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Relationships Between Sleep Apnea, Cardiovascular Disease Risk Factors, and Aortic Pulse Wave Velocity over 18 Years: The Wisconsin Sleep Cohort

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Abstract

Purpose—To determine if apnea-hypopnea index (AHI) severity would predict future aortic pulse wave velocity (PWV) in the Wisconsin Sleep Cohort.

Methods—Applanation tonometry was used to derive carotid-to-femoral PWV a mean of 18 (standard deviation 4) years after overnight polysomnography. Multivariable regression models were created to describe prospective associations between baseline AHI and future PWV.

Results—The 618 adults were mean 65 (7) years old (55% male) with a mean body-mass index of 31 (7) kg/m^2 at the tonometry visit. Mean baseline AHI was 4.6 (9.7) events/hour. In multiple linear regression models adjusted for age (β=0.13/year, standard error [SE]=0.01, p<0.001) and sex, higher $\log_{10}$AHI (β=0.43/events/hour, SE=0.18, p=0.02) was associated with PWV. After adjustment for waist circumference (β=0.01/cm, SE=0.01, p=0.05) and height, the association between baseline $\log_{10}$AHI and future PWV was not statistically significant (p=0.11), although the association with age persisted unchanged. Addition of covariates such as smoking status (current smoker β=0.66, SE=0.22, p=0.002), diabetes mellitus status (β=2.89, SE=0.59, p<0.001), and systolic blood pressure (BP, β=0.03/mmHg, SE=0.01, p<0.001) did not change the association. AHI did not interact with age or smoking status to predict PWV. A secondary analysis of nocturnal oxygen saturation parameters in 517 participants, 9 (2) years prior also did not show any significant relationships with future PWV.

Conclusions—The prospective association between AHI and PWV is confounded by body size and influenced by smoking, diabetes mellitus, and BP. Weight management, BP control, and smoking cessation may help prevent arterial stiffening associated with obstructive sleep apnea.

Keywords

Arteries; Hypertension; Sleep apnea; Vascular disease

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Access to data

James H. Stein and Paul E. Peppard had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

The authors have no potential conflicts of interest related to financial interests, activities, relationships, or affiliations.

Both obstructive sleep apnea (OSA) and obesity are associated with increased risk of cardiovascular disease (CVD) as well as CVD risk factors such as hypertension, dyslipidemia, inflammation, and insulin resistance [1-3]. Increased arterial stiffness is both a cause and consequence of hypertension and systemic inflammation that has been associated with future CVD risk, including myocardial infarction, stroke, heart failure, and all-cause mortality as well as cognitive decline [4-6]. Although OSA has been associated with arterial stiffening, the relationship between OSA severity and arterial stiffness is not clear [7-10]. We evaluated aortic pulse wave velocity (PWV), a validated measure of arterial stiffness, in the Wisconsin Sleep Cohort, a longitudinal, community-based study of OSA in 1,589 State of Wisconsin employees. We hypothesized that baseline OSA severity would predict later PWV.

Methods

Participants

All participants provided written, informed consent. This study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board. The inception of the Wisconsin Sleep Cohort was in 1988 when a stratified random sample of 2,884 individuals were invited for overnight, in-laboratory polysomnography [11]. These studies were repeated approximately every four years. Lipid and glucose measurements began in 1993. Assessment of nocturnal oxygen desaturation parameters began in 2000. Applanation tonometry was performed beginning in 2006. Starting in 2009 tonometry was performed approximately one month after participants had sleep studies. Prior to 2009, tonometry was performed approximately 2 years after sleep studies. For analytical purposes, a tonometry and polysomnogram occurring within a 3-year window were considered concurrent.

Polysomnography

Methods for performing and interpreting the polysomnograms have been described previously [11]. An apnea event was identified as cessation of airflow lasting at least 10 seconds. A hypopnea event was identified as a discernible reduction in the sum of thoracic plus abdomen respiratory inductance plethysmography amplitude associated with ≥4% reduction in oxyhemoglobin saturation. The average number of apnea plus hypopnea events per hour of sleep defined the apnea-hypopnea index (AHI), our summary parameter of OSA. Oxygen desaturation measurements were performed on polysomnograms starting in 2000 and included minimum and mean $Sa0_2$ as well as time with $Sa0_2$ <90%.

Arterial Tonometry

PWV was measured by arterial tonometry using the AtCor SphygmoCor PX system (AtCor Medical, Sydney, Australia) [5,12]. Participants were instructed to refrain from ingesting food, caffeine, and alcohol for 12 hours prior to the study. Subjects rested in the supine position for at least 10 minutes in a quiet, dark, temperature-controlled room before data collection began. Tonometry recordings of carotid and femoral arteries were taken when a reproducible signal with a clear upstroke was obtained. PWV (m/s) was calculated as the distance to transit time ratio of the pulse wave. The quality and stability of the tonometry

signals were insured by requiring an operator index higher than 80% for all analyzed tracings.

Statistical Analysis

Analyses used SAS, version 9.2 (SAS Institute Incorporated, Cary, NC). The primary outcome was PWV. Pearson correlations were computed to examine associations of baseline characteristics with PWV. Using multiple linear regression, we evaluated associations of PWV with the following predictors from the baseline visit (*i.e.,* the visit with the first overnight polysomnogram): log-transformed AHI (log_{10}[AHI+1],"log_{10}AHI", transformed because AHI had a skewed distribution), age, sex, waist circumference, height, smoking history (never, past, current), diabetes mellitus status (self-reported or use of diabetes medications), systolic blood pressure (BP), anti-hypertensive and lipid medications. Sequential models of baseline variables were used to predict tonometry measures assessed an average of 18 (4) years after baseline measurements. Model 1 included baseline age, sex, and AHI. Model 2 added waist circumference and height to model 1. Model 3 added the remaining baseline parameters. Additional, separate modes explored the possibility of an interaction between age and AHI and between smoking status and AHI. AHI also was modeled categorically (<5 [reference], 5 to <15, ≥15 or using continuous positive airway pressure [CPAP]). A supplementary analysis explored relationships between $Sa0_2$ parameters (minimum, mean, and time below 90%) performed a mean of 9 (2) years prior to PWV measurements using the same modeling approaches. A two-tailed p-value <0.05 was considered significant.

Results

Participant Characteristics

Participant characteristics at the baseline polysomnography visit and at the visit with oxygen desaturation measures are described in Table 1. Most subjects were white (96%), and 55% were male. Only three reported using CPAP at baseline. As participants aged between the baseline and follow-up visits, large numbers of participants developed hypertension, started on hypertension and lipid medications, and were diagnosed with diabetes mellitus. On average, participants gained weight, had larger waist circumferences, and more started using CPAP.

Baseline AHI Predicting Future Pulse Wave Velocity (18 Years Later)

Among non-CPAP users, baseline log_{10}AHI was correlated with future PWV (rho=0.19, p<0.001). After simultaneous adjustment for age (β=0.13/year, standard error [SE]=0.01, p<0.001) and sex (p=0.47), higher log_{10}AHI (β=0.42/events/hour, SE=0.18, p=0.02) was associated with PWV; however, after waist circumference (β=0.01/cm, SE=0.01, p=0.05) and height (p=0.19) both were added to the regression models, the association between baseline log_{10}AHI and future PWV was not statistically significant (p=0.12), although the association with age persisted unchanged. Simultaneous addition of all other covariates such as current smoking (β=0.66, SE=0.22, p=0.002), diabetes mellitus status (β=2.89, SE=0.59, p<0.001), systolic BP (β=0.03/mmHg, SE=0.01, p<0.001), past smoking (p=0.98), use of lipid-lowering medications (p=0.56), and use of antihypertensive medications (p=0.61) did

not alter the association between baseline AHI and future PWV. Age remained a significant predictor of later PWV (β=0.13/events/hr, SE=0.01, p<0.001) but did not interact with log_{10}AHI (p=0.70). Smoking status did not interact with log_{10}AHI. The category of AHI 5-<15 events/hour independently predicted later PWV (β=0.56, SE=0.22, p=0.01), but AHI ≥15 events/hour or CPAP use (p=0.13) did not. There was an interaction with age for this category (β=0.07/years*events/hour, SE=0.03, p=0.02). All other baseline predictors of later PWV essentially were unchanged in magnitude and statistical significance.

Nocturnal Oxygen Saturation Parameters Predicting Future Pulse Wave Velocity (9 Years Later)

In a supplementary analysis, among non-CPAP users (n=517/551, 94%), mean $Sa0_2$ (rho=−0.19, p<0.001), minimum $Sa0_2$ (rho=−0.14, p=0.002), and percent time sleeping with Sa02<90% (rho=−0.09, p=0.05) were correlated inversely with future PWV. After simultaneous adjustment for age (p<0.001) and sex (p=0.78), lower mean $Sa0_2$ (β=−0.15/%, SE=0.05, p=0.007) was associated with PWV as was minimum $Sa0_2$ (β=−0.03/%, SE=0.01, p=0.009), but not percent time sleeping with Sa02<90% (p=0.11). After waist circumference (p=0.002) and height (p=0.54) both were added to the model, the association between mean $Sa0_2$ and future PWV was not statistically significant (p=0.32), although the association with age persisted. Similar findings were noted for minimum $Sa0_2$ (p=0.23). Age, diabetes mellitus status, and systolic BP were the only statistically significant covariates in the final models for the oxygen saturation parameters that included all covariates (all p≤0.001).

As with the 18-year baseline visit data, interim log_{10}AHI was associated independently with PWV 9 years later after adjustment for age and sex (β=0.49/events/hour, SE=0.19, p=0.01), but no longer significant (p=0.37) after adding in waist circumference and height. The same predictors of future PWV from this interim visit (age, diabetes mellitus status, and systolic BP) were identified, though not current smoking. There was no significant interaction between log_{10}AHI and age or smoking. No AHI category predicted future PWV after adjustment for age and sex.

Discussion

In this large, well-characterized cohort, we did not find strong evidence of an independent association between baseline AHI and PWV over a mean of 18 years from baseline polysomnography or a mean of 9 years from interim polysomnography. We did not find any independent associations between mean $Sa0_2$, minimum $Sa0_2$, or time spent asleep with $Sa0_2$<90%. These findings suggest that the prospective associations between AHI and nocturnal oxygen saturation with PWV are largely confounded by body size and influenced by smoking, diabetes mellitus, and BP. Previous studies have had conflicting results, likely due to incomplete adjustment for confounders, differing study designs, and differing techniques for evaluating arterial stiffness [7-10].

Aortic PWV is a validated measured of regional arterial stiffness, since the aorta dampens the ejected aortic pulse wave; aortic PWV is an independent predictor of adverse cardiovascular disease events [4-6]. Given the strong associations of OSA with other factors that also influence arterial stiffness, such as increasing age, increasing body size,

hypertension and insulin resistance, it is not a surprise that an independent effect of OSA severity on PWV was not detected. OSA severity was assessed by AHI at two time points and by three markers of nocturnal oxygen saturation that are associated with CVD risk and other markers of arterial injury, such as carotid intima-media thickness [1,13]. Our inability to detect an independent association appears to be due to confounding by increased body size – specifically waist circumference – which also is associated increased CVD risk and diabetes mellitus [14]. We used waist circumference and height measurements in our models rather than body-mass index or weight measurements because in univariate analyses, waist circumferences at the baseline polysomnogram visit when AHI and at the polysomnogram visit when $Sa0_2$ were first measured were more strongly correlated with future PWV than contemporaneous body-mass index or weight measurements (data not shown). A type II error due measurement variability in OSA and PWV, relatively mild sleep apnea in the cohort including a low rate of moderate-severe OSA, exclusion of 6% of subjects in the supplementary analysis because of use of CPAP, use of intermittent use of CPAP, and treatment of hypertension cannot be excluded as explanations of the lack of association due to the study's observational design; however, we detected other known associates of increased PWV, including age, systolic BP, and smoking [4,5]. Furthermore, adjustment for antihypertensive medications, as well as a categorical analysis that considered AHI severity and CPAP use did not identify a strong association between OSA severity and PWV, though a small effect cannot be excluded.

Conclusion

The longitudinal association between AHI and nocturnal oxygen saturation parameters and PWV is confounded by body size. PWV is more strongly influenced by smoking, diabetes mellitus, and BP than OSA severity. Weight management, BP control, and smoking cessation may help prevent arterial stiffening associated with OSA.

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Table 1

Descriptive Statistics

	Baseline AHI Visit	Interim SaO_2 Visit[a]	Pulse Wave Velocity Visit
Number	618	517	618
Years Prior to PWV Visit - years	18 (4)	9 (2)	-
Sex (Male) – N (%)	342 (55)	278 (54)	342 (55)
Age – years	47 (8)	56 (7)	65 (7)
Ethnicity (Caucasian) – N (%)	601 (97)	503 (97)	601 (97)
Body mass index - kg/m^2	29 (6)	30 (6)	31 (7)
Waist circumference – cm	94 (14)	97 (15)	102 (16)
Systolic blood pressure – mmHg	123 (14)	125 (15)	132 (16)
Diastolic blood pressure – mmHg	81 (10)	77 (9)	75 (9)
Hypertension[c] – N (%) Hypertension medication use – N (%) Beta blocker medication use – N (%)	163 (26) 80 (13) 29 (5)	206 (40) 158 (31) 64 (12)	365 (60) 321 (53) 140 (23)
Diabetes mellitus[b] – N (%)	10 (2)	33 (6)	98 (16)
Lipid-lowering medication use – N (%)	23 (4)	111 (22)	288 (47)
Smoking status – N (%) Never Past Current	294 (48) 231 (37) 93 (15)	263 (51) 202 (39) 52 (10)	317 (51) 265 (43) 36 (6)
Apnea-Hypopnea Index[a] – events/hr <5 – N (%) 5-15 – N (%) ≥15 – N (%) CPAP user – N (%)	4.6 (9.7) 477 (77) 87 (14) 51 (8) 3 (1)	5.9 (7.8) 324 (59) 141 (26) 52 (9) 34 (6)[d]	6.1 (7.9) 315 (53) 142 (28) 53 (9) 87 (15)
Mean SaO_2 saturation[a] - %	-	95.4 (1.5)	94.7 (2.0)
Minimum SaO_2 saturation[a] - %	-	85.7 (7.0)	82.9 (9.4)
Sleep time with SaO_2<90%[a] - %	-	1.8 (7.6)	4.0 (11.4)
Pulse wave velocity - m/s	-	-	8.7 (2.2)

All values are mean (standard deviation) unless noted otherwise.

CPAP: continuous positive airway pressure, PWV: Pulse wave velocity

[a] No CPAP users included

[b] Diabetes mellitus = self-report or use of diabetes medications

[c] Hypertension = systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg or use of anti-hypertensive medications

[d] The 34 CPAP users were excluded from all analyses of nocturnal SaO_2 saturation.