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Longitudinal Association of Sleep-Disordered Breathing and Nondipping of Nocturnal Blood Pressure in the Wisconsin Sleep Cohort Study

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Study Objectives: The association of sleep-disordered breathing (SDB) and blunting of normal nocturnal lowering of blood pressure (BP) (nondipping) has only been examined cross-sectionally. The purpose of this study is to investigate whether SDB is prospectively associated with nondipping.

Methods: The longitudinal association between SDB and incident nondipping was examined in a subsample of 328 adults enrolled in the Wisconsin Sleep Cohort Study who completed 2 or more 24-hour ambulatory BP studies over an average of 7.2 years of follow-up. SDB identified by baseline in-laboratory polysomnography was defined by apnea-hypopnea index (AHI) categories. Systolic and diastolic nondipping was defined by systolic and diastolic sleep-wake BP ratios > 0.9. All models were adjusted for age, sex, body mass index at baseline and follow-up, smoking, alcohol consumption, hypertension, sleep time, length of follow-up time, and antihypertensive medication use.

Results: There was a dose-response increased odds of developing systolic nondipping in participants with SDB. The adjusted odds ratios (95% confidence interval) of incident systolic nondipping for baseline AHI 5 to < 15 and AHI ≥ 15, versus AHI <5, were 3.1 (1.3-7.7) and 4.4 (1.2-16.3), respectively (P trend = 0.006). The adjusted odds ratios (95% confidence interval) of incident diastolic nondipping for corresponding SDB categories were not statistically significant: 2.0 (0.8-5.6) and 1.3 (0.2-7.1).

Conclusions: Our longitudinal findings of a dose-response increase in development of systolic nondipping of BP with severity of SDB at baseline in a population-based sample provide evidence consistent with a causal link. Nocturnal systolic nondipping may be a mechanism by which SDB contributes to increased cardiovascular disease.

Keywords: sleep apnea, cardiovascular disease, nondipping

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BLOOD PRESSURE (BP) NORMALLY VARIES DURING DIFFERENT PHYSIOLOGIC STATES AND DECLINES BY 10% TO 20% AT NIGHTTIME DURING SLEEP, compared with BP at daytime during wakefulness.[1,2] A nocturnal BP decrease less than 10% of daytime BP is defined as "nondipping."[1,2] Nondipping has been described in patients with refractory or malignant hypertension, pheochromocytoma, cardiac transplantation, congestive heart failure and, chronic renal insufficiency.[3-8] Nondipping has also been shown in patients with clinically symptomatic obstructive sleep apnea, regardless of hypertension status.[9] This nondipping has been described as a marker for future development of hypertension in those who are normotensive at baseline. In patients with hypertension, nondipping has been associated with worse cardiovascular prognosis and increased target organ damage, including left ventricular hypertrophy, microalbuminuria, myocardial infarction, angina, ischemic stroke, and cardiovascular death.[10-20]

Sleep-disordered breathing (SDB) has been associated with hypertension and cardiovascular disease (CVD) in several population-based studies.[21-24] Researchers postulate that nocturnal BP elevations during apneic episodes, possibly secondary to increased sympathetic activity from arousals or hypoxia, may result in a higher occurrence of nondipping in those with SDB. Since nondipping has been implicated in increased CVD and end-organ disease, the increased prevalence of nondipping in SDB has been postulated as one of the mechanisms by which SDB contributes to increased CVD.[25]

Currently, data on the association of SDB and nocturnal nondipping are limited mostly to cross-sectional studies of patients with sleep apnea syndrome.[5,26-28] Cross-sectional associations of SDB and nondipping suggest, but cannot provide conclusive evidence for, a causal role of SDB in nondipping. Therefore, we performed longitudinal analyses of 24-hour ambulatory BP recordings on a sample of Wisconsin Sleep Cohort Study participants to investigate whether SDB is prospectively associated with the development of nocturnal nondipping over a 7.2 years average follow-up period. We also examined the effects of potential confounding or interacting factors including age, sex, body mass index (BMI) at baseline and at follow-up; current smoking, alcohol consumption, hypertension, habitual sleep time, reported sleepiness from the baseline visit; time interval between baseline SDB and follow-up 24-hour BP measurements; self-reported continuous positive airway pressure (CPAP) use, history of physician-diagnosed CVD (myocardial infarction, congestive heart failure, or cerebrovascular accidents) at baseline and follow-up; and antihypertensive medication use at any time during the follow-up time period.

Disclosure Statement

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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METHODS

Study Sample

Informed consent documents and study protocols, described in detail previously,[29] for the ongoing Wisconsin Sleep Cohort Study were approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board. Briefly, the study sample consisted of a probability sample of employees of 4 Wisconsin state agencies, aged 30 to 60 years, invited to undergo an overnight study protocol at baseline and follow-up studies at 4-year intervals. The Cohort was initiated in 1989 and has provided the opportunity for adding ancillary studies. In this study, a protocol for 24-hour ambulatory BP monitoring (ABPM) was added to the overnight sleep-study protocol in 1991 with sequential enrollment. From a total of 491 participants with baseline ABPM studies, 328 men and women successfully completed 2 or more 24-hour ABPM follow-up studies. Reasons for lack of follow-up data on the remaining 163 subjects with baseline data only included refusal (mostly due to inconvenience), laboratory scheduling difficulties, and inadequate data.

Of the 328 subjects with multiple studies, we excluded those whose follow-up period was less than 3 years (n = 18). We then excluded participants who were on antihypertensive medications or were nondippers at their baseline ABPM study (assessed separately for systolic and diastolic analyses) to create an inception cohort, free of the condition of nocturnal BP nondipping, to follow for the development of new nondipping over a range of 3 to 13.2 years. According to these criteria, 83 participants were excluded from the systolic analyses, and 68 were excluded from the diastolic analyses. The remaining sample comprised 227 subjects to follow for development of systolic BP nondipping and 242 to follow for development of diastolic BP nondipping.

Sleep studies were conducted at the University of Wisconsin, General Clinical Research Center, in a sleep-laboratory suite with home-like bedrooms. Data collection relevant to this analysis included 24-hour ABPM, body habitus measurements, a detailed medical and health history questionnaire, and overnight polysomnography.

Data Collection

Sleep Study

Full overnight in-laboratory 18-channel nocturnal polysomnography was performed, and sleep stages were identified using standard methods.[30] SDB was summarized by the apnea-hypopnea index (AHI, the average number of apnea and hypopnea events per hour of sleep). Apnea was defined as a complete cessation of airflow for longer than 10 seconds at the mouth and nose, and hypopnea as a decrease in respiratory effort with a greater than 4% drop in Sao_2. Three SDB severity levels, representing typical clinical cutpoints, were examined: no or minimal SDB (AHI < 5), mild SDB (AHI 5 to < 15), and moderate to severe SDB (AHI ≥ 15).

24-Hour ABPM

Typically, the baseline 24-hour ABPM was performed within 6 weeks (mean: 11, SD = 8 weeks) following the overnight sleep study, with the Accutracker II (SuntechMedical Instruments/ Eutectics Electronics, Raleigh, NC), a 24-hour BP monitoring device that uses a modified auscultatory method. Details of the study protocol and ABPM quality data have been previously published.[23] ABPM readings were obtained at random intervals averaging every 15 to 20 minutes during wakefulness and every 30 minutes during sleep. Activity, posture, bedtime, and time on awakening from sleep were recorded by participants on diaries. ABPM data were edited using predetermined established criteria.[23]

Individual mean BPs were computed by averaging ABPM measurements during sleep and wake defined by participants' recorded sleep and wake times, not by preset nighttime and daytime cutoffs. Systolic BP nondipping is defined as mean systolic sleep BP/mean systolic wake BP ratio greater than 0.9. Diastolic BP nondipping is defined similarly using mean diastolic sleep and wake BP. New incidence of BP nondipping status was prospectively examined with 227 participants for systolic BP and 242 for diastolic BP over the entire follow-up time period. An outcome variable was created to represent no change in dipping status (no development of nondipping over the entire follow-up) or incident nondipping (development of nondipping during any subsequent follow-up visit). Those individuals who fluctuated between dipping, nondipping, and dipping again were excluded (n = 7 for systolic BP and n = 3 for diastolic BP). Of the 220 remaining participants examined for systolic BP, 141 had 1 follow-up ABPM study, 69 had 2 follow-up studies, and 10 had 3 follow-up studies. Of the 239 participants examined for diastolic BP, 155 had 1 follow-up ABPM study, 68 had 2 follow-up studies, and 16 had 3 follow-up studies. The mean follow-up period and range for each AHI category were similar: 7.1 (3.1-13.2) years for AHI 0 to 5, 7.5 (3.2-12.6) years for AHI 5 to < 15, and 7.2 (3.0-11.3) years for AHI ≥15, indicating that a potential bias due to unequal follow-up periods by SDB status was unlikely. However, a variable for the follow-up interval was used in all analyses to account for individual differences.

Other Data Collection

BMI was calculated from measured body weight and height (kg/m^2) at both baseline and follow-up study. Participants completed a questionnaire on the night of the sleep study regarding the following covariates: current smoking, alcohol consumption (number of alcoholic drinks per week), use of CPAP for 4 or more nights per week, sleepiness (based on response to the question "Many people have periods of low energy or fatigue, but, during a typical day, do you experience excessive sleepiness when it is difficult to fight an uncontrollable urge to fall asleep?"), antihypertensive medication use, and reported usual sleep duration on weekdays and weekends. Habitual sleep time in hours was calculated as the weighted average of weekday and weekend sleep time (i.e., [5 × weekday + 2 × weekend]/ 7). A variable was created to represent any new antihypertensive medication use over the course of the study. Hypertension was

Table 1—Comparison of Baseline Characteristics of Participants Who had Repeat 24-Hour BP Studies Versus All Those Eligible in the Sample for Longitudinal Data Analysis

Characteristic	Baseline Sample	
	With follow-up 24-h BP data (n = 328)	Overall (n = 491)
Mean age, y	49.4	49.4
Male sex, %	62.5	59.8
Mean BMI, kg/m^2	29.3	29.9
Current smoker, %	16.8	16.7
Mean alcohol consumption, number of drinks/wk	3.7	3.8
Antihypertensive medication users, %	15.5	15.9
Median AHI, events/h	1.7	1.5
AHI ≥ 15 events/h, %	9.2	9.9
Nondipping systolic BP, %	14.6	18.2
Nondipping diastolic BP, %	7.3	9.8

BP refers to blood pressure; BMI, body mass index; AHI, apnea-hypopnea index.

defined as systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg, as measured in the overnight laboratory or as use of antihypertensive medication.

Data Analysis

Logistic regression was performed to estimate odds ratios (OR) and 95% confidence interval (CI) for the relationship between SDB and incident nondipping over an average of 7.2 years follow-up, for systolic nondipping and diastolic nondipping separately. In addition to baseline AHI, the models included the following covariates: age, sex, BMI, current smoking, hypertension, and alcohol consumption based on data from baseline visit, BMI at follow-up, follow-up time between baseline SDB and follow-up 24 hour BP measurements, habitual sleep time, and whether or not an individual was on antihypertensive medication ever during the follow-up time period. We investigated potential confounding factors and interactions of the covariates and SDB, including an interaction term for AHI severity level and sleepiness. Finally, we analyzed additional models: (1) with and without participants who were on antihypertensive medications at any subsequent visits during the follow-up period(n = 42), (2) with and without participants who reported they used CPAP (n = 11) to investigate the effect of use of antihypertensive medication or CPAP on the association between SDB and development of nondipping, and (3) with and without those with history of physician-diagnosed myocardial infarction, congestive heart failure, or cerebrovascular accidents at baseline and follow-up.

All analyses were performed with SAS software, release 9.1.[31] Logistic regression model coefficients were assessed by Wald χ^2 tests, and 2-tailed P values of < 0.05 indicated statistical significance. SDB severity was entered as a categorical variable, except when testing for trend.

Table 2—Study Sample Characteristics Stratified by AHI Severity (n = 328)

Baseline Characteristic	AHI Category		
	< 5	5-15	≥ 15
Age, y	48 (8)	52 (8)	52 (8)
Male sex, %	56	72	91
BMI, kg/m^2	28 (5)	31 (5)	34 (5)
Current smoker, %	15	23	19
Alcohol, number of drinks/wk	3 (5)	4 (6)	5 (8)
Antihypertensive medication users, %	13	23	22
Median AHI, events/h	0.8	8.2	26.2
Nondipping systolic BP, %	13	20	19
Nondipping diastolic BP, %	6	6	16

Data are presented as mean (SD) or percentage; apnea-hypopnea index (AHI) is presented as median. BP refers to blood pressure.

RESULTS

Table 1 shows the key descriptive statistics for the respondents in the study sample with follow-up 24-hour BP data (n = 328) versus the total eligible sample (N = 491). There were no substantial differences in the main predictor and outcome variables between the two groups except for a higher percentage of baseline systolic nondipping in the total sample. Table 2 depicts the baseline participants' characteristics and covariates used in the analyses stratified by AHI category.

Over the follow-up period of an average of 7.2 years, 18% developed systolic nondipping and 11% developed diastolic nondipping. SDB severity at baseline was significantly associated with the onset of nondipping in systolic BP. Table 3 shows the unadjusted and adjusted ORs for development of both new systolic and new diastolic nondipping in AHI 5 to <15 and AHI ≥ 15 versus AHI < 5. Relative to AHI < 5, the association with systolic nondipping was seen for AHI 5 to <15 and for AHI ≥ 15 in a dose-response fashion: the ORs (95% CI) adjusted for age, sex, BMI, current smoking, hypertension, and alcohol consumption at baseline visit, BMI at follow-up, time between baseline SDB and follow-up 24 hour BP measurements, habitual sleep time, and ever having been on antihypertensive medication were 3.1 (1.3, 7.7) and 4.4 (1.2, 16.3), respectively (P trend = 0.006). Removing participants who reported CPAP use (n = 11) showed no significant difference: the ORs for incident systolic BP nondipping over an average of 7.2-years-follow-up period were 2.7 (1.1, 6.8) and 4.3 (0.9, 19.8) for AHI 5 to < 15 and AHI ≥ 15 versus AHI <5, respectively. In addition, excluding those who reported antihypertensive medication use at any visit (n = 42) did not substantially change ORs for systolic nondipping; 3.3 (1.1, 9.5) and 6.1 (1.2, 29.9) for AHI 5 to <15 and AHI ≥ 15 versus AHI < 5, respectively. Removing participants with reported CVD (n = 8) (myocardial infarction, congestive heart failure and strokes) did not change the results significantly: the ORs for developing new systolic BP nondipping for AHI 5 to < 15 and AHI ≥ 15 versus AHI < 5 in those with no CVD were slightly higher at 3.9 (1.5, 10.1) and 4.6 (1.2, 18.3), respectively.

In the analysis of diastolic nondipping, there was no dose-response relationship seen with increased SDB severity: com-

Table 3—The Association of Sleep-Disordered Breathing with Incident[a] Systolic and Diastolic Nondipping Over an Average of 7.2-Year Follow-Up Period

AHI Category	Total sample overall, no.	Incident nondipping, no. (%)	OR (95% CI)	
			Unadjusted	Adjusted[b]
Systolic Nondipping (n = 220)				
< 5	162	22 (13.5)	1.0 (reference)	1.0 (reference)
5 to < 15	39	12 (30.8)	2.8 (1.3, 6.4)	3.1 (1.3, 7.7)
≥ 15	19	6 (33.3)	2.9 (1.0, 8.5)	4.4 (1.2, 16.3)
Diastolic Nondipping (n = 239)				
< 5	175	18 (10.3)	1.0 (reference)	1.0 (reference)
5 to < 15	43	9 (20.9)	2.3 (1.0, 5.6)	2.0 (0.7, 5.6))
≥ 15	21	3 (14.3)	1.5 (0.4, 5.4)	1.1 (0.2, 6.3)

AHI refers to apnea-hypopnea index; OR, odds ratio; CI, confidence interval.
[a]Among participants with baseline normal blood pressure (BP) dipping and no use of antihypertensive medication, followed over an average of 7.2 years.
[b]All models adjusted for age, sex, body mass index at baseline and follow-up, current smoking, hypertension, habitual sleep time and alcohol consumption from the baseline visit; time between baseline SDB and follow-up 24-h BP; and whether or not an individual was on antihypertensive medication ever during the follow-up time period.

pared to AHI < 5, AHI 5 to < 15 and AHI ≥ 15 had a similar unadjusted risk of developing new diastolic nondipping: 2.3 (1.0, 5.6) and 1.5 (0.4, 5.4), respectively, and a similar adjusted risk of developing new diastolic nondipping: 2.0 (0.7, 5.6) and 1.1 (0.2, 6.3), respectively.

We did not find any interactions between SDB and our covariates, including reported sleepiness and baseline hypertension status. The effect of SDB on developing systolic and diastolic nondipping was the same for sleepy versus nonsleepy participants and for those who were hypertensive versus normotensive. We also examined the change in AHI from baseline to follow-up. AHI change was not associated with development of new nondipping.

DISCUSSION

In this population-based sample, we found a significant longitudinal association between baseline SDB status and development of nocturnal BP systolic nondipping among participants who initially had normal nocturnal BP dipping. This was a strong association, with individuals who had mild SDB (AHI between 5 and 15 events/h) at baseline having a 3-fold increased odds of developing systolic nondipping, compared with persons with no or minimal SDB at baseline (AHI < 5 events/h) over an average follow-up period of 7.2 years. The association showed a dose-response gradient: persons with a baseline AHI ≥ 15 had a 4.4 fold greater odds of developing systolic nondipping, compared with those with no or minimal SDB at baseline. These unique findings suggest the role of SDB in the development of systolic nondipping.

Similar results have been reported in cross-sectional studies consisting of patients with sleep apnea.[26-28] Pankow et al reported an increased prevalence of hypertension and nondipping, determined by a 24-hour ABPM with preset sleep and wake periods, in 93 patients with moderate and severe SDB, determined by oxygen saturation index.[26] Loredo et al found that, in a highly selective sample of 44 subjects with sleep apnea, 84% were nondippers.[27] Ancoli-Israel et al reported that the increased preponderance of nondipping in African American elderly patients was related to sleep apnea.[28] Furthermore, treatment of sleep apnea with CPAP has been shown to lower nighttime systolic BP more than daytime BP.[33-34] We did not see an association between diastolic nondipping and SDB in our study. The effect of SDB as well as its treatment with CPAP on blood pressure in both normotensive and hypertensive subjects has been more consistently seen with systolic BP than with diastolic BP.[21,26,32,33] In general, systolic BP is more labile, whereas diastolic BP is less sensitive to acute physiologic insults, such as apnea and hypopnea episodes, during sleep.

Our findings, as well as prior findings, of an association between SDB and nocturnal nondipping are important because of demonstrated associations between nondipping and advanced target organ damage and poor cardiovascular prognosis.[11-19] SDB, too, has been associated with poor cardiovascular outcomes, including hypertension, myocardial infarction, coronary artery disease, strokes, and congestive heart failure.[20-24] Thus, our data suggest that nondipping may be one of several possible mechanisms by which such outcomes may be initiated or exacerbated in SDB. The acute respiratory breathing events of SDB—apneas and hypopneas—cause temporary elevations of BP, likely via pathways initiated with intrathoracic pressure perturbations, as well as via hypoxia/hypercapnia and arousal with sympathetic activation.[35] It is possible that these repeated bouts of sympathetic activation prevent complete normalization of BP in the time between events, causing systolic BP to fail to fully experience the nocturnal dip typically seen in persons without SDB. This failure to experience normal dipping adds to the amassing evidence that SDB has a causal role in CVD, possibly via multiple pathways.[36,37]

Our findings of the longitudinal association of SDB and systolic nondipping are unique. First, our data were based on 24-hour ABPM using actual sleep and wake times recorded by participants and not arbitrary preset times. This allowed for better accuracy in defining sleep and wake BP. Second, our study was performed in a population-based cohort, enabling us to prospectively determine the association of SDB and nondipping in a nonclinical population with occult or undiagnosed

SDB and to also examine the potential for bias due to follow-up loss. Third, we were able to carefully examine the confounding effects and interactions of important covariables, such as hypertension, antihypertensive medication use, smoking, alcohol use, BMI, change in BMI and SDB status over time, sleep duration, and sleepiness, on the relationship between SDB and nondipping. Excluding those with CVD (myocardial infarction, congestive heart failure, and cerebrovascular disease) did not significantly change the association. Lastly, our longitudinal analysis, with the advantage of having the correct temporal sequence, strengthens the evidence that SDB has a causal role in the development of systolic nondipping.

Our study has a few limitations. We included participants using CPAP in the main analyses because we could not be certain that their SDB was being treated optimally (e.g., adequate compliance with CPAP use or CPAP pressure level). Our comparisons of analyses including CPAP users versus excluding CPAP users demonstrated no meaningful differences. Although this seems to contradict the published data of the effect of CPAP on nighttime BP,[26,32-34] our study was not designed or powered to look at the effect of CPAP use on dipping status. Finally, we did not follow-up all participants who had a baseline 24-hour BP study. However, our analysis of the population characteristics (Table 1) in the total eligible follow-up sample versus the actual follow-up sample showed no differences except for a higher percentage of baseline systolic nondipping in the total sample. Although the proportion of nondippers was slightly higher in the total sample, all nondippers were excluded for the longitudinal analysis. It is possible that the difference reflects better health among those who underwent multiple, follow-up, 24-hour BP measurement studies and may have led to fewer cases of nondipping. Although this possible difference would reduce study power, it would not lead to an overestimation of the association.

Our findings of a strong longitudinal association of SDB with nocturnal systolic nondipping of BP have clinical and public health relevance, since SDB and hypertension both are very prevalent in the general population.[29,38] The development of systolic BP nondipping, a well-established CVD risk, in those with mild to moderate SDB underscores the importance of diagnosing SDB even in its milder forms (an apnea hypopnea index of 5 to 15). Our findings support the need to consider the presence of occult SDB as one of the causes of secondary hypertension, as stated in the most recent (Seventh) Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure,[38] especially in those whose 24 hour BP studies yielded blunted nocturnal dipping. Further research is necessary to determine if nondipping attributed to SDB results in increased CVD in our cohort.

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