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SCIENTIFIC INVESTIGATIONS

Associations Between Obstructive Sleep Apnea and Measures of Arterial Stiffness

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Study Objectives: The aim of this study was to determine whether severity measures of obstructive sleep apnea (OSA) are associated with arterial stiffness and central blood pressure (two important cardiovascular risk factors) in a large group of patients with OSA.

Methods: Baseline data from six studies on OSA in which arterial stiffness and central aortic blood pressure measures were determined using applanation tonometry were pooled. Associations between measures of arterial stiffness (heart rate corrected augmentation index [AI75]), central aortic blood pressure (central systolic pressure [CSP] and heart rate corrected central augmentation pressure [CAP75]) and measures of OSA severity were explored using stepwise regression modelling.

Results: Data from 362 participants (M:F ratio 13:1) with mean (standard deviation) age 49.2 (11.0) years, body mass index 31.9 (5.3) kg/m^2, apnea-hypopnea index (AHI) 35.7 (20.7) events/h were included in the analyses. The AHI, oxygen desaturation index (ODI3%), and sleep time with SpO_2 < 90% (T90) were all associated with arterial stiffness (AI75), (AHI: adj. β = .069; *P* = .01; ODI3%: adj. β = .072; *P* = .01; T90: adj. β = .18; *P* < .0001) and CAP75 (AHI: adj. β = .030; *P* = .01; ODI3%: adj. β = .027; *P* = .02; T90: adj. β = .080; *P* < .0001). AHI was also associated with CSP (AHI: adj. β = .11; *P* = .002).

Conclusion: OSA severity was significantly associated with augmentation index and CAP75 although the relationships were not strong.

Keywords: arterial stiffness, obstructive sleep apnea, patient cohort

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea is a risk factor for cardiovascular morbidity and mortality. Because recent large intervention trials have been negative, there is a need to focus on endpoints such as arterial stiffness to further explore the relationship. To our knowledge, no previous studies have explored the effect of different measures of sleep apnea severity on measures of arterial stiffness.

Study Impact: In a large patient group, we show associations between measures of sleep apnea severity and several aspects of arterial stiffness. The results support a relationship between sleep apnea and cardiovascular disease beyond standard peripheral blood pressure measures. Further studies on the effect of sleep apnea on arterial stiffness are needed to clarify the mechanisms for increased vascular dysfunction.

INTRODUCTION

Obstructive sleep apnea (OSA) has been shown to be an independent risk factor for cardiovascular morbidity and mortality[1,2] and in recent years, the strong association between OSA and cardiovascular disease has gained considerable interest.[3–7] The intermittent hypoxia, arousals, and sympathetic activation that occur with apneas and hypopneas result in both temporary elevations in blood pressure during sleep as well as sustained daytime hypertension.[6] However, hypertension does not develop in all patients with even severe OSA and there remains a need to better understand whether other nontraditional risk factors, such as arterial stiffness, may provide improved risk stratification.

Arterial stiffness caused by structural changes in the vascular wall or sustained vascular smooth muscle contraction (vasoconstriction) is a composite marker of declining arterial health that is strongly associated with atherosclerosis[8,9] and poorer cardiovascular outcomes including fatal and nonfatal cardiovascular events.[10–14] Markers of arterial stiffness include pulse wave velocity and pulse wave analysis (PWA) derived variables such as aortic augmentation index and central aortic blood pressure. These markers provide prognostic information beyond standard risk factors including hypertension, diabetes, obesity, dyslipidemia, and smoking.[10] In particular, central aortic blood pressure is a superior prognostic marker than conventional brachial blood pressure[15] because it better correlates with target organ damage.[16]

Table 1—Characteristics of the study population (n = 362).

Age (years)	49.2 ± 11.0
Sex	
Female	26 (7.2)
Male	336 (92.8)
Body mass index (kg/m^2)	31.9 ± 5.3
Waist circumference (cm)	109.4 ± 13.6
Height (cm)	175.2 ± 7.8
Peripheral systolic pressure (mmHg)	123.9 ± 12.6
Peripheral diastolic pressure (mmHg)	78.1 ± 9.0
Mean arterial pressure (mmHg)	95.8 ± 10.0
Heart rate (beats/min)	66.3 ± 10.8
Total cholesterol (moll/L)	5.2 ± 0.98
Diabetes mellitus*	26 (7.3)
Hypertension*	145 (40.1)
Hyperlipidemia*	79 (22.2)
Smoking status*	
Nonsmoker	160 (94.1)
Current smoker	10 (5.9)

Data presented as mean ± standard deviation or n (%). * = data available for diabetes mellitus (n = 356), hypertension (n = 362), hyperlipidemia (n = 356), smoking status (n = 170), waist circumference (n = 337), total cholesterol (n = 216).

To our knowledge, no previous studies have explored the effect of different measures of OSA (apnea-hypopnea index [AHI], oxygen desaturation index [ODI3%] and arousal index) on several variables of PWA. The aim of this study was therefore to determine whether different measures of OSA severity were associated with arterial stiffness and central blood pressure in a large group of patients with OSA.

METHODS

Participants and Setting

The patients included in this analysis were originally referred for investigation of OSA through sleep clinics at the Woolcock Institute of Medical Research and at Royal Prince Alfred and Royal North Shore Hospitals in Sydney, Australia. The analysis included pooled data from 6 studies in 362 patients (336 men and 26 women) where measures of arterial stiffness were made. All studies and study participants have been described in detail previously.[7,17–21] In cases where a participant took part in more than one study, only data from their first study were included. Five of the six studies were randomized controlled trials with 121,[7] 60,[17] 56,[18] 33,[19] and 44[21] participants, respectively. The sixth study was an observational, open-label, intervention study and for the current study, data from 48 patients were included.[21] Of the studies, only two included both men and women.[7,19] In all the studies, only baseline data were included.

OSA Measurements

Sleep and breathing variables in all participants were assessed using an attended overnight, in-laboratory polysomnography (PSG) device (Sandman Elite, V.9.2, Tyco Healthcare, Denver, Colorado, United States; E-Series, Compumedics, Melbourne, Australia, or Alice 5, Philips Respironics, Andover, Massachusetts, United States. For the current study, PSG data from baseline were used (standard diagnostic PSG, scored according to standard criteria[22,23]) and measures of OSA were as follows: AHI, ODI3%, nighttime oxygen saturation nadir, sleep time with oxygen saturation with < 90%. Additional details have been reported elsewhere.[7,17–20]

Arterial Stiffness Measures Using PWA

In all of the six pooled studies, arterial stiffness was assessed by PWA using applanation tonometry of the radial artery (SphygmoCor, AtCor Medical, Inc., Australia). Apart from conduit arterial stiffness, PWA provides measures of central and peripheral blood pressure, pulse pressure amplification, and cardiac perfusion potential.[10] Measures were rigorously performed with participants who had fasted for 5 hours and who were caffeine and smoke free. This therefore resulted in most measurements occurring in the morning or first half of the day. Because a diagnosis of OSA was an eligibility criterion for all source studies, most of the arterial stiffness measurements were performed on a different day after PSG. However, the measurements were conducted within 1 to 2 weeks of diagnosis.

In all studies, the following measures of arterial stiffness were collected: central systolic pressure (CSP), central diastolic pressure (CDP), central pulse pressure (CPP), peripheral systolic pressure (PSP), peripheral diastolic pressure (PDP), peripheral pulse pressure (PPP), pulse pressure amplification (PPA), augmentation index corrected to a heart rate of 75 bpm (AI75), central augmentation pressure corrected to a heart rate of 75 bpm (CAP75), subendocardial viability ratio (SEVR; a measure of cardiac perfusion potential) and, time to reflection (TR; reflected component of the pulse pressure wave). In addition, the participants' age, sex, body mass index (BMI), smoking status, and comorbidities (diagnosis of diabetes, hypertension, or hyperlipidemia; or medication) were also included in the current dataset.

Statistics

Statistical analyses were performed using Stata 13 (Stata Corporation, College Station, Texas, United States). Correlation analyses for OSA variables with PWA variables were conducted. The association between variables of OSA and measures of arterial stiffness were then assessed using a backward stepwise regression model approach for each of the measures of arterial stiffness and OSA variables. The threshold for exclusion of variables from the model was set at $P \geq .10$. In all regression analyses age, sex, mean arterial pressure (MAP), smoking status, total cholesterol, height, weight, medical conditions (diabetes mellitus, hypertension, hyperlipidemia), and Epworth Sleepiness Scale were entered in the starting model and each of the OSA variables were entered separately. The results of the stepwise regression models are presented as adjusted β-coefficients with 95% confidence intervals (95% CI). A value of $P < .05$ was considered significant.

Table 2—Measures of obstructive sleep apnea in the study population (n = 362).

	Mean ± SD	Minimum	Maximum
Apnea-hypopnea index (events/h)	35.7 ± 20.7	6.4	109.9
Oxygen desaturation index 3% (events/h)	29.6 ± 21.7	0.0	122.4
Saturation nadir (%)	80.2 ± 9.0	34.0	93.0
Time with saturation < 90% (minutes)	7.4 ± 11.9	0.0	80.0
Total sleep time (minutes)	356.9 ± 62.0	90.5	517.0
Arousal index (events/h)	34.1 ± 18.4	6.3	111.1

SD = standard deviation.

Ethics Statement

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 Central Ethics Committee (RPAH Zone) or the Human Research Ethics Committee at Sydney University. All except one of the included studies were registered with the Australia New Zealand Clinical Trials Registry (http://www.anzctr.org.au).

RESULTS

Table 1 shows the baseline characteristics for the participants depicting a population with OSA and obesity who are middle aged. Of this population, 7.3% had a diagnosis of diabetes mellitus, 40.1% had hypertension, 22.2% had hyperlipidemia, and 5.9% were smokers. **Table 2** shows that the participants had severe OSA with AHI and ODI3% ≥ 30 events/h and hypoxia variables showing a clear effect of OSA with mean saturation nadir of 80% and time with saturation < 90% of 7.4 minutes. Within the group, the total sleep time was 6 hours, with a range of 1.5 to 8.5 hours and the arousal index was on par with AHI and ODI3% (**Table 2**). **Table 3** shows that most of the measures of arterial stiffness were within normal limits,[24–29] although time to reflection was somewhat long (**Table 3**).

Several of the OSA variables correlated with measures of arterial stiffness in the unadjusted analysis (**Table 4**). AHI and arousal index were primarily correlated with CDP, PSP, and PDP whereas the hypoxia variables seemed primarily correlated with SEVR, TR, and AI75. None of the OSA variables showed correlations with CPP and PPP (**Table 4**).

From the stepwise regression models, only heart rate corrected CAP and augmentation index were associated with all of the OSA variables (**Table 5**). However, several of the OSA variables were associated with different measures of arterial stiffness as AHI was associated with CSP (adj. β = .11; P = .002), CDP (adj. β = .059; P = .03), CPP (adj. β = .071; P = .01), PSP (adj. β = .093; P = .01), AI75 (adj. β = .069; P = .01), and CAP75 (adj. β = .030; P = .01) and ODI3% was associated with AI75 (adj. β = .072; P = .01) and CAP75 (adj. β = .027; P = .02). In addition, arousal index was associated with CSP (adj. β = .079; P = .03), CPP (adj. β = .059; P = .05), PSP (adj. β = .077; P = .04), PPA (adj. β = −.00090; P = .04), AI75 (adj. β = .075; P = .02), and CAP75 (adj. β = .034; P = .01). Both measures of hypoxia showed associations with arterial stiffness with saturation nadir being associated with PPA (adj. β = .0030; P = .001), AI75 (adj. β = −.21; P = .001), and CAP75 (adj. β = −.071; P = .01) and T90 being associated with CPP (adj. β = .11; P = .02), PPA (adj. β = −.0022; P = .002), AI75 (adj. β = .18; P < .0001) and CAP75 (adj. β = .080; P < .0001).

Table 3—Measures of arterial stiffness in the study population (n = 362).

Peripheral pulse pressure (PPP; mmHg)	45.8 ± 10.0
Central systolic pressure (CSP; mmHg)	114.2 ± 12.6
Central diastolic pressure (CDP; mmHg)	79.2 ± 9.1
Central pulse pressure (CPP; mmHg)	35.0 ± 9.4
Pulse pressure amplification (PPA; mmHg)	1.3 ± 0.2
Subendocardial viability ratio (SEVR; %)	163.0 ± 29.0
Time to reflection (TR; ms)	157.0 ± 49.5
Central augmentation pressure (CAP; mmHg)*	6.3 ± 4.4
Augmentation index (AI; %)*	17.7 ± 10.5

Data presented as mean ± standard deviation. * = heart rate corrected. Normal values for the arterial stiffness measures[24–29]: PPP 30–50 mmHg; CSP 100–130 mmHg; CDP 70–85 mmHg; CPP 35–45 mmHg; PPA 1.25–1.45 mmHg; SEVR 130–200%; TR 120–160 ms; CAP 4–12 mmHg and AI 10–40 %.

DISCUSSION

The main finding of this study is that OSA is associated with measures of arterial stiffness and central blood pressure. Both OSA severity and hypoxia were correlated with measures of arterial stiffness but after adjusting for confounders, only CAP and the augmentation index were associated with all the OSA variables. Although the relationships were relatively weak, this suggests that OSA influences arterial stiffness and that further research into the relationship and its pathways is warranted.

In the current study OSA severity, measured as either AHI, ODI3%, or arousal index was related to increased central pressure, peripheral pressure, CAP and/or the augmentation index. Several observational studies have shown relationships between OSA and arterial stiffness primarily using augmentation index as the measure of arterial stiffness and AHI as

Table 4—Correlations between OSA variables and measures of arterial stiffness.

		CSP	CDP	CPP	PSP	PDP	PPP	PPA	SEVR	TR	CAP75	AI75
AHI (events/h)	*r*	.08	.15*	−.03	.13*	.14*	.04	−.07	−.12*	−.04	.007	−.004
	P	.12	.005	.53	.015	.008	.50	.16	.018	.4406	.90	.94
	n	362	362	362	362	362	362	362	362	361	361	361
ODI3% (events/h)	*r*	.09	.14*	−.02	.11*	.14*	.02	.005	−.09	−.08	.03	.04
	P	.10	.008	.74	.035	.011	.68	.93	.09	.15	.53	.44
	n	342	342	342	342	342	342	342	342	341	341	341
Saturation nadir (%)	*r*	−.06	−.07	−.02	−.05	−.07	−.00001	.02	.11*	.11*	−.10	−.13*
	P	.22	.18	.74	.35	.19	.999	.74	.041	.033	.056	.017
	n	358	358	358	358	358	358	358	358	357	357	357
Time with saturation < 90 (%)	*r*	.02	.03	.005	.03	.02	.02	.03	−.16*	−.04	.07	.06
	P	.67	.62	.92	.58	.72	.70	.57	.003	.51	.18	.28
	n	345	345	345	345	345	345	345	345	344	344	344
Arousal index (events/h)	*r*	.16*	.14*	.08	.15*	.14*	.07	−.17*	−.04	−.06	.07	.05
	P	.003	.009	.14	.005	.011	.21	.001	.49	.26	.22	.34
	n	354	354	354	354	354	354	354	354	353	353	353

AHI = apnea-hypopnea-index, AI75 = augmentation index corrected for a heart rate set at 75 beats/min, CAP75 = central augmentation pressure corrected for a heart rate set at 75 beats/min, CDP = central diastolic pressure, CPP = central pulse pressure, CSP = central systolic pressure, ODI3% = oxygen desaturation-index, OSA = obstructive sleep apnea, PDP = peripheral diastolic pressure, PPA = pulse pressure amplification, PPP = peripheral pulse pressure, PSP = peripheral systolic pressure, SEVR = subendocardial viability ratio, TR = time to reflection.

Table 5—Results from the stepwise regression model.

	Augmentation Index*		
	Adj. β	***P***	**R^2 for model**
Apnea-hypopnea index (events/h)	.069	.01	.41
Oxygen desaturation index 3% (events/h)	.072	.01	.41
Saturation nadir (%)	−.21	.001	.43
Time with saturation < 90% (minutes)	.18	< .0001	.44
Arousal index (events/h)	.075	.02	.40
	Central Augmentation Pressure*		
	Adj. β	***P***	**R^2 for model**
Apnea-hypopnea index (events/h)	.030	.01	.49
Oxygen desaturation index 3% (events/h)	.027	.02	.48
Saturation nadir (%)	−.071	.01	.49
Time with saturation < 90% (minutes)	.080	< .0001	.53
Arousal index (events/h)	.034	.01	.49

* = heart rate corrected. Analysis performed by entering each of the obstructive sleep apnea variables separately and including age, sex, mean arterial pressure, smoking status, total cholesterol, height, weight, medical conditions (diabetes mellitus, hypertension, hyperlipidemia), and Epworth Sleepiness Scale score as variables in accordance with the stepwise regression model.

the measure of OSA severity.[30–32] In addition, both randomized controlled trials and case-control studies have shown that treatment of OSA with continuous positive airway pressure may reduce arterial stiffness.[11,33–36] Within the current study, the relationship between OSA and arterial stiffness was relatively weak whereas a case-control study Seetho et al. showed significantly stronger associations.[36] This could possibly be explained by the fact that patients in the Seetho et al. study had more obesity. To our knowledge, no previous studies have explored the effect of different measures of OSA (AHI, ODI3% and arousal index) on other variables of PWA.

Both hypoxia variables (ie, nighttime saturation nadir and time with saturation < 90%) were negatively associated with pulse pressure amplification but also central augmentation pressure and the augmentation index in the present study. Few previous studies have explored the effects of different hypoxia variables in patients with OSA on different variables of arterial stiffness. Nonetheless, within a group of patients with OSA Chung et al. showed that time with saturation < 90% was correlated with increased arterial stiffness measured using carotid-femoral pulse wave velocity,[37] indicating that the relationship may at least in part be mediated though hypoxic pathways.

Within the current study only CAP and the augmentation index were associated with all OSA variables after adjusting for potential confounders. However, as previous studies have

mainly focused on AHI as the measure of OSA and augmentation index as the measure of arterial stiffness, the exact relationship between OSA and arterial stiffness is still not fully understood. Further studies on the effect of other OSA severity measures on arterial stiffness are needed to further clarify the mechanisms for increased vascular dysfunction in OSA.

This study included a large clinical population pooled from several well-conducted clinical trials in patients with OSA. However, there are considerations when interpreting the results. Although all participants were patients with OSA and within the population age and BMI was representative, blood pressure levels were within the normal range as were measures of arterial stiffness. Furthermore, although hypertension was present in 40% of cases, blood pressure appeared to be well controlled. Overall, this may indicate that the group was relatively healthy. In addition, there were few women included in the current study as only two of the source studies included both sexes, making the results less generalizable and studies in a larger group of women are warranted. Finally, given the cross-sectional nature of the analysis and lack of a non-OSA control group, we cannot assume the relationship between OSA and arterial stiffness is causative. Causality can only be supported through findings from robustly designed randomized trials, which currently are scarce.[18,19]

To conclude, the current study showed that after adjusting for confounders (including comorbidities), several measures of OSA severity were significantly associated with augmentation index and CAP. Although the associations were relatively weak, the results nevertheless indicate that OSA might influence vascular function. This may in turn play a role in the relationship between OSA and cardiovascular disease beyond standard peripheral blood pressure measures.

ABBREVIATIONS

AHI, apnea-hypopnea-index
AI75, augmentation index corrected for a heart rate set at 75 beats/min
CAP75, central augmentation pressure corrected for a heart rate set at 75, beats/min
CI, confidence interval
CSP, central systolic pressure
CDP, central diastolic pressure
CPP, central pulse pressure
MAP, mean arterial pressure
ODI3%, oxygen desaturation index
OSA, obstructive sleep apnea
PSP, peripheral systolic pressure
PDP, peripheral diastolic pressure
PPP, peripheral pulse pressure
PPA, pulse pressure amplification
SEVR, subendocardial viability ratio
SpO_2, oxygen saturation
T90, sleep time with oxygen saturation < 90%
TR, time to reflection

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