The Effects of Sleep-Disordered Breathing on Arterial Stiffness are Modulated by Age

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Study Objectives: To identify associations between sleep-disordered breathing (SDB) and arterial stiffness.
Setting: Nested cross-sectional study.
Participants: One hundred fifty-three participants (ages 45-77 years, 43% women) in the population-based Wisconsin Sleep Cohort. Eighty-three had SDB and were not using continuous positive airway pressure therapy.
Interventions: Measurement of aortic pulse wave velocity (PWV) by arterial tonometry. Nocturnal polysomnography.
Measurements and Results: SDB was defined as an apnea-hypopnea index (AHI) ≥ 5 events/hour of sleep. By study design those with SDB had higher mean (SD) AHI (17.6 [16.2] vs 2.2 [1.3] events/h), as well as lower average nocturnal O_2 saturation (91.5 [2.1] vs 93.0 [1.4] %, P < 0.001) and larger waist circumference (102.5 [13.2] vs 92.5 [12.5] cm, P < 0.001), but they had similar central aortic systolic (122.8 [15.1] vs 119.1 [11.8] mm Hg, P = 0.100) and diastolic blood pressures (77.1 [9.4] vs 77.4 [8.6] mm Hg, P = 0.834), and PWV (9.06 [2.15] vs 8.51 [1.88] m/s; all P > 0.10). Markers of SDB that were correlated with PWV were nocturnal O_2 saturation (r = -0.24, P = 0.004) and AHI (r = 0.18, P = 0.032); however, these associations were not statistically significant after adjustment. In subjects not on antihypertensive medications, a significant interaction between nocturnal O_2 saturation and age was identified (β = -0.019, P = 0.039), such that the effect of nocturnal oxygen O_2 on PWV increased with age (adjusted R^2 = 0.468).
Conclusions: Adverse effects of nocturnal oxygen desaturation on PWV are seen among normotensive individuals and are amplified with aging. Integrated assessment of SDB is necessary to characterize its effects on arterial stiffness.
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OBSTRUCTIVE SLEEP APNEA AND SLEEP-DISORDERED BREATHING (SDB) ARE COMMON DISORDERS THAT ARE ASSOCIATED WITH INCREASED cardiovascular disease risk.[1,2] SDB is common[3] and is characterized by repeated episodes of airway obstruction with a concomitant decrease in O_2 saturation, increased ventilatory effort, and nocturnal arousals.[4] Repetitive hypoxic insults associated with SDB alter cardiovascular hemodynamics and are associated with endothelial dysfunction and vascular inflammation.[5-7] These pathophysiological changes may contribute to arterial stiffening, systemic hypertension, atherosclerosis, atrial fibrillation, and increased risk of cardiovascular disease.[8] Arterial stiffening is one of the earliest signs of arterial remodeling, causing earlier wave reflections and elevation of central aortic pressures. Central systolic and pulse pressures have stronger correlations with measures of atherosclerotic burden and are better predictors of cardiovascular disease events than are peripheral (brachial) blood pressures.[9,10] Aortic pulse wave velocity (PWV) is a highly reproducible[11] noninvasive measure of arterial stiffness associated with higher cardiovascular disease mortality, coronary heart disease, and stroke.[12-15]

Although associations between SDB severity and arterial stiffness have been described, the findings are not consistent between studies, in part because of differing study designs, varying severity of SDB, differing techniques for evaluating arterial stiffness, and, in some studies, lack of adjustment for potential confounders.[16-18] In order to overcome some of these limitations, we measured aortic PWV in a subset of participants with mild to moderate SDB in a well-characterized longitudinal cohort. The purpose of this study was to determine if PWV is associated with SDB severity and to evaluate the effects of aging and SDB on arterial stiffness.

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METHODS

Subjects and Polysomnography

This study was approved by the University of Wisconsin Health Sciences Institutional Review Board. All subjects provided informed consent prior to participation. Data were collected between July 2006 and December 2007. This was a nested cross-sectional analysis of participants in the Wisconsin Sleep Cohort Study, a longitudinal, community-based evaluation of SDB in 1589 State of Wisconsin employees. Each participant had at least 3 overnight polysomnograms or was over 50 years old and had 2 overnight polysomnograms. Methods for performing and interpreting the polysomnograms have been described previously.[3] An apnea event was identified as the cessation of airflow lasting at least 10 seconds. A hypopnea event was identified as a discernable reduction in the sum of thoracic plus abdomen respiratory inductance plethysmography amplitude associated with at least a 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 SDB. The leg-movement arousal index was defined as the number of leg movements associated with

electroencephalographic arousal divided by the total sleep time and was used in exploratory analyses.

The first 105 subjects were recruited consecutively; however, we observed that the individuals identified as having SDB only had mild to moderate sleep apnea (mean ± SD AHI 16.8 ± 13.9 events/h), so further recruitment required individuals identified as having SDB to have an AHI of more than 10 events per hour at their last overnight study. Of the initial 176 participants, 23 were excluded because of past or current continuous positive airway pressure use. The final analysis included 153 subjects. Reliable tracings for the determination of PWV were obtained in 138 subjects (90%). Reasons for exclusion included significant R-R interval variability due to arrhythmia, reduced signal-to-noise ratio due to respiratory effort, back pain, and large body habitus.

Measurement of PWV and Central Aortic Pressures

PWV was measured by arterial tonometry using the AtCor SphygmoCor PX system (AtCor Medical, Sydney, Australia). Participants were instructed to refrain from ingesting food, caffeine, and alcohol for 12 hours prior to the study. All studies were performed between 9:00 and 10:00 by 2 sonographers who were blinded to the results of the sleep tests. Subjects rested in the supine position for at least 10 minutes in a quiet, darkened, temperature-controlled room before data collection started. Tonometry recordings of carotid and femoral arteries were taken when a reproducible signal with a clear upstroke was obtained. The PWV was determined by the intersecting tangents method.[19] PWV (m/s) was calculated as the distance-to-transit time ratio of the pulse wave. Transit time was calculated as follows. The mean and SD time delay (seconds) from the electrocardiogram R-wave to the foot of the pulse waveform measured at the proximal (carotid) and distal (femoral) sites, based on an analysis of 10 seconds of stable tonometry tracings. Tracings with more than 10% beat-to-beat variation were rejected. The difference in the proximal and distal delay is the carotid-femoral transit time. The PWV distance was calculated as the difference in the absolute distance between the suprasternal notch and the carotid and femoral tonometry sites, respectively.

Central aortic pressures were derived from radial tonometry using a generalized, validated, transfer function.[20,21] The radial artery tonometry tracing was calibrated by inputting the mean and diastolic brachial arterial pressures, measured noninvasively using a high-fidelity oscillometric blood pressure monitor (Dinamap, GE Medical Systems, Tampa, FL). Tonometry tracings were calibrated using the mean and diastolic brachial blood pressure values as input pressures to avoid variability in systolic pressures. Three brachial blood pressure readings were obtained after 10 minutes of rest. Bilateral measurements were performed to exclude the presence of occlusive subclavian artery disease. Additional left brachial artery blood pressure measurements were obtained to ensure a steady state (i.e., mean blood pressure measurements varied < 5 mm Hg between readings). Quality and stability of the tonometry signals was ensured by requiring an operator index higher than 80% for all analyzed tracings. This index is based on the weighted value of 5 quality-control indices (average pulse height, pulse height variation, diastolic point variation, curve shape variation, maximum dP/dT as the first derivative of the systolic upstroke).

Measurement of Carotid Intima-Media Thickness

Digital B-mode ultrasound images of each carotid artery were obtained using an 8.0-MHz linear array transducer (8L5, Acuson Sequoia, Siemens Medical Solutions, Munich, Germany), based on a standardized protocol.[22,23] Images of the far walls of the common, bifurcation, and internal segments of each carotid artery were optimized, acquired, and measured by manual tracing (Camtronics Vericis, Emageon, Hartland, WI). Composite Carotid intima-media thickness (CIMT) was calculated as the mean of the segmental mean scores from all measurable segments (maximum of 6).[24] Tonometry and ultrasound examinations were performed and interpreted by a single investigator.

Data Analysis

All values reported are means and SD. Unpaired Student t-tests were used for comparisons of variables between subjects with SDB and subjects without SDB. Univariate associations were evaluated using Pearson correlations. Determinants of PWV as a continuous outcome variable were identified using robust regression models,[25-27] rather than least-squares regression models, to minimize the effects of outliers in the predictor variables, which were centered on their mean values. Because PWV is highly dependent on age, sex, and body size, all models included age, sex, and body-mass index (BMI) as predictor variables. SDB markers that were evaluated as predictor variables were AHI and average nocturnal O_2 saturation; total arousal index was evaluated in an exploratory analysis. Because of skewed distributions and some zero values, AHI and total arousal index were natural log-transformed after adding 3, as described previously.[28] Serum triglycerides concentrations also were natural log-transformed. Statistical analyses were performed using SigmaStat 3.0 (SPSS, Inc., Chicago, IL) and NCSS 2007 (NCSS, LLC. Kaysville, UT; WWW.NCSS.COM, Hintze, J., 2007)

RESULTS

Characteristics of the 153 subjects with analyzable data are in Table 1. As expected, subjects with SDB had higher AHI, lower mean O_2 saturation, and higher total arousal index ($P < 0.001$), as well as higher BMI, waist circumference, glucose, and prevalence of metabolic syndrome ($P < 0.001$). On average, subjects with SDB had mild SDB, based on their AHI and average nocturnal O_2 saturation. Brachial and central systolic, diastolic, mean, and pulse pressures were not significantly different between subjects with and without SDB, likely because 61.2% of subjects with SDB and 32.5% of subjects without SDB were taking antihypertensive medications ($P = 0.014$). However, subjects with SDB had higher triglycerides and lower high-density lipoprotein cholesterol concentrations and used more statin medications. CIMT was higher among those with SDB ($P = 0.030$); however, PWV was not significantly higher among subjects with SDB than those without SDB (9.06 [2.15] vs 8.51 [1.88] m/s, $P = 0.112$).

PWV was correlated significantly with age ($r = 0.61$, $P < 0.001$), brachial systolic pressure ($r = 0.44$, $P < 0.001$), brachial pulse pressure ($r = -0.18$, $P = 0.04$), mean brachial blood pressure ($r = 0.35$, $P < 0.001$), central systolic pressure ($r = 0.48$, $P < 0.001$), pulse pressure ($r = 0.42$, $P < 0.001$), CIMT

(r = 0.26, P = 0.002), and triglycerides concentration (r = 0.24, P = 0.006) but not BMI (r = 0.10, P = 0.250) or waist circumference (r = 0.15, P = 0.072). The markers of SDB—AHI (r = 0.18, P = 0.032) and average nocturnal O_2 saturation (r = -0.24, P = 0.005)—were significantly correlated with PWV. Current, former, and never smokers had similar PWV (P = 0.872). After controlling for age, sex, and BMI, however, neither AHI (P = 0.849) nor average O_2 saturation (P = 0.373) were independent predictors of PWV. The best regression model for predicting PWV (Table 2) had independent contributions of age, central systolic blood pressure, and triglycerides concentration (adjusted $R^2 = 0.46$).

Because of the large number of subjects using antihypertensive medications and the varying effects of different classes of these medications on determinants of PWV such as heart rate, cardiac output, systemic vascular resistance, and arterial compliance,[29] we performed an analysis restricted to the 99 subjects not on antihypertensive medications to see if markers of SDB were associated with PWV. On average, these subjects had mild sleep apnea (AHI 7.4 [8.9] events/h) and a PWV of 8.56 m/s (1.94 m/s). In this subgroup, PWV again was significantly correlated with AHI (r = 0.22, P = 0.032) and average nocturnal O_2 saturation (r = -0.28, P = 0.008). In regression analysis (adjusted $R^2 = 0.47$, Table 3), PWV was independently predicted by BMI (P = 0.041) and the interaction between nocturnal O_2 saturation and age, such that the effect of average nocturnal O_2 saturation on PWV increased with age (P = 0.039). For example, at an age of the 59.3 years, each 1% elevation in average nocturnal O_2 saturation predicted a decrease in PWV of 0.11 m/s. Unlike the average nocturnal O_2 saturation, the AHI did not interact with age in predicting PWV and was not a significant predictor of PWV (P = 0.558) independent of age, sex, and BMI.

In an exploratory analysis, the leg-movement arousal index was strongly correlated with PWV (r = 0.39, P < 0.001), but this relationship no longer was significant after adjustment for age, sex, and BMI (P = 0.637). In subjects not on antihypertensive medications, the leg-movement arousal index correlated significantly with AHI (r = 0.373, P < 0.001) and average nocturnal O_2 saturation (r = -0.21, P = 0.011). The leg-movement arousal index was not an independent predictor of PWV (P = 0.085); however, an interaction with age was identified such that the effect of total arousal index on PWV increased with age (P = 0.041).

Table 1—Subject characteristics

	No SDB[a]	SDB[a]	P Value
Number	70	83	-
Age, y	60.1 (7.3)	62.3 (8.1)	0.085
Male sex	57.1	56.6	0.964
Race/ethnicity			0.613
White	66	80	
Other	1	2	
Native American	0	1	
Asian	3	0	
Smoking status			0.504
Current	15.7	9.6	
Past	37.1	42.2	
Never	47.1	48.2	
AHI, events/h	2.2 (1.3)	17.6 (16.2)	< 0.001
Mean nocturnal SaO_2, %	93.0 (1.4)	91.5 (2.1)	< 0.001
Total arousal index, events/h	12.87 (10.8)	20.07 (18.9)	0.005
Body mass index, kg/m²	27.6 (4.9)	32.0 (6.0)	< 0.001
Waist circumference, cm	92.5 (12.4)	102.5 (13.1)	< 0.001
Serum glucose concentration, mg/dL	100.4 (17.8)	107.9 (20.4)	0.014
Metabolic syndrome	28.6	50.6	0.009
Diabetes mellitus, %	5.7	10.8	0.399
Heart rate, bpm	56.9 (10.1)	58.39 (8.9)	0.347
Blood pressure, mm Hg			
Brachial systolic	127.7 (12.3)	131.2 (16.2)	0.144
Central mean	94.5 (8.2)	95.6 (10.0)	0.481
Central systolic	119.1 (11.8)	122.8 (15.1)	0.100
Central diastolic	77.4 (8.6)	77.1 (9.4)	0.834
Central pulse pressure, mm Hg	41.9 (11.3)	45.7 (13.5)	0.064
Use of antihypertensive medication, %	24.3	44.6	0.014
HDL, mg/dL	61.7 (15.50)	55.3 (13.24)	0.006
Triglycerides, mg/dL	108.2 (70.5)	145.0 (104.9)	0.018
Use of statins, %	20.0	36.1	0.044
CIMT, mm	0.780 (0.189)	0.860 (0.254)	0.030
[b]Pulse wave velocity, m/s	8.51 (1.88)	9.06 (2.15)	0.112

Data are reported as mean (SD) or percentage, unless otherwise indicated. AHI refers to apnea-hypopnea index; HDL, high-density lipoprotein; CIMT, carotid intima-media thickness. [a]Sleep disordered breathing (SDB) is defined as an AHI ≥ 5 events/h; "No SDB" is defined as an apnea-hypopnea index (AHI) < 5 events/h; [b]Data from 138 subjects with analyzable tracings.

DISCUSSION

In this study, we found a non-significantly higher PWV among subjects with SDB compared with those without SDB. Statistically significant, but modest, correlations were observed between PWV and both AHI and average O_2 saturation; however, the only independent predictors of PWV were age, systolic blood pressure, and serum triglycerides concentration. Because many subjects were receiving antihypertensive medications, an analysis restricted to subjects not on these medications showed that that nocturnal O_2 saturation, but not AHI, independently predicted PWV, a finding mediated through an interaction between nocturnal O_2 saturation and aging. Similar findings were observed in an exploratory analysis with the leg-movement arousal index. These findings suggest that changes in aortic stiffness associated with SDB may be present prior to the development of clinical hypertension and that the AHI may not be the best sleep-related predictor of early arterial injury. The interaction between aging and nocturnal O_2 desaturation suggests that the adverse effects of nocturnal O_2 desaturation on PWV are more prominent with aging.

Our findings are concordant with those of the Sleep Heart Health Study,[30] in which the sleep time with O_2 saturation less than 90% predicted incident hypertension. In women and older subjects, the percentage of sleep time with low O_2 satura-

Table 2—Predictors of pulse wave velocity in 138 subjects

Variable	Standardized β Coefficient	P Value
Constant	8.720	< 0.001
Age (per year)	0.128	< 0.001
Sex	0.079	0.727
Body mass index	0.007	0.742
Use of antihypertensive medication	-0.425	0.089
Central systolic blood pressure	0.032	< 0.001
Ln (triglycerides)	0.424	0.019

Robust regression centered model where a pulse wave velocity of 8.72 m/s is expected at a mean age of 61.3 years, sex 0 = female, body mass index = 30.1 kg/m^2, use of antihypertensive medications yes = 1, Ln (triglycerides) = 4.56 mg/dL, and systolic blood pressure = 129.5 mm Hg. Adjusted R^2 = 0.472.

Table 3—Predictors of pulse wave velocity among 99 individuals not on anti-hypertensive medications

Variable	β Coefficient	P Value
Constant	8.402	< 0.001
Age (per year)	0.144	< 0.001
Sex	0.089	0.756
Body mass index (per kg/m^2)	0.060	0.041
Nocturnal oxygen saturation	-0.107	0.223
Nocturnal oxygen saturation * age	-0.019	0.039

Robust regression centered model where a pulse wave velocity level of 8.40m/s is expected with an age of 59.3 years, sex 0 = female, body-mass index = 22.5 kg/m^2, and nocturnal oxygen saturation = 92.7%. Overall model adjusted R^2 = 0.468.

tion predicted incident hypertension better than did increased AHI.[30] Another study demonstrated that the hypoxia index was a better marker of increased left ventricular mass than was AHI, especially in women.[31] In normotensive patients with OSA, changes in aortic distensibility, CIMT, and endothelium-dependent vasodilation have been described before blood pressure reached clinically abnormal values.[17] A recent study showed that individuals with mild to moderate sleep apnea had worse brachial artery reactivity and a higher aortic augmentation index, another marker of arterial stiffness.[32] Our study used a measure of arterial stiffness that is considered the gold standard and is less sensitive to heart rate and loading conditions.[12]

We showed that nocturnal O_2 desaturation, rather than AHI, predicts PWV, an established measure of arterial stiffness significantly associated with future cardiovascular disease events,[12-15] and that arterial abnormalities can be detected in individuals with even mild levels of SDB. We also identified an important interaction with age, such that the effects of SDB on PWV are more marked with aging, corroborating the need for further studies of "age-dependent" versus "age-related" findings in individuals with SDB.[33,34] Interestingly, the best predictor of PWV was the leg-movement arousal index, which includes arousals that may or may not be related to SDB, raising the hypothesis that the pathophysiological consequences of arousal per se, in addition to the sequelae of hypoxia and apnea, may influence arterial function.

Snoring is less prevalent in older patients than in middle-aged adults, and daytime sleepiness among older patients may be mistakenly considered as normal.[35] The mechanisms influencing SDB may be different in older than in middle-aged and younger adults, with different chemoreceptor responses to hypoxia and hypercapnia.[36,37] Since older patients are at higher cardiovascular disease risk and the effect of nocturnal saturation on PWV is greater in older adults, increased surveillance for SDB and more aggressive monitoring for early signs of arterial injury for older individuals appears prudent. Similarly, the age-related effects observed in this study suggest that, if SDB in young adults is treated, arterial injury, including stiffening, hypertension, and their consequences, may be prevented or even reversed. Evaluation of average nocturnal O_2 saturation and total arousal index as indicators of SDB severity and disordered sleep, rather than AHI alone, offers a more comprehensive assessment of the subjects' disease state, complications of SDB, and ultimately cardiovascular disease risk. This study underscores the need for a prospective study of individuals with a wider range of ages and SDB severity looking at cardiovascular disease risk markers and events to help discern the intrinsic effects of aging, risk factors, and SDB on cardiovascular disease risk.[33]

Limitations

Although relatively large compared with those in the published literature, the sample size still was small, relative to the methodological variability in PWV measurements. Statistical power was further limited by the mild degree of SDB among subjects with SDB and the confounding effects of antihypertensive therapy. The duration and severity of SDB of participants likely affected PWV, as did chronic exposure to cardiovascular disease risk factors; however, they were not assessed longitudinally in this cross-sectional study. Because our findings are based on subgroup analysis, they should be considered preliminary. Also, our participants were almost exclusively Caucasian, so these findings may not be generalized to non-white populations. Longitudinal evaluation of these parameters may be better suited for studying current levels of arterial dysfunction. An adequately powered, prospective, randomized clinical trial of continuous positive airway pressure therapy would be needed to address these limitations. Despite these limitations, expected independent predictors of PWV were identified, as were age-related interactions and associations with SDB markers beyond AHI.

CONCLUSION

Nocturnal O_2 desaturation, a marker of SDB, is associated with increased PWV among normotensive individuals. The association between SDB and arterial stiffness is amplified with aging.

ABBREVIATIONS

apnea-hypopnea index, AHI
body-mass index, BMI
obstructive sleep apnea, OSA
pulse wave velocity, PWV
sleep-disordered breathing, SDB

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