± 16.5	<0.05
UA (umol/L)	423.3 ± 83.7	411.0 ± 91.5	0.39
Diabetes (n)	10	65	<0.01
Hypertension (n)	75	216	<0.01
Smoking (n)	28	94	<0.01
Drink (n)	26	68	0.716
office-SBP (mmHg)	139 ± 19	148 ± 21	<0.01
office-DBP (mmHg)	89 ± 14	92 ± 15	0.81
24 h SBP (mmHg)	132 ± 15	132 ± 14	0.996
24 h DBP (mmHg)	88 ± 10	86 ± 11	0.071
Day SBP (mmHg)	135 ± 14	134 ± 15	0.788
Day DBP (mmHg)	91 ± 10	87 ± 11	<0.05
Night SBP (mmHg)	127 ± 16	126 ± 16	0.932
Night DBP (mmHg)	83 ± 12	81 ± 12	0.226

BMI, Body Mass Index; WHR, Waist-Hip ratio; HR, Heart Rate; IMT, intima-media thickness; eGFR, estimated Glomerular Filtration Rate; LVMI, Left Ventricular Mass index; PWV, pulse wave velocity; UA, uric acid; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; AHI, Apnea Hyponea Index.

with moderate–severe OSA and in patients with metabolic syndrome (MS) [20] only in patients who used the device for a minimum of 4 h/night. The concentrated redistribution of body fluids during sleep is related to the high prevalence of drug-resistant hypertension and OSA, both of which show clinical features that indicate extracellular fluid volume overload [21]. Future research will study the correlation between OSA and PWV.

CPAP seems to be an effective method to improve arterial stiffness in OSA patients, but this has been contradicted by a study [22] that showed that CPAP treatment for 6 months was not associated with reduced aortic stiffness as measured by cf-PWV, in patients with resistant hypertension and moderate to severe OSA. However, in contrast to no-CPAP therapy, treatment may prevent its progression. The timing of initiating CPAP therapy and the duration of CPAP therapy may have a higher effect on the efficacy, which requires further research.

It is theorized that the severity of OSA has no independent effect on PWV [23]. However, our study suggests that the cf-PWV value of subjects with moderate to severe OSA was significantly higher than in those with mild OSA. Both OSA and high blood pressure can cause arterial stiffness and abnormality of heart structures. When these two conditions coexist, there will likely be a cumulative effect. The ventricular afterload increases and the heart remodels [7]. We therefore believe that the severity of OSA also affects arterial stiffness.

The results of this study suggest that the office systolic blood pressure in patients with moderate to severe OSA group was significantly higher than in those with mild OSA, but there was no difference between the office diastolic blood pressure, 24 h systolic blood pressure, 24 h diastolic blood pressure, and day and night BP between the two groups. AHI, office diastolic blood pressure and age are independent risk factors for arteriosclerosis.

Table 3. Pearson correlation among variables.

	Age	BMI	PWV	AHI	N-SBP	N-DBP	HbA1c	eGFR	LDL-c
Age									
BMI	–0.213**								
PWV	0.606**	–0.117							
AHI	0.148**	0.228**	0.217**						
Night SBP	–0.034	0.325**	0.199**	0.116					
Night DBP	–0.312**	0.206**	–0.164*	0.07	0.659**				
HbA1c	0.238**	0.12	0.384**	0.172**	0.13	–0.061			
eGFR	–0.590**	0.07	–0.368**	–0.095	0.013	0.180**	–0.133		
LDL-c	–0.125*	0.057	–0.111	0.045	–0.08	–0.046	0.181**	0.018	

$*p < 0.05$, $**p < 0.01$.

Table 4. Risk factors for arteriosclerosis.

	B	S.E	Wald	df	Sig	Exp (B)	95% CI for EXP (B)	
							lower	Upper
Constant	–9.408	4.478	4.414	1	0.036	0.000		
age	0.115	0.028	16.771	1	0.000	1.122	1.062	1.186
BMI	–0.082	0.067	1.520	1	0.218	0.921	0.808	1.050
LDL-c	–0.233	0.198	1.380	1	0.240	0.792	0.537	1.168
FPG	0.219	0.173	1.607	1	0.205	1.244	0.887	1.745
AHI	0.030	0.011	7.920	1	0.005	1.031	1.009	1.052
eGFR	0.001	0.017	0.005	1	0.942	1.001	0.969	1.034
Night-DBP	0.005	0.031	0.024	1	0.877	1.005	0.945	1.069
o-DBP	0.039	0.019	4.362	1	0.037	1.040	1.002	1.079
Day-DBP	–0.010	0.037	0.070	1	0.791	0.990	0.921	1.065

Increasing age, increasing body size, hypertension and insulin resistance may all lead to increased OSA and arterial stiffness [23]. OSA can lead to marked nocturnal blood pressure fluctuations (NBPFs) and can be associated with increased arterial stiffness and nocturnal hypertension [24]. Of course, both pharmacological and nonpharmacological treatments, including antihypertensive therapy, will affect the association between OSA and blood pressure. CPAP therapy reduces NBPFs, arterial stiffness and nocturnal BP in patients with OSA and coexisting cardiovascular diseases [24]. Therefore, the correlation between blood pressure and OSA in this study may be interfered by the above confounding factors. In addition, the increased blood pressure in the office and the influence of occult hypertension cannot be ignored. For example, studies have suggested that compared with matched control groups, OSA patients have a higher incidence of unadjusted occult hypertension [25]. When OSA and hypertension coexist, there is an additive effect of subclinical arteriosclerosis markers. OSA may lead to poor blood pressure control, and its mechanisms include increased sympathetic nerve activity, decreased baroreflex sensitivity, disturbance of sodium metabolism and extracellular water distribution, impaired endothelial function, hypoxia and circulatory reoxygenation [16]. Therefore, we also need to emphasize the role of blood pressure control in OSA patients.

Our research also shows the correlation between HbA1c, BMI and AHI. There have been many studies on the correlation between obesity and OSA. The relationship between blood glucose, vessel function and OSA is complicated. A previous cross-sectional analysis showed that a decrease in heart rate variability (HRV) in young patients with type 1 diabetes was associated with an increase in arterial stiffness [26]. An association between HbA1c (hemoglobin A1c) and the severity of OSA and has been reported in both nondiabetic and diabetic cohorts [27,28]. OSA is also a risk factor for lower extremity arterial disease (LEAD) in patients with type 2 diabetes [17]. The accumulation of advanced glycation end products (AGEs), insulin resistance, and excess reactive oxygen species (ROS) accumulation caused by hypoxia may be the pathophysiological mechanisms related to the three conditions [17].

This study has some limitations. First, the sample size was small, and the influence of lipid-regulating drugs and antiplatelet drugs was not excluded. Second, most subjects were male and we did not adjust for sex.

5. Conclusions

The severity of OSA was positively correlated with pulse wave velocity. AHI, office blood pressure and age were independent risk factors for arteriosclerosis. Further studies will enhance the sample size to investigate underlying relationships and potential mechanisms of arterial stiffness in patients with obstructive sleep apnea/hypopnea.

Abbreviations

BMI, Body Mass Index; WHR, Waist-Hip ratio; HR, Heart Rate; IMT, intima-media thickness; LDL-c, low density lipoprotein cholesterin; FPG, fasting plasma glucose; eGFR, estimated Glomerular Filtration Rate; LVMI, Left Ventricular Mass index; cf-PWV, Carotid-femoral pulse wave velocity; PWV, pulse wave velocity; AHI, apnea-hypopnea index; OSA, Obstructive sleep apnea; UA, uric acid; BP, Blood Pressure; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; PSG, Overnight polysomnography.

Author Contributions

BWT and JLZ designed the research study. YYB performed the research. HY and AA provided help and advice on BWT analyzed the data. BWT, JHZ and JLZ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

All studies were in compliance with the Declaration of Helsinki, the Good Clinical Practice guidelines, and applicable regulatory requirements. All participants provided written informed consent to participate for the respective study, which was approved by the Human Research Ethics Committee at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (2017(1)-1).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, Sajid H, *et al*. Serum Inflammatory Markers in Obstructive Sleep Apnea: A Meta-Analysis. Journal of Clinical Sleep Medicine. 2013; 09: 1003–1012.

[2] Korcarz CE, Stein JH, Peppard PE, Young TB, Barnet JH, Nieto FJ. Combined Effects of Sleep Disordered Breathing and Metabolic Syndrome on Endothelial Function: the Wisconsin Sleep Cohort Study. Sleep. 2014; 37: 1707–1713.

[3] Kim NH, Cho NH, Yun C, Lee SK, Yoon DW, Cho HJ, *et al*. Association of Obstructive Sleep Apnea and Glucose Metabolism in Subjects with or without Obesity. Diabetes Care. 2013; 36: 3909–3915.

[4] Floras JS. Sleep Apnea and Cardiovascular Disease: An Enigmatic Risk Factor. Circulation Research. 2018; 122: 1741–1764.

[5] Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, *et al*. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010; 122: 352–360.

[6] Loke YK, Brown JWL, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. Circulation Cardiovascular Quality and Outcomes. 2012; 5: 720–728.

[7] Drager LF, Bortolotto LA, Figueiredo AC, Silva BC, Krieger EM, Lorenzi-Filho G. Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. Chest. 2007; 131: 1379–1386.

[8] Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, *et al*. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005; 45: 142–161.

[9] Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, *et al*. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. Journal of Clinical Sleep Medicine. 2012; 8: 597–619.

[10] Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, *et al*. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018; 71: e13–e115.

[11] American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018; 41: S13–S27.

[12] Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. Journal of the American College of Cardiology. 2010; 55: 1318–1327.

[13] Wang J, Yu W, Gao M, Zhang F, Gu C, Yu Y, *et al*. Impact of Obstructive Sleep Apnea Syndrome on Endothelial Function, Arterial Stiffening, and Serum Inflammatory Markers: An Updated Meta-analysis and Metaregression of 18 Studies. Journal of the American Heart Association. 2015; 4: e002454.

[14] Sarinc Ulasli S, Sariaydin M, Ozkececi G, Gunay E, Halici B, Unlu M. Arterial stiffness in obstructive sleep apnoea: is there a difference between daytime and night-time? Respirology. 2016; 21: 1480–1485.

[15] Drager LF, Bortolotto LA, Krieger EM, Lorenzi-Filho G. Addi-

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tive effects of obstructive sleep apnea and hypertension on early markers of carotid atherosclerosis. Hypertension. 2009; 53: 64–69.

[16] Borsini E, Blanco M, Bosio M, Schrappe M, Ernst G, Nosetto D, *et al*. Prevalence of sleep apnea and cardiovascular risk factors in patients with hypertension in a day hospital model. Clinical and Experimental Hypertension. 2018; 40: 231–237.

[17] Zhao X, Yu X, Xin S, Zhang W, Zhang X, Ji L. Correlation between OSAHS and Early Peripheral Atherosclerosis Indices in Patients with Type 2 Diabetes Mellitus in China: A Cross-Sectional Inpatient Study. Journal of Diabetes Research. 2021; 2021: 6630020.

[18] Sforza E, Millasseau S, Hupin D, Barthélémy J, Roche F. Arterial stiffness alteration and obstructive sleep apnea in an elderly cohort free of cardiovascular event history: the PROOF cohort study. Sleep and Breathing. 2019; 23: 201–208.

[19] Mineiro MA, Silva PMD, Alves M, Papoila AL, Marques Gomes MJ, Cardoso J. The role of sleepiness on arterial stiffness improvement after CPAP therapy in males with obstructive sleep apnea: a prospective cohort study. BMC Pulmonary Medicine. 2017; 17: 182.

[20] Zota IM, Statescu C, Sascau RA, Roca M, Anghel L, Mitu O, *et al.* Arterial Stiffness Assessment Using the Arteriograph in Patients with Moderate-Severe OSA and Metabolic Syndrome-A Pilot Study. Journal of Clinical Medicine. 2021; 10: 4238.

[21] Friedman O, Bradley TD, Chan CT, Parkes R, Logan AG. Relationship between overnight rostral fluid shift and obstructive sleep apnea in drug-resistant hypertension. Hypertension. 2010; 56: 1077–1082.

[22] Cardoso CRL, Roderjan CN, Cavalcanti AH, Cortez AF, Muxfeldt ES, Salles GF. Effects of continuous positive airway pressure treatment on aortic stiffness in patients with resistant hypertension and obstructive sleep apnea: a randomized controlled trial. Journal of Sleep Research. 2020; 29: e12990.

[23] Stein JH, Stern R, Barnet JH, Korcarz CE, Hagen EW, Young T, *et al*. Relationships between sleep apnea, cardiovascular disease risk factors, and aortic pulse wave velocity over 18 years: the Wisconsin Sleep Cohort. Sleep & Breathing. 2016; 20: 813–817.

[24] Picard F, Panagiotidou P, Weinig L, Steffen M, Tammen A, Klein RM. Effect of CPAP therapy on nocturnal blood pressure fluctuations, nocturnal blood pressure, and arterial stiffness in patients with coexisting cardiovascular diseases and obstructive sleep apnea. Sleep and Breathing. 2021; 25: 151–161.

[25] Drager LF, Diegues-Silva L, Diniz PM, Bortolotto LA, Pedrosa RP, Couto RB, *et al*. Obstructive sleep apnea, masked hypertension, and arterial stiffness in men. American Journal of Hypertension. 2010; 23: 249–254.

[26] Jaiswal M, Urbina EM, Wadwa RP, Talton JW, D'Agostino RB, Hamman RF, *et al*. Reduced heart rate variability is associated with increased arterial stiffness in youth with type 1 diabetes: the SEARCH CVD study. Diabetes Care. 2013; 36: 2351–2358.

[27] Kent BD, Grote L, Bonsignore MR, Saaresranta T, Verbraecken J, Lévy P, *et al*. Sleep apnoea severity independently predicts glycaemic health in nondiabetic subjects: the ESADA study. The European Respiratory Journal. 2014; 44: 130–139.

[28] Kent BD, Grote L, Ryan S, Pépin J, Bonsignore MR, Tkacova R, *et al*. Diabetes Mellitus Prevalence and Control in Sleep-Disordered Breathing: The European Sleep Apnea Cohort (ESADA) study. Chest. 2014; 146: 982–990.