Sleep-Disordered Breathing and Cardiovascular Disease in the Bay Area Sleep Cohort

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Study Objectives: To examine the relationship between sleep-disordered breathing (SDB) and cardiovascular disease among community-dwelling older adults. Previous studies have suggested relatively stronger associations between SDB and such morbidity in middle-aged, relative to elderly, populations.

Design: Cross-sectional analysis of an elderly ambulatory, non–clinic-based cohort (Bay Area Sleep Cohort, BASC)

Setting: Community population studied in a sleep laboratory

Participants: One hundred twenty-nine older adults (mean [± SD] age = 72.6 [8.3]) (78 women; 51 men)

Interventions: NA.

Measurements: Complete clinical history including list of current medications, physical examination, selected blood chemistries, multiple blood pressure measurements, 12-lead electrocardiogram, and 2 consecutive nights of polysomnography

Results: Fifty-one individuals (40%) were taking 1 or more cardiovascular medications and 24 (19%) had an apnea-hypopnea index (AHI) of 10 or more per hour of sleep. Cardiovascular medication use was related to cardiac events or procedures, history of angina, higher systolic or diastolic blood pressure, and abnormal electrocardiogram. Logistic regression showed statistically significant association between cardiovascular medication use and AHI of 10 or greater per hour, independent of age, sex, and body mass index. Supplementary analyses indicated that rapid eye movement AHI of 10 or greater per hour was significantly associated with elevated diastolic blood pressure.

Conclusions: The results suggest that sleep-disordered breathing may contribute to increased cardiovascular morbidity in older adults.

Keywords: Sleep-disordered breathing, Cardiovascular disease, Older adults

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CARDIOVASCULAR DISEASES ARE COMMON CAUSES OF MORBIDITY, HOSPITALIZATION, AND MORTALITY AMONG OLDER ADULTS.[1] INTERVENTIONS TO PREVENT MORBIDITIES AND MORTALITIES ASSOCIATED with cardiovascular diseases have focused on lifestyle modifications such as dietary management, exercise, and cessation of smoking and pharmacologic treatment of risk factors and existing cardiovascular disease (CVD).[2-4] Although a decline in prevalence of morbidity and mortality due to these diseases has been reported,[5-7] CVD still remains the number 1 cause of hospitalization and mortality.[1] Sleep-disordered breathing (SDB), characterized by repetitive apnea and hypopnea during sleep associated with oxygen desaturation, arousals, and awakenings[8] is a common disorder among older adults.[9,10] Previous reports have showed independent associations between CVD and SDB,[11-14] but these associations were stronger among middle-aged adults, implying that the relationship between SDB and CVD among the elderly may not be as important. In this study, we present data bearing upon the relationship between SDB and CVD derived from an elderly cohort (Bay Area Sleep Cohort, BASC).

METHODS

Study Participants

The BASC is a community-based, nonclinic, convenience sample of middle-aged and elderly subjects (n=256) who were recruited for studies of sleep and aging between the years of 1974 and 1985. All participants gave informed consent and the study was approved by the Stanford University Institutional Review Board. Participants were recruited via advertisements in senior citizen centers, small-circulation newspapers, and word of mouth. They resided in the midpeninsula area south of San Francisco. The population from which BASC was sampled was an upper-middle-class, predominantly Caucasian population (1.2% Hispanic, 2.0% Asian), which was representative of the population of Santa Clara and San Mateo counties in the mid-1970s. Inclusion criteria at baseline included willingness to spend at least 1 night in the sleep laboratory and relatively good self-reported health; individuals with known cancer or overt cardiac or cerebrovascular disease were excluded. Subjects with highly prevalent conditions in the aged population, such as hypertension and arthritis, were included. No attempt was made to exclude subjects who experienced poor sleep. Details of subjects responding to advertisements but not meeting these criteria are not available.

Disclosure Statement

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Table 1—Comparison of Baseline Data on BASC Subjects Included and Not Included in Current Study

Variable	*Study participants*		*Comparison*
	Included (n = 129)	**Not included** (n = 127)	
Age at entry, y	63.9 ±8.9	66.4 ± 9.4	t = 2.24, P = 0.026
Men, %	39.5	25.2	χ^2 = 6.00, P = 0.014
College degree, %	62.2	37.8	χ^2 = 1.15, P = 0.283
Married or cohabiting, %	68.4	31.6	χ^2 = 2.65, P = 0.104
TST, min[a]	398.9 ± 81.1	376.2 ± 83.8	t = 2.04, P = 0.043
Sleep latency, min[a]	29.6 ± 41.7	45.7 ± 46.8	t = 2.65, P = 0.009
Awakenings per night, no.[a]	2.2 ± 1.3	2.4 ± 1.4	t = 0.67, P = 0.500
Blood pressure			
Systolic	137.0 ±18.8	140.4 ± 20.1	t = 1.18, P = 0.240
Diastolic	80.2 ± 11.5	80.5 ± 10.3	t = 0.18, P = 0.856
Using cardiovascular medications, %	16.3	26.8	χ^2 = 4.18, P = 0.041
Apnea Hypopnea Index[b]	4.2 ± 8.3	4.7 ± 11.1	t = 0.34, P = 0.733

Data are presented as mean ± SD unless otherwise indicated. TST refers to total sleep time.
[a]By history.
[b]Oxygen saturation was not measured during baseline sleep study.

Beginning in 1987, BASC was converted to a prospective cohort study, and subjects have been followed intermittently since that time. The data reported upon in this report were all based on the initial follow-up examination conducted between 1987 and 1992. At the time of this follow-up, 129 BASC subjects (51 men, 78 women), representing about 50% of the baseline sample of BASC, were studied, ranging in ages from 49 to 95 years (mean ± SD = 72.6, ± 8.3). Follow-up was limited to those BASC participants who survived and were willing to continue in the study. Table 1 compares baseline characteristics of those 129 individuals in BASC who participated in the 1987 to 1992 round of data collection to the 127 individuals in BASC who were not willing or unable to participate. BASC members who participated in this round of follow up were significantly younger and more likely to be men. Included subjects were likely to be slightly better sleepers. They did not differ in their apnea-hypopnea index (see below), and they were less likely to be using cardiovascular medications. Measured baseline blood pressures did not differentiate the groups.

Procedures

During the 1987to 1992 follow-up, BASC subjects participated in a number of procedures, including 2 consecutive nights of in-lab polysomnography; a complete review of systems, medical history, and current medication use; measurements of height and weight; a 12-lead electrocardiogram (ECG); fasting blood samples (obtained the morning after the first night in the lab); and multiple measurements of blood pressures made at different times of day. A total of 4 blood pressure measurements were made by trained technical staff. Measurements were made with subjects in the seated position on each of the 2 evenings in the sleep lab and then repeated with the subject in the seated position immediately upon awakening in the morning. A final fifth blood pressure in seated position was taken by a physician during an afternoon examination between the first and second nights in the sleep laboratory.

Polysomnography was performed with Grass Model 78 polysomnographs (Grass Instruments, Quincy, MA) and scored on paper by trained technologists not familiar with subjects' clinical findings. We employed multiple channels for electroencephalography, electrooculography, surface mentalis electromyography, respiratory airflow (thermistors), abdominal and thoracic respiratory efforts (piezoelectric sensors), pulse oximetry, single-lead (modified lead II) ECG, and bilateral anterior tibialis electromyography. Sleep architecture, allowing for discrimination of rapid eye movement (REM) and non-REM sleep, was scored with conventional criteria.[15] Breathing disturbance in sleep was quantified as the apnea hypopnea index (AHI), with apneas classified by a cessation of breathing and hypopneas classified by a reduction in airflow of at least 50% from the immediately preceding baseline associated with oxygen desaturation of 4% or greater, or arousals accompanying each event. For supplementary analyses, we also examined rapid eye movement (REM) AHI, which was calculated as the number of events in stage REM sleep divided by total time asleep in stage REM, corrected to an hourly basis. Finally, we examined the number of desaturations, defined as the number of drops in oxygenation of 4% or greater per hour of sleep. We did not record upper airway flow limitation (via a nasal pressure transducer), as these studies were conducted before upper airway resistance syndrome was described. Data from the 2 nights in the sleep laboratory were averaged and each subject's mean values were used for all polysomnographic data analyzed, except in 6 cases that were studied for only 1 night or who had very short total sleep times on 1 of the 2 nights (less than 60 minutes), for whom single night data were used.

Data collected relevant to cardiovascular status included history of cardiovascular disease (i.e., history of myocardial infarction, coronary artery bypass surgery, coronary angioplasty, history of cerebrovascular accidents), medication use, and angina pectoris using a standardized angina questionnaire.[16] Information about use of medications was obtained by self-report and confirmed during the in-person evaluation period when the

Table 2—Selected Characterization of Study Participants by Cardiovascular Medication Use

Variable	Cardiovascular medication use		P value[a]
	No (n = 78)	Yes (n = 51)	
Age, y	71.7 ± 8.1	73.9 ± 8.3	0.128
Women, %	62	59	0.758
Cardiovascular event or procedure, %[b]	4	33	0.0001
Angina, %[b,c]	4	14	0.041
BMI, kg/m^2	24.9 ± 4.1	25.7 ± 5.8	0.378
Systolic or diastolic hypertension, %[d]	19	39	0.013
Fasting blood glucose, mg/dL	99.4 ± 19.0	107.6 ± 31.6	0.069
Abnormal ECG, %[e]	32	73	0.001
AHI	5.2 ± 9.5	9.3 ± 13.1	0.062
ODI	1.1± 2.4	3.4 ± 7.5	0.013
AHI ≥ 10, %[f]	12	29	0.011

Data are presented as mean ± SD unless otherwise indicated. BMI refers to body mass index; ODI, oxygen desaturation index (the number of oxygen desaturations ≥ 4% per hour of sleep).
[a]Comparisons employed 2-tailed t-tests for continuous measures and $\chi 2$ for categorical measures.
[b]By history.
[c]As determined by response to the Rose questionnaire.
[d]Systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.
[e]Includes atrial fibrillation, t-wave abnormalities, atrioventricular block, or left-axis deviation.
[f]AHI (apnea-hypopnea index) is defined as the number of apnea and hypopnea events per hour of sleep.

subjects were in the sleep laboratory. Subjects taking antihypertensive agents (hydrochlorothiazide, β-blockers, α-blockers, calcium-channel blockers, or angiotensin-converting enzyme inhibitors), lipid-lowering agents, nitrates, diuretics, or drugs for cardiac arrhythmia, including digitalis preparations, were all considered positive for use of cardiovascular medications. Aspirin was not considered a cardiovascular medication in this study. A standard 12-lead ECG was interpreted by a board-certified cardiologist not familiar with polysomnographic or other clinical results. All ECGs were Minnesota coded[16] for atrial fibrillation (8-3), left axis deviation (2-1), T-wave abnormalities (5-1 to 5-4), and atrioventricular conduction defects (6-1 to 6-5 and 7-1 to 7-6). Morning blood samples were analyzed for fasting glucose, fibrinogen, triglycerides, and lipids, including high- and low-density lipoprotein cholesterol levels.

Statistical Analysis

Independent t tests and χ^2 tests were used to compare continuous and categorical clinical characteristics, respectively, in study participants with an AHI of 10 or greater (SDB) and less than 10 (no SDB) per hour of sleep. Multivariate logistic regression analysis was performed to determine independent associations between SDB status and covariates of interest. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Men and women did not differ significantly in age, body mass index, or systolic or diastolic blood pressures. There was also no statistically significant difference between the two genders in the proportion of individuals currently using cardiovascular medications, endorsing history of cardiovascular disease, or demonstrating abnormal ECGs. Men had significantly higher AHIs than women (mean ± SD, 11.5 ± 15.3 vs 3.7 ± 5.5, t = 3.5, P = 0.001), but there was no difference in REM AHI between sexes (9.0 ± 13.5 vs 8.7 ± 14.6, NS).

Analysis of blood pressure measurements indicated very high generalizability for both systolic and diastolic blood pressures across the 5 measurements, with α coefficients of 0.87 for systolic and 0.85 for diastolic values. Despite these stable individual differences, evening systolic blood pressures were consistently lower than morning systolic blood pressures (mean ± SD, 131.4 ± 15.8 mm Hg vs 135.6 ± 17.5 mm Hg for first night; 131.6 ± 16.0 vs 136.9 ± 19.7 for second night; t = 3.09, P < 0.003 and t = 3.06, P < 0.003, respectively). A similar pattern was seen for diastolic blood pressures for the second night (mean ± SD 73.6 ± 9.3 vs 76.4 ± 10.1; t = 3.56, P < 0.001) but not for the first night (75.5± 10.3 mm Hg vs. 76.4 ± 11.2, t = 1.02, P = 0.310). Because of the high α coefficients, we calculated simple (unweighted) means to derive a systolic and diastolic blood pressure for each participant that were then used in further analyses.

Table 2 compares subjects using (n = 51) and not using (n = 78) cardiovascular medications. Most measures of cardiovascular disease (relevant medical history, Rose angina questionnaire, blood pressure, abnormal ECG) differentiated the 2 groups, but there were no significant differences in serum-derived measures (not shown) with the exception of a trend for fasting glucose to be higher in those individuals taking cardiovascular medications. Of note, is that individuals receiving cardiovascular medications had a higher prevalence of systolic (39% vs 19%; χ^2 = 6.015, P = 0.014) and marginally higher prevalence of diastolic 10% vs 3%; χ^2 = 3.121, P = 0.077) hypertension, suggesting that optimal blood pressure was not achieved routinely in these subjects. Similar findings were obtained when individuals specifically taking antihypertension medications were compared with those not taking these medications. Table 2 also indicates that

Table 3—Selected Demographic and Clinical Characteristics of Subjects by AHI Status

Variable	AHI		P value
	< 10 (n = 105)	≥ 10 (n = 24)	
Age, y, no. (%)			0.020
< 60	4 (80)	1 (20)	
60-75	67 (89)	8 (11)	
≥ 75	34 (69)	15 (31)	
Sex, %			0.011
Women	66	38	
Men	34	62	
BMI, kg/m^2	25.5 ± 5.1	24.3 ± 3.2	0.271
History of cardiovascular disease, %	13	25	0.154
Cardiovascular medication use, %	34	63	0.011
HDL, < 40 mg/dL,%	11	29	0.027
Abnormal ECG, %	35	40	0.715
AHI	2.5 ± 2.4	25.5 ± 14.8	<0.001
ODI	0.59 ± 1.3	8.3 ± 9.5	<0.001

AHI refers to apnea-hypopnea index (the number of apneas and hypopneas per hour of sleep); BMI, body mass index; HDL, high-density lipoprotein; ECG, electrocardiogram; ODI, oxygen desaturation index (the number of oxygen desaturations ≥ 4% per hour of sleep).

[a]Comparisons employed 2-tailed t-tests for continuous measures and χ^2 for categorical measures.

[b]Includes history of myocardial infarction, coronary artery bypass graft surgery, coronary angioplasty, and cerebrovascular accidents.

[c]Includes atrial fibrillation, t-wave abnormalities, atrioventricular block, and left axis deviation.

Table 4—Multivariate Logistic Regression Predicting AHI ≥ 10

Variable	β coefficient	P value	OR	CI
Sex				
Female = 0				
Male = 1	1.050	0.043	2.858	1.035-7.893
Age, 1-y increment	0.059	0.062	1.061	0.997-1.130
BMI, 1-unit increment	-0.036	0.597	0.965	0.846-1.101
Cardiovascular medication use				
No = 0				
Yes = 1	1.070	0.033	2.916	1.092-7.788
HDL level				
≥ 40 mg/dL = 0				
< 40 mg/dL = 1	0.549	0.368	1.731	0.525-5.711

Hosmer and Lemeshow Test P = 0.701.

AHI, apnea-hypopnea index (the number of apneas and hypopneas per hour of sleep); OR, odds ratio; CI, confidence interval; BMI, body mass index (in kg/m^2); HDL, high-density lipoprotein.

measures of sleep apnea were related to cardiovascular medication use in BASC.

Table 3 examines bivariate relationships between SDB (defined as AHI ≥ 10 per hour of sleep) and demographic and cardiovascular measures. Subjects with SDB were older, more likely to be male, have lower high-density lipoprotein levels and more likely to be receiving cardiovascular medications. These relationships were examined in a logistic regression model (Table 4), which showed a significant relationship between SDB and cardiovascular medication use independent of age, sex, and body mass index. Because several different definitions of AHI have been proposed,[17] we also examined how SDB was related to cardiovascular medication use in alternative logistic models paralleling those presented in Table 4. Specifically, cases with AHI values of 10 or greater and relying on arousals alone (n = 21/129) (odds ratio [OR] = 3.71 [1.27-10.85]), hypopneas with desaturations of 4% or greater (n = 18/129) (OR = 3.49 [1.15- 10.54]), or breathing events without reference to arousals or desaturations (n = 31/129) (OR = 3.02 [1.36-9.01]) were all predicted by cardiovascular medication use, suggesting relative robustness of this finding.

Finally, because recent data have suggested that isolated systolic hypertension may be unrelated to AHI regardless of age, and that relationships between systolic or diastolic hypertension and AHI were present only in individuals younger than 60 years,[13] we more closely examined a potential relationship between blood pressure and AHI. In these analyses, we examined AHI for the entire night, as well as AHI occurring specifically during REM sleep (REM sleep is the stage of sleep associated with maximal autonomic reactivity[18]). For whole-night AHI, we found no relationships with either blood pressure measure, even after stratifying participants by blood pressure medication status (those taking and not taking antihypertension medications). However, the proportion of individuals whose diastolic blood pressure was 90 mmHg or greater was significantly higher for the group with a REM AHI of 10 or greater versus the group with a REM AHI less than 10 (Fisher exact test = 5.19, P = 0.043). No difference was seen for systolic blood pressure of 140 mmHg or higher. There was also a trend for subjects with a REM AHI of 10 or more to be more likely to have T-wave abnormalities on ECG, relative to those with a REM AHI of less than 10 (P = 0.139).

DISCUSSION

This cross-sectional study of an elderly, community-dwelling cohort showed associations between SDB and cardiovascular morbidity that were independent of age, sex, and body mass index. In our study, we employed use of cardiovascular medication as a broad-based marker for CVD. Although individuals who used such medications were also more likely to have history of cardiovascular events or procedures and angina, medication-based definitions of CVD relying on reported cardiovascular medication use may afford higher validity than reported medical history. For example, analyses from the Behavioral Risk Factors Survey and the Nurses Health Study have shown that events such as reported myocardial infarct, stroke, cardiac bypass surgery and even hypertension tend to be underestimated in community-based surveys.[19-21] In contrast, pharmacy and medical records indicate that cardiovascular medications, including nitrates, β blockers, and angiotensin-converting enzyme inhibitors, are reported far more accurately when compared with other classes of medication, including insulin, narcotics or nonsteroidal antiinflammatory medications.[22] These

recent data from managed care organizations confirmed earlier reports suggesting far more accuracy in the report of cardiovascular medications when compared to sedative-hypnotics,[23] daily aspirin use,[24] or even hormone replacement therapy.[25] The fact that individuals in our population receiving such medications also had significantly higher systolic and diastolic blood pressures is not at all unusual in community-based studies[20, 21] and may serve to underscore the strength of the associations that we have reported here.

Our data contrast to some degree with recent reports from the Sleep Heart Health Study (SHHS), a very large composite cohort examining cardiovascular risk factors in relation to polysomnographically assessed SDB. Results from SHHS have suggested age dependence in characterizing relationships between SDB and hypertension,[11,13] apolipoprotein ε4 genotype,[26] high-density lipoprotein and triglycerides,[14] stroke,[12] and endothelial function[27] in that relationships were stronger in younger subjects relative to older subjects. We have no ready explanation for the discrepancy between our results with BASC and those of the SHHS. Despite being elderly, there is no reason to suspect that BASC subjects were particularly predisposed to CVD, and the prevalence of history of CVD in our much smaller cohort was comparable with that of the SHHS (15.5% in BASC, 15.9% in SHHS[12]). It is possible that, when examined for the 1987-1992 follow-up, BASC subjects were less influenced by selective survivorship. Longitudinal data may represent a partial, but not total, solution to understand more completely survivorship bias in studies of SDB.

Of note in our study is that, although our whole-night AHI measure was unrelated to measured blood pressures, we noted an association between REM AHI of 10 or greater and diastolic hypertension. These findings parallel the recent work by Hass et al[13], who have shown that (whole-night) AHI is unrelated to isolated systolic hypertension but is related to systolic or diastolic hypertension, a finding that is compatible with the known physiology of elevated sympathetic tone documented to accompany SDB.[18] That study also reported that such relationships between hypertension and SDB did not occur in individuals over the age of 60, compatible with the age-dependence mentioned above. Hass et a[13] did not note whether the relationships observed were more pronounced in association with SDB occurring in REM sleep, though, given the vulnerability of REM sleep as a time of intense autonomic activation,[28] such associations would not be unanticipated at the population level. It is interesting to note that increased blood pressure during REM sleep has been reported in children with SDB. In the pediatric age group, SDB is also reported to occur predominantly in REM sleep, and, given the proportion of REM sleep in this age group, the finding of increased blood pressure during this period may have significant adverse consequences.[29,30] Whether a specific focus on correlates of SDB during REM sleep might be particularly revealing for other comorbidities in older populations remains uncertain, though age-dependent changes in REM sleep are widely acknowledged.[31]

One limitation of our study is small sample size and, consequently, limited power and possible type II error. This may be one reason for the lack of relationship between AHI and measured blood pressures in this cohort, but similar results have been reported among older adults by other groups using a much larger data set (SHHS).[11,13] Although use of blood pressure medication may confound the relationship between AHI and measured blood pressure, we did not find any significant association between these variables even after stratifying by status of blood pressure mediation use. One obvious shortcoming with regard to blood pressure measurement in both the current study and previous studies is that wake-time blood pressure was utilized to determine the relationship between AHI and hypertension. It is possible that sleep-time blood pressure may be elevated or not show the normal decline (nondipping pattern) in older adults with SDB.[32] Previous studies have shown significant association between nondipping sleep-time blood pressure pattern and increased cardiovascular morbidity.[33]

In summary, in contrast with previous studies, the results of our study leave open the possibility that SDB may contribute to increased cardiovascular morbidity in the elderly.

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