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ORIGINAL RESEARCH

Association Between Arousals During Sleep and Hypertension Among Patients With Obstructive Sleep Apnea

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BACKGROUND: Sleep fragmentation induced by repetitive arousals is a hallmark of obstructive sleep apnea (OSA). Sleep fragmentation has been linked to hypertension in community-based studies, but it is unclear if this association is manifest in OSA. We aimed to explore whether frequent arousals from sleep modify the relationship between OSA and prevalent hypertension.

METHODS AND RESULTS: A total of 10 102 patients with OSA and 1614 primary snorers were included in the study. Hypertension was defined on either direct blood pressure measures or diagnosis by a physician. Spontaneous, respiratory, and movement arousals were derived by polysomnography. Logistic regression models were used to estimate the associations between arousals and prevalent hypertension in patients with OSA and primary snorers. For every 10-unit increase of total arousal index, odds of hypertension significantly increased in both the total sample (odds ratio [OR], 1.08; 95% CI, 1.03–1.14; P=0.002) and patients with OSA (OR, 1.10; 95% CI, 1.04–1.16; P<0.001), but not in the primary snoring group. Total arousal index was significantly associated with systolic blood pressure and diastolic blood pressure in the total sample (β=0.05 and β=0.06; P<0.001) and in patients with (β=0.05 and β=0.06; P<0.01), but not in primary snorers. In addition, a greater influence of respiratory events with arousals than respiratory events without arousals on blood pressure in OSA was also noted. Results were independent of confounders, including apnea-hypopnea index and nocturnal hypoxemia.

CONCLUSIONS: We conclude that repetitive arousals from sleep are independently associated with prevalent hypertension in patients with OSA.

Key Words: high blood pressure ■ hypertension ■ obstructive sleep apnea ■ repetitive arousals ■ sleep fragmentation

Characterized by recurrent episodes of upper airway obstruction,[1] obstructive sleep apnea (OSA) is the most common sleep breathing disorder, occurring in 9% to 38% of the general population.[2] It is well accepted that OSA increases the risk of cardiovascular diseases, such as hypertension and coronary heart disease.[3] Although the underlying pathogenesis is complex and multifactorial, upregulation of sympathetic nerve activity is thought to be implicated in the heightened cardiovascular risk observed in OSA. In this population, sympathetic activation has been proposed to be associated with intrathoracic pressure swings, intermittent hypoxia, and sleep fragmentation attributable to recurrent arousals from sleep.[4] Arousals from sleep are abrupt changes toward faster electroencephalographic rhythms that can be spontaneous (cortical) or induced by movements or abnormal breathing. As arousals can be triggered by ventilatory

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CLINICAL PERSPECTIVE

What Is New?

- Patients with obstructive sleep apnea generally exhibit more frequent arousals than normal subjects, which could be sustained for some patients even under treatment with continuous positive airway pressure attributable to the discomfort.
- This study provides novel data indicating that, in addition to nocturnal hypoxemia and apnea-hypopnea index, sleep fragmentation induced by repetitive arousals is also an important metric of hypertension in patients with obstructive sleep apnea, especially when combining with respiratory events.

What Are the Clinical Implications?

- Physicians may consider reducing sleep fragmentation at this situation to decrease the risk of cardiometabolic comorbidities.

Nonstandard Abbreviations and Acronyms

AHI	apnea-hypopnea index
AI	arousal index
DBP	diastolic blood pressure
SBP	systolic blood pressure
SpO_2	oxygen saturation

efforts in response to hypoxia, hypercapnia, or inspiratory resistive load,[5,6] patients with OSA generally exhibit more frequent arousals than normal subjects.[4]

The association between repetitive arousals and increased sympathetic activity has been receiving increasing attention.[4,7] Several studies have found short bursts in muscle sympathetic activity in association with transient blood pressure (BP) increases in response to arousals evoked by auditory stimuli during sleep.[8,9] Two consecutive nights of sleep fragmentation by acoustic stimulation are sufficient to alter daytime sympathovagal balance, as measured by spectral analysis of heart rate variability.[10,11] In patients with OSA, Taylor et al[12] and Kim et al[13] both found that the arousal index was a better predictor of sympathetic activation during wakefulness and of cardiovascular complications than the apnea-hypopnea index (AHI) or nocturnal hypoxemia levels. Thus, it is conceivable that repetitive arousals could initiate and maintain hypertension through sympathetic stimulation, especially in patients with OSA who already exhibit increased sympathetic activity.

Several studies have investigated the relationship between arousals and hypertension in community-based samples, and found that recurrent arousals were associated with elevated daytime systolic BP (SBP) and higher risk of hypertension.[14,15] Only few, small studies explored this relation in individuals with OSA, yielding inconsistent results. Furthermore, the relative contribution of arousal types (ie, spontaneous, respiratory, and movement-related arousals) to BP increases is debated,[16–19] and whether there is a synergistic effect of respiratory events with concomitant arousals remains unclear.

We examined a large sample of patients with and without OSA, and sought to assess (1) whether arousals from sleep are independently associated with increased odds of hypertension; (2) what type of arousal (spontaneous, respiratory, or leg movement arousals) is more closely associated with BP; and (3) whether the presence of respiratory events modulates such risk.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Subjects

This was a cross-sectional study including consecutive patients from the Sleep Medicine Center, West China Hospital. The study protocol was approved by the local Institutional Review Board, and informed consent was obtained from all participants. Parts of the data have been previously published.[20,21]

Patients were evaluated at the Sleep Medicine Center for clinical suspicion of OSA. Data on health status, comorbidities, medical therapies, and history of sleep complaints were obtained. Tobacco use (current or past use of any tobacco product), alcohol consumption (>2 drinks per day), and coffee consumption (>2 cups per day) were also ascertained. Body weight and height were measured by scale and stadiometer (Shengyuan HGM 600, China), with light clothing and no shoes. Body mass index was calculated as body weight (in kilograms) divided by the square of height (in meters). Sleepiness was measured by Epworth Sleepiness Scale. Participants with an Epworth Sleepiness Scale score >10 were considered to have excessive daytime sleepiness.[22]

Patients with an AHI <5 events/h were included in the primary snoring group, whereas those with AHI ≥5 were classified as patients with OSA. We excluded subjects who were aged <18 years and those who had medical conditions causing sleep disturbance (eg, chronic pain); current major psychiatric conditions (eg, depression); current or recent (within the past

3 months) use of antidepressants, anxiolytics, antipsychotics, or hypnotics; and other comorbid sleep disorders (eg, insomnia).

BP Measures

A pneumoelectric, microprocessor-controlled instrument (Nissei, DS-1902, Japan) with accuracy within 3 mm Hg was used for BP measurements. According to standard methods,[23] 3 consecutive BP measurements during a 5-minute period were taken following ≥10 minutes of rest. We collected BP data at 2 time points: about 2 hours before polysomnography recording in the evening and following completion of the sleep study the next morning. Hypertension was defined as (1) SBP ≥140 mm Hg or diastolic BP (DBP) ≥90 mm Hg at either evening or morning measurement or (2) physician diagnosis of hypertension as per use of antihypertensive medication or clinical history (affirmative answer to the question "Have you been diagnosed with hypertension by a physician?").[20,24] The average of evening and morning BP was used for all analyses.

Polysomnography

Sleep data were collected via a full-night polysomnogram in the sleep laboratory (Alice 5 Diagnostic Sleep System; Philips Respironics, Bend, OR) and scored following the American Academy of Sleep Medicine criteria by senior polysomnography technicians.[25] All participants were asked to follow their usual sleep times while in the laboratory. AHI was defined as total number of apneas and hypopneas per hour of sleep, with hypopneas defined as at least 50% reduction in airflow for ≥10 seconds associated with ≥3% decrease in oxygen desaturation or an arousal. Arousals were identified as rapid shifts in electroencephalographic frequency, including α, θ, and/or frequencies >16 Hz (excluding spindles) lasting at least 3 seconds, with at least 10 seconds of stable sleep preceding the electroencephalographic shift. Arousals occurring in response to respiratory events or to leg movements were classified as respiratory or leg movement associated arousals, respectively, whereas those manifesting in absence of discernable stimuli were considered as spontaneous arousals. Total arousal index (AI) was defined as the total number of arousals per hour of sleep. Respiratory, leg movement, and spontaneous AIs were calculated in a similar manner. We categorized all participants into quartiles based on total AI (<16.4, 16.4–27.7, 27.7–45.3, and >45.3 events/h).

Statistical Analysis

Subject characteristics and sleep parameters were summarized using means and SDs for continuous variables and frequencies for categorical variables. Between-group differences in sample characteristics were tested by ANOVA or Mann-Whitney *U* tests for normally and nonnormally distributed continuous variables, respectively. χ^2 Tests were applied for categorical variables.

Logistic regression analysis was performed to assess the association between arousals from sleep (total, respiratory, leg movement, and spontaneous AIs) and hypertension. As the interaction of OSA and AI on hypertension was significant ($P<0.001$), we calculated the odds for hypertension associated with OSA in different strata of AI. Results are presented as odds ratio (OR) and 95% CI. Multivariable models were adjusted for variables associated with OSA and/or hypertension, including age, sex, body mass index, tobacco use, alcohol drinking, coffee drinking, heart failure, atrial fibrillation, Epworth Sleepiness Scale, total sleep time, lowest oxygen saturation (SpO_2), percentage of time spent in sleep below 90% oxygen saturation, and AHI (or AI, depending on the primary exposure). Furthermore, multivariable regression analysis was also conducted to evaluate the relationship between AI and BP treated as continuous variables in both OSA and primary snoring groups.

Given the significant interaction of OSA severity and AI and lowest SpO_2 and AI on hypertension (both $P<0.001$), we performed the same multivariable logistic and linear regression analyses across OSA severity (mild, moderate, and severe) and different levels of lowest SpO_2 (>85% and ≤85%) (Data S1). Multivariable regression was also used in a similar manner to further explore the association of respiratory events (apneas and hypopneas) occurring with or without arousal and BP.

Stata 14.0 was used for analysis. Comparisons with $P<0.05$ were considered statistically significant.

RESULTS

The sample was composed of 11 716 subjects, of whom 10 102 were patients with OSA. The mean age was 44.32 (SD, 11.99) years, and the mean body mass index was 26.41 kg/m^2 (SD, 3.74 kg/m^2). Demographic, clinical, and sleep characteristics of the study population are described in Table S1. We also showed demographic, clinical, and sleep characteristics in different OSA severity categories in Table S2.

Table 1 shows demographic, clinical, and sleep characteristics of patients stratified according to quartiles of total AI. Patients with higher total AI had higher body mass index, higher Epworth Sleepiness Scale scores, higher AHI, and lower nocturnal oxygen saturation than those with lower AI. Prevalence of hypertension and levels of SBP and DBP increased with increasing total AI.

Multivariable logistic regression analysis showed that odds of hypertension were significantly higher with

Table 1. Demographic, Clinical, and Sleep Characteristics of Patients, Stratified by Quartiles of Total AI

Characteristics	AI				*P* value
	<16.4 (n=2954)	16.4–27.7 (n=2903)	27.7–45.3 (n=2942)	>45.3 (n=2917)	
Demographic and clinical characteristics					
Men, n (%)	1918 (64.9)	2225 (76.6)	2516 (85.5)	2723 (93.3)	<0.001
Age, y	44.17±13.17	43.77±12.10	45.24±11.62	44.10±10.89	<0.001
Body mass index, kg/m^2	25.53±3.72	25.72±3.53	26.21±3.57	28.18±3.55	<0.001
Hypertension, n (%)	1268 (42.9)	1201 (41.4)	1420 (48.3)	1888 (64.7)	<0.001
SBP, mm Hg	122.50±15.50	122.10±14.96	124.45±14.79	128.96±15.44	<0.001
DBP, mm Hg	78.58±10.23	78.92±10.47	80.96±10.91	85.60±11.38	<0.001
Smoking, n (%)	800 (27.1)	999 (34.4)	1245 (42.3)	1536 (52.7)	<0.001
Alcohol drinking, n (%)	924 (31.3)	1091 (37.6)	1358 (46.2)	1548 (53.1)	<0.001
Coffee drinking, n (%)	633 (21.4)	702 (24.2)	823 (28.0)	957 (32.8)	<0.001
ESS	7.70±6.63	7.78±5.66	8.34±5.50	11.47±7.04	<0.001
Polysomnography					
Sleep-onset latency, min	16.11±24.27	15.24±22.46	14.03±19.31	10.40±15.04	<0.001
Total sleep time, min	425.37±68.20	431.36±63.80	435.72±62.13	456.11±60.63	<0.001
Sleep efficiency, %	82.99±11.63	84.01±10.60	84.50±10.33	87.91±8.86	<0.001
Total AI, events/h	11.03±3.56	21.90±3.16	35.39±5.12	62.53±13.11	<0.001
Respiratory AI, events/h	3.20±2.92	8.71±6.15	20.25±10.45	51.67±17.15	<0.001
Leg movement AI, events/h	2.50±1.73	3.63±2.39	3.39±2.70	1.94±2.00	<0.001
Spontaneous AI, events/h	4.68±2.79	7.95±4.91	9.21±6.94	6.80±7.14	<0.001
Stage N1, % TST	20.51±12.98	24.27±13.31	31.74±16.00	48.70±20.48	<0.001
Stage N2, % TST	51.39±12.88	49.36±12.38	44.58±13.91	32.43±18.30	<0.001
Stage N3, % TST	9.03±7.91	8.30±7.30	6.77±6.54	2.67±4.47	<0.001
Stage REM, % TST	19.07±6.06	18.07±5.31	16.91±5.22	16.19±5.01	<0.001
AHI, events/h	19.28±20.32	25.66±22.21	39.97±24.83	70.02±19.22	<0.001
Lowest SpO_2, %	80.94±13.16	78.80±13.81	73.16±16.12	56.88±18.45	<0.001
T90%, %	5.14±12.37	6.25±12.37	12.61±17.39	36.57±24.31	<0.001

Data are reported as numbers (percentages) for categorical variables and as mean±SD for continuous variables. AHI indicates apnea-hypopnea index; AI, arousal index; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; REM, rapid eye movement; SBP, systolic blood pressure; SpO_2, oxygen saturation; T90%, percentage of time spent in sleep below 90% SpO_2; and TST, total sleep time.

greater total AI and respiratory AI in both the total sample (OR for every 10-unit increase in total AI, 1.08; 95% CI, 1.03–1.14; *P*=0.002; OR for every 10-unit increase in respiratory AI, 1.13; 95% CI, 1.07–1.19; *P*<0.001) and in the OSA group (total AI: OR, 1.10; 95% CI, 1.04–1.16; *P*<0.001; respiratory AI: OR, 1.16; 95% CI, 1.07–1.20; *P*<0.001), but not in the primary snoring group (Table 2). Leg movement AI and spontaneous AI were not associated with increased odds of hypertension in any groups of patients.

We also applied linear regression models to examine the association between AI and BP as continuous variables (Table 3), after adjusting for confounders. Both total AI and respiratory AI were significantly associated with SBP and DBP values in the total sample (for total AI: β=0.05 and β=0.06; *P*<0.001; for respiratory AI: β=0.06 and β=0.10; *P*<0.001) and in the OSA group (for total AI: β=0.05 and β=0.06; *P*<0.001; for respiratory AI: β=0.06 and β=0.09; *P*<0.001), but not in primary snoring patients.

When we stratified the sample according to OSA severity, we found that odds of hypertension were significantly higher for every 10-unit increase in total AI and in respiratory AI only in patients with severe OSA (total AI: OR, 1.04; 95% CI, 1.01–1.11; *P*=0.017; respiratory AI: OR, 1.08; 95% CI, 1.01–1.13; *P*=0.005), but not in mild and moderate OSA groups (Table 4). Consistently, both total AI and respiratory AI were significantly associated with SBP and DBP in those with severe OSA, but not in those with mild or moderate OSA (Table S3). Meanwhile, we also found that odds of hypertension were significantly higher for every 10-unit increase in total AI and in respiratory AI only in patients with lowest SpO_2 ≤85% (total AI: OR, 1.24; 95% CI, 1.18–1.30; *P*<0.001; respiratory AI: OR, 1.27; 95% CI, 1.21–1.33; *P*<0.001) (Table S4). Both total AI and respiratory AI were significantly associated with SBP and DBP in those with lowest SpO_2 ≤85%, but not in those with lowest SpO_2 >85% (Table S5).

In Table 5, linear regression models showed significant relationships between BP and respiratory events with

Table 2. Adjusted ORs and 95% CIs of Risk of Hypertension Associated With AI, Respiratory AI, Leg Movement AI, and Spontaneous AI

Independent variable	OR*	95% CI	*P* value
		Lower–upper	
All patients			
Total AI	1.08	1.03–1.14	0.002
Respiratory AI	1.13	1.07–1.19	<0.001
Leg movement AI	0.94	0.83–1.05	0.269
Spontaneous AI	0.96	0.84–1.11	0.612
Primary snoring patients			
Total AI	0.63	0.48–1.01	0.073
Respiratory AI	0.76	0.57–1.01	0.055
Leg movement AI	0.61	0.45–1.00	0.051
Spontaneous AI	0.67	0.48–1.02	0.057
Patients with OSA			
Total AI	1.10	1.04–1.16	<0.001
Respiratory AI	1.16	1.07–1.20	<0.001
Leg movement AI	0.60	0.49–1.10	0.403
Spontaneous AI	1.06	0.90–1.25	0.472

Models were adjusted for age, sex, body mass index, tobacco use, alcohol drinking, coffee drinking, heart failure, atrial fibrillation, Epworth Sleepiness Scale, total sleep time, lowest oxygen saturation (SpO_2), percentage of time spent in sleep below 90% SpO_2, and apnea-hypopnea index. AI indicates arousal index; OR, odds ratio; and OSA, obstructive sleep apnea.

*ORs for every 10-unit increase in AI measures.

Table 3. Multivariate Regression Analysis of BP With Total AI, Respiratory AI, Leg Movement AI, and Spontaneous AI

Independent variable	SBP		DBP	
	β	*P* value	β	*P* value
All patients				
Total AI	0.05	<0.001	0.06	<0.001
Respiratory AI	0.06	<0.001	0.10	<0.001
Leg movement AI	−0.01	0.130	−0.03	0.341
Spontaneous AI	0.01	0.408	−0.01	0.759
Primary snoring patients				
Total AI	−0.04	0.072	−0.01	0.073
Respiratory AI	0.01	0.658	0.01	0.572
Leg movement AI	−0.03	0.115	−0.02	0.079
Spontaneous AI	−0.04	0.127	−0.03	0.249
Patients with OSA				
Total AI	0.05	<0.001	0.06	<0.001
Respiratory AI	0.06	<0.001	0.09	<0.001
Leg movement AI	−0.01	0.392	−0.03	0.235
Spontaneous AI	0.02	0.064	0.01	0.600

Models were adjusted for age, sex, body mass index, tobacco use, alcohol drinking, coffee use, heart failure, atrial fibrillation, Epworth Sleepiness Scale, the use of antihypertension medication, apnea-hypopnea index, lowest oxygen saturation (SpO_2), and percentage of time spent in sleep below 90% SpO_2. AI indicates arousal index; BP, blood pressure; DBP, diastolic BP; OSA, obstructive sleep apnea; and SBP, systolic BP.

and without arousal. β Coefficients for respiratory events with arousals were also higher than those of respiratory events without arousals in the total sample (β for SBP: 0.12 versus 0.11; β for DBP: 0.17 versus 0.13) and in the OSA group (β for SBP: 0.13 versus 0.10; β for DBP: 0.18 versus 0.13). The association between respiratory events with and without arousal and BP values did not achieve statistical significance in the primary snoring group.

Considering that some respiratory arousal caused by central sleep apnea might be different from that caused by obstructive sleep apnea, we added a sensitivity analysis removing subjects with >5 central sleep apnea events (n=4319). Results remained consistent with those from the entire sample, supporting absent or negligibly different effects of central versus obstructive respiratory events (Table S6).

As shown in Table S7, the association between hypertension and OSA was present in stratified analysis of different categories of AI. Compared with primary snoring within the same AI stratum, odds of prevalent hypertension in those with OSA and total AI <16.4 (OR, 1.08; 95% CI, 0.89–1.32) were not significant, whereas odds were significant in the other three AI strata.

DISCUSSION

In this study, we examined the relationship between arousals and hypertension in a large population of patients with primary snoring and OSA. Our findings show that arousals, and especially respiratory arousals, are significantly associated with increased odds of hypertension in patients with OSA. This relationship is independent of other sleep-related variables that have been linked to hypertension, including nocturnal desaturation, AHI, and daytime sleepiness.[24,26] Respiratory events with arousals may be more closely associated with BP than those without arousals.

Intermittent hypoxia is thought to be a major contributor in the heightened risk of hypertension associated with OSA.[27] However, OSA remains associated with short-term increases in BP when hypoxemia is prevented with administration of supplemental oxygen,[14,28] suggesting that hypoxemia alone does not fully account for BP elevation. Another mechanism possibly implicated in the association between OSA and hypertension may be sleep fragmentation, which ensues from frequent arousals from sleep and is common in patients with OSA.

Several small studies have explored this hypothesis in individuals with OSA, with inconsistent results. In a cross-sectional examination of the Wisconsin Sleep Cohort,[14] there was no independent association between sleep fragmentation index and awake BP in subjects with an AHI >1 events/h, and the authors speculated that the significance of the contribution of arousals on BP decreased as AHI and apnea duration

Table 4. Adjusted ORs and 95% CIs of Risk of Hypertension Associated With Total AI, Respiratory AI, Leg Movement AI, and Spontaneous AI Across OSA Severity Groups

Independent variable	OR*	95% CI	*P* value
		Lower–upper	
Mild OSA			
Total AI	0.98	0.79–1.19	0.780
Respiratory AI	0.88	0.67–1.15	0.352
Leg movement AI	0.95	0.59–1.54	0.831
Spontaneous AI	0.89	0.65–1.22	0.477
Moderate OSA			
Total AI	0.94	0.79–1.13	0.529
Respiratory AI	0.91	0.72–1.16	0.450
Leg movement AI	0.86	0.54–1.37	0.533
Spontaneous AI	0.96	0.68–1.37	0.838
Severe OSA			
Total AI	1.04	1.01–1.11	0.017
Respiratory AI	1.08	1.01–1.13	0.005
Leg movement AI	0.55	0.40–1.01	0.053
Spontaneous AI	1.11	0.87–1.40	0.386

Models were adjusted for age, sex, body mass index, tobacco use, alcohol drinking, coffee drinking, heart failure, atrial fibrillation, Epworth Sleepiness Scale, total sleep time, lowest oxygen saturation (SpO_2), percentage of time spent in sleep below 90% SpO_2, and apnea-hypopnea index. AI indicates arousal index; OR, odds ratio; and OSA, obstructive sleep apnea.

*ORs for every 10-unit increase in AI measures.

increased.[29] Conversely, both Sulit et al[17] and Kuwabara et al[26] identified AI as an independent determinant of hypertension and BP. In addition, sleep fragmentation induced in the absence of hypoxemia in subjects with treated OSA[30] produces similar BP changes compared with those elicited by hypoxic respiratory events, thus supporting an important and independent role of arousals from sleep in BP regulation. Meanwhile, experimentally induced sleep fragmentation studies documented acute BP elevations following arousals without hypoxemia, with the degree of BP elevation being commensurate with the intensity of the arousal itself.[31] Vascular endothelial dysfunction and BP increases were also noted in animals exposed to long-term sleep fragmentation caused by frequent arousals alone.[32]

Our study corroborates these latter findings, and further adds to the literature by showing a greater influence of arousals in combination with respiratory events on BP. A previous study observed a similar phenomenon in a canine model, showing that apnea-induced arousals result in BP increases, with larger BP elevations observed in the presence of arousals than when apneas terminated before the occurrence of arousals.[19] Thus, it is conceivable that the combination of arousal, hypoxemia, and/or airway obstruction leads to potentiated hypertensive responses, and this might be attributed to the alteration in autonomic activity associated with arousals.

On the other hand, the implications of arousal types for hypertension risk are unclear. Studies by Noda et al[33] and Loredo et al[16] identified movement arousal as a significant factor contributing to elevated SBP and DBP, whereas other studies found increases in BP to be primarily associated with respiratory arousals.[17,18] Herein, we also noted that the association between arousals and BP was mainly driven by respiratory arousals. However, considering the distribution of arousal types in the OSA group, this result may merely be attributable to the fact that the vast majority of arousals were of respiratory origins, especially among patients with severe disease.

In our study, we found a significant interaction between AI and OSA severity and lowest SpO_2, with the relationship with prevalent hypertension and BP values being stronger in patients with severe OSA with lower lowest SpO_2. This was unexpected. Given that

Table 5. Multivariable Regressions Between BP and Respiratory Events With and Without Arousals

Independent variable	SBP		DBP	
	β	*P* value	β	*P* value
All patients				
Respiratory events with arousals	0.12	<0.001	0.17	<0.001
Respiratory events without arousals	0.11	<0.001	0.13	<0.001
Primary snoring patients				
Respiratory events with arousals	0.23	0.097	0.26	0.059
Respiratory events without arousals	0.27	0.058	0.29	0.052
Patients with OSA				
Respiratory events with arousals	0.13	<0.001	0.18	<0.001
Respiratory events without arousals	0.10	<0.001	0.13	<0.001

Models were adjusted for age, sex, body mass index, tobacco use, alcohol drinking, coffee use, heart failure, atrial fibrillation, Epworth Sleepiness Scale, the use of antihypertension medication, lowest oxygen saturation (SpO_2), and percentage of time spent in sleep below 90% SpO_2. BP indicates blood pressure; DBP, diastolic BP; OSA, obstructive sleep apnea; and SBP, systolic BP.

patients with OSA who have high arousal thresholds typically have severe disease,[34,35] this observation might imply that arousals are more detrimental in this patient group. However, considering that AI increases as OSA severity worsens, we cannot exclude that this result may merely be attributable to increased arousal frequency in patients with severe OSA.

With regard to the general population, Chouchou et al showed that, in older adults, arousals during sleep were closely associated with daytime and 24-hour SBP, as well as with increased risk of systolic hypertension.[15] These data are in line with prior findings from the Wisconsin Sleep Cohort Study,[14] where a significant association of sleep fragmentation with hypertension was evident in subjects without sleep-disordered breathing (AHI, <1 events/h). In our study, we did not observe a relationship between arousals and BP in primary snorers, which might be attributed to the low AI in this population (mean AI, 17.27 events/h), the relatively small sample size of this group, and/or the different methods used to measure arousals. For instance, in the study done by Chouchou and colleagues, arousals were determined by pulse transit time measurements rather than from electroencephalography.[15]

When exploring the mechanisms underlying the relationship between repetitive arousals and hypertension, previous studies have suggested AI, rather than hypoxemia or AHI, as an indicator for heightened sympathetic activation during wakefulness.[12,13] In a sample of 67 subjects with OSA, Loredo et al[16] observed a weak but significant relationship between arousals and daytime plasma concentrations of norepinephrine, a crude estimate of sympathetic tone.[36] More important, this association was independent of AHI. Thus, it is plausible that repetitive arousals may link OSA with hypertension risk via stimulation of sympathetic activity. Furthermore, sleep fragmentation could promote alterations in gut microbiota that modify gut permeability, change intestinal content of several important microbial-derived biologically active metabolites, and promote translocation of bacterial toxins to the systemic circulation, which may lead to several adverse consequences of OSA, including hypertension.[37,38]

Our findings of an association between arousals and hypertension risk in OSA are directly relevant to the debate relative to the role of arousals in this population. Frequent arousals can disrupt sleep continuity and impede achievement and maintenance of deep sleep, contributing to poor sleep and daytime consequences. They can also directly perpetuate respiratory control instability in patients with OSA, thus exacerbating abnormal breathing.[6,21,39,40] Meanwhile, as the recommended treatment for abolishing the disturbed respiratory events, continuous positive airway pressure could reduce the frequency of arousals after sleep onset and eliminate sleep fragmentation,[41,42] which might be one of the mechanisms through which continuous positive airway pressure can lower BP.

Strengths of this study include a large sample of patients exhibiting a wide range of AHI values, hence degrees of OSA severity, and the use of in-laboratory full polysomnography to determine sleep parameters. A few limitations of the current study should be addressed: (1) Because only clinic BP was obtained, we cannot exclude "white coat" effects nor comment on 24-hour BP pattern. (2) Given that our patients underwent a single night of polysomnography recording, night-to-night variation and first night effects cannot be ruled out. (3) As this was a cross-sectional examination, the causal relationship between arousals and hypertension cannot be fully determined. Evaluations of longitudinal data are required to further define causal associations. (4) As another important indicator to measure sleep fragmentation, duration of arousals was also noted to be associated with cardiovascular mortality in a community study.[43] However, because this measure was not obtained in the current study, more studies are warranted to explore the relationship between duration of arousals and hypertension in patients with OSA.

CONCLUSIONS

In conclusion, our study suggests that repetitive arousals are independently associated with hypertension in patients with OSA. Combinations of respiratory events and arousals may actually be more detrimental for hypertension risk. Further studies with longitudinal designs are warranted to delineate the temporal association between repetitive arousals and hypertension, and to determine whether interventions to reduce repetitive arousals may also contribute to lower BP in patients with OSA.

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Disclosures

Dr Somers is a consultant for Jazz Pharmaceuticals, Respicardia, Bayer, and Baker Tilly, and serves on the Sleep Number Scientific Advisory Board. The remaining authors have no disclosures to report.

Supplemental Material

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Supplemental Material

Data S1.

Supplemental Methods

Statistical analysis

Subject characteristics and sleep parameters were summarized using means and standard deviations for continuous variables and frequencies for categorical variables. Between-group differences in sample characteristics were tested by ANOVA, independent-sample t-tests or Mann–Whitney U tests for normally and non-normally distributed continuous variables, respectively. Chi-square tests were applied for categorical variables.

To investigate the association between arousal index (AI) and hypertension across different OSA severity categories and different levels of lowest SpO2, multivariable logistic regression analyses were performed. The following covariates were adjusted for: age, sex, BMI, tobacco, alcohol drinking, coffee drinking, heart failure, atrial fibrillation, ESS, total sleep time, lowest SpO2, T90% and AHI. Results are presented as adjusted odds ratio (OR) and 95% confidence intervals (CI).

Multivariable regression analyses were also performed to assess the relationship between AI and blood pressure (BP) in different OSA severity and different levels of lowest SpO2 groups. Age, sex, BMI, tobacco, alcohol drinking, coffee use, heart failure, atrial fibrillation, ESS, total sleep time, lowest SpO2, T90%, AHI and antihypertensive medications were included as covariates.

To exclude potential confounding effects of central sleep apnea, we also did a similar multivariable logistic regression analysis after removing subjects with >5 central sleep apnea events (n=4319)

Stata 14.0 was used to conduct analyses. Comparisons with p-values <0.05 were considered statistically significant.

Table S1. Demographic, clinical and sleep characteristics of primary snoring and OSA patients.

	Total (N=11716)	Primary snoring (n=1614)	OSA (n=10102)	P
Demographic and clinical characteristics				
Men, n (%)	9382 (80.08)	912 (56.5)	8470 (83.8)	<0.001
Age (years)	44.32± 11.99	40.55±12.13	44.93 ±11.86	<0.001
Body mass index (kg/m^2)	26.41 ±3.74	23.88 ±3.62	26.81 ±3.60	<0.001
Hypertension, n (%)	5777 (49.31)	445 (27.6)	5332 (52.8)	<0.001
Antihypertensive medications, n (%)	2839 (24.23)	202 (12.52)	2637 (26.10)	<0.001
SBP (mmHg)	124.50±15.42	117.89 ±14.44	125.55 ±15.31	<0.001
DBP (mmHg)	81.01 ±11.11	75.36±9.93	81.90±11.02	<0.001
Smoking, n (%)	4580 (39.09)	390 (24.2)	4190 (41.5)	<0.001
Alcohol drinking, n (%)	4921 (42.00)	416 (25.8)	4505 (44.6)	<0.001
Coffee drinking, n (%)	3115 (26.59)	295 (18.3)	2820 (27.9)	<0.001
ESS	8.83± 6.43	7.12 ±5.69	9.09±6.50	<0.001
Polysomnography				
Sleep onset latency (min)	13.95± 20.69	17.63±25.85	13.36±19.68	<0.001
Total sleep time (min)	437.11± 64.79	420.95 ±69.64	439.69±63.61	<0.001
Sleep efficiency (%)	84.85± 10.57	82.58 ±11.86	85.21± 10.30	<0.001
Total AI (events/h)	31.89±20.30	17.27±9.68	33.74±20.54	<0.001
Respiratory AI (events/h)	20.14 ±21.12	0.71± 0.69	22.60±21.18	<0.001
Leg movement AI (events/h)	2.88±2.33	4.15±2.79	2.72± 2.22	<0.001
Spontaneous AI (events/h)	7.15±5.91	11.40±7.55	6.61±5.44	<0.001
N1 (% TST)	31.28± 19.29	16.57 ±9.68	33.63±19.40	<0.001
N2 (% TST)	44.46± 16.30	52.63±11.38	43.15 ±16.59	<0.001
N3 (% TST)	6.70±7.12	11.46 ±8.05	5.94 ±6.66	<0.001
REM (% TST)	17.56± 5.53	19.34±5.57	17.28 ±5.47	<0.001
AHI (events/h)	38.69 ±29.24	2.17 ±1.45	44.52±27.28	<0.001
Lowest SpO2 (%)	72.47 ±18.15	88.48 ±9.71	69.91 ±17.88	<0.001
T90% (%)	15.11 ± 21.45	0.89 ± 6.43	17.39 ± 22.13	<0.001

Data are reported as numbers and percentages for categorical variables and as mean ± SD for continuous variables; P for comparison between OSA and primary snoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; AI, arousal index; TST, total sleep time; AHI, apnea-hypopnea index; REM, rapid eye movement; SpO2, oxygen saturation; T90%, percentage of time spent in sleep below 90% oxygen saturation

Table S2. Demographic, clinical and sleep characteristics stratified by OSA severity.

	Mild OSA (n=1905）	Moderate OSA (n=1891)	Severe OSA (n=6306)	P
Demographic and clinical characteristics				
Men, n (%)	1379 (72.4%)	1530 (80.9%)	5561 (88.2%)	<0.001
Age (years)	44.11± 12.40	45.11 ± 12.21	45.12 ± 11.57	0.004
Body mass index (kg/m^2)	25.40 ± 3.48	25.80 ± 3.37	27.53 ± 3.51	<0.001
Hypertension, n (%)	717 (38.5%)	776 (41.7%)	3839 (61.3%)	<0.001
SBP (mmHg)	121.20 ± 14.74	122.92 ± 14.62	127.65 ± 15.28	<0.001
DBP (mmHg)	77.87 ± 10.06	79.12 ± 9.95	83.96 ± 11.09	<0.001
Smoking, n (%)	633 (34.3%)	711 (38.2%)	2846 (45.4%)	<0.001
Alcohol drinking, n (%)	683 (36.9%)	748 (40.2%)	3074 (49.1%)	<0.001
Coffee using, n (%)	436 (23.7%)	451 (24.3%)	1933 (31.1%)	<0.001
ESS	7.73 ± 6.31	7.54 ± 5.43	9.96 ± 6.69	<0.001
Polysomnography				
Sleep onset latency (min)	15.96 ± 22.93	15.13 ± 20.56	12.04 ± 18.17	<0.001
Total sleep time (min)	425.50 ± 64.73	427.52 ± 64.24	447.63 ± 61.74	<0.001
Sleep efficiency (%)	83.13 ± 11.00	83.46 ± 11.01	86.37 ± 9.66	<0.001
Total AI (events/h)	19.15 ± 10.10	22.96 ± 11.23	43.64 ± 21.62	<0.001
Respiratory AI (events/h)	3.32 ± 2.29	8.18 ± 4.83	33.79 ± 21.46	<0.001
Leg movement AI (events/h)	4.46 ± 4.24	4.50 ± 4.33	2.83 ± 3.51	<0.001
Spontaneous AI (events/h)	9.65 ± 6.57	7.99 ± 5.70	5.34 ± 4.74	<0.001
N1 (% TST)	20.46 ± 10.74	23.54 ± 11.74	40.64 ± 19.87	<0.001
N2 (% TST)	51.23 ± 11.84	49.77 ± 11.70	38.72 ± 17.46	<0.001
N3 (% TST)	9.39 ± 7.52	8.40 ± 7.13	4.16 ± 5.48	<0.001
REM (% TST)	18.92 ± 6.00	18.29 ± 5.50	16.48 ± 5.12	<0.001
AHI (events/h)	9.70 ± 2.86	21.97 ± 4.32	61.81 ± 19.14	<0.001
Lowest-SpO2 (%)	83.56 ± 9.88	79.26 ± 10.89	62.98 ± 17.78	<0.001
T90% (%)	1.89 ± 7.52	3.86 ± 9.21	26.12 ± 23.20	<0.001

Data are reported as numbers and percentages for categorical variables and as mean ± SD for continuous variables; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; AI, arousal index; TST, total sleep time; AHI, apnea-hypopnea index; REM, rapid eye movement; SpO2, oxygen saturation; T90%, percentage of time spent in sleep below 90% oxygen saturation.

Table S3. Multivariate regression analysis of blood pressure with total arousal index (AI), respiratory AI, leg movement AI and spontaneous AI across OSA severity groups.

	SBP		DBP	
Independent Variable	β	P	β	P
Mild OSA				
Total AI	-0.01	0.509	-0.02	0.324
Respiratory AI	-0.03	0.205	-0.03	0.152
Leg movement AI	-0.02	0.327	-0.03	0.110
Spontaneous AI	-0.02	0.342	-0.02	0.422
Moderate OSA				
Total AI	0.01	0.561	0.01	0.542
Respiratory AI	0.01	0.788	0.01	0.746
Leg movement AI	0.01	0.789	-0.03	0.120
Spontaneous AI	0.01	0.556	0.02	0.392
Severe OSA				
Total AI	0.03	0.035	0.05	0.027
Respiratory AI	0.03	0.048	0.06	0.008
Leg movement AI	-0.02	0.136	-0.04	0.107
Spontaneous AI	0.03	0.124	0.01	0.984

Models were adjusted for age, sex, BMI, tobacco use, alcohol drinking, coffee use, heart failure, atrial fibrillation, ESS, the use of antihypertension medication, AHI, lowest SpO2, and T90%; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index, ESS, Epworth Sleepiness Scale

Table S4. Adjusted odd ratios (ORs) and 95% confidence intervals (CIs) of risk of hypertension associated with total arousal index (AI), respiratory AI, leg movement AI and spontaneous AI across different levels of lowest SpO2.

Independent Variable	OR[a]	95% CI		P
		Lower	Upper	
Lowest SpO2>85%				
Total AI	0.88	0.76	1.01	0.059
Respiratory AI	0.89	0.76	1.06	0.186
Leg movement AI	0.59	0.41	1.00	0.073
Spontaneous AI	0.85	0.68	1.06	0.150
Lowest SpO2≤85%				
Total AI	1.24	1.18	1.30	<0.001
Respiratory AI	1.27	1.21	1.33	<0.001
Leg movement AI	0.97	0.56	1.03	0.150
Spontaneous AI	1.04	0.86	1.25	0.702

Models were adjusted for age, sex, BMI, tobacco use, alcohol drinking, coffee use, heart failure, atrial fibrillation, ESS, total sleep time and AHI; BMI, body mass index, ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index. [a]Odds ratios for every10-unit increase in arousal index measures.

Table S5. Multivariate regression analysis of blood pressure with total arousal index (AI), respiratory AI, leg movement AI and spontaneous AI across different levels of lowest SpO2.

	SBP		DBP	
Independent Variable	β	P	β	P
Lowest SpO2>85%				
Total AI	-0.01	0.614	-0.01	0.492
Respiratory AI	-0.01	0.913	0.01	0.546
Leg movement AI	-0.02	0.302	-0.04	0.310
Spontaneous AI	-0.02	0.165	-0.02	0.199
Lowest SpO2≤85%				
Total AI	0.10	<0.001	0.14	<0.001
Respiratory AI	0.11	<0.001	0.16	<0.001
Leg movement AI	-0.02	0.146	-0.04	0.110
Spontaneous AI	0.02	0.149	0.01	0.793

Models were adjusted for age, sex, BMI, tobacco use, alcohol drinking, coffee use, heart failure, atrial fibrillation, ESS, the use of antihypertension medication and AHI; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index, ESS, Epworth Sleepiness Scale

Table S6. Adjusted odd ratios (ORs) and 95% confidence intervals (CIs) of risk of hypertension associated with arousal index (AI), respiratory AI, leg movement AI and spontaneous AI in patients with central sleep apnea events less than 5.

Independent Variable	OR[a]	95% CI		P
		Lower	Upper	
All patients				
Total AI	1.10	1.03	1.18	0.004
Respiratory AI	1.20	1.11	1.29	< 0.001
Leg movement AI	0.87	0.76	1.01	0.082
Spontaneous AI	0.94	0.79	1.12	0.520
Primary snoring patients				
Total AI	0.67	0.51	1.01	0.062
Respiratory AI	0.79	0.62	1.00	0.053
Leg movement AI	0.63	0.52	1.00	0.051
Spontaneous AI	0.68	0.49	1.02	0.057
OSA patients				
Total AI	1.13	1.06	1.21	< 0.001
Respiratory AI	1.18	1.09	1.27	< 0.001
Leg movement AI	0.73	0.54	1.10	0.109
Spontaneous AI	0.97	0.77	1.14	0.506

Models were adjusted for age, sex, BMI, tobacco use, alcohol drinking, coffee drinking, heart failure, atrial fibrillation, ESS, total sleep time, lowest SpO2, T90% and AHI; BMI, body mass index, ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index. [a]Odds ratios for every10-unit increase in arousal index measures.

Table S7. Adjusted odd ratios (ORs) and 95% confidence intervals (CIs) of risk of hypertension associated with OSA across quartiles of total arousal index.

Independent Variable	OR[a]	95% CI		P
		Lower	Upper	
Total AI <16.4				
Primary snoring patients	1	/	/	/
OSA	1.08	0.89	1.32	0.438
Total AI 16.4-27.7				
Primary snoring patients	1	/	/	/
OSA	1.44	1.11	1.88	0.007
Total AI 27.7-45.3				
Primary snoring patients	1	/	/	/
OSA	1.56	1.09	2.24	0.015
Total AI >45.3				
Primary snoring patients	1	/	/	/
OSA	2.57	1.27	3.98	0.023

Models were adjusted for age, sex, BMI, tobacco use, alcohol drinking, coffee drinking, heart failure, atrial fibrillation, ESS, total sleep time, lowest SpO2, T90% and AI; BMI, body mass index, ESS, Epworth Sleepiness Scale; AI, arousal index.