Twenty-four–hour Ambulatory Blood Pressure in Children with Sleep-disordered Breathing

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Obstructive sleep apnea causes intermittent elevation of systemic blood pressure (BP) during sleep. To determine whether obstructive apnea in children has a tonic effect on diurnal BP, 24-hour ambulatory blood pressure was obtained from 60 children with mean age of 10.8 ± 3.5 years. Thirty-nine children had obstructive apnea and 21 had primary snoring. Children with obstructive apnea had significantly greater mean BP variability during wakefulness and sleep, a higher night-to-day systolic BP, and a smaller nocturnal dipping of mean BP. Variability of mean arterial pressure during wakefulness was predicted by the desaturation, body mass, and arousal indices, whereas variability during sleep was predicted by apnea–hypopnea and body mass indices. Nocturnal BP dipping was predicted by the desaturation index. There were no significant differences in systolic, diastolic, or mean arterial BP during sleep between the groups. Diastolic BP during wakefulness was significantly different between the groups and correlated negatively with apnea–hypopnea index. We conclude that obstructive apnea in children is associated with 24-hour BP dysregulation and that, independent of obesity, the frequency of obstructive apnea, oxygen desaturation, and arousal contributes to abnormal BP control.

Keywords: obstructive apnea; ambulatory blood pressure; child; cardiovascular

Obstructive sleep apnea (OSA) in adults increases the risk for heart failure, coronary artery disease, and stroke (1–3). The mechanisms underlying the link between OSA and cardiovascular diseases are not completely understood; however, systemic hypertension is thought to be one pathway leading to end-organ damage and cardiovascular morbidity (4–6). The early stages of abnormal blood pressure (BP) control may present with autonomic dysfunction in the form of increased sympathetic activity and/or decreased vagal tone. These autonomic changes alter the diurnal control and variability of BP (7). The adverse effect of abnormal BP control on the cardiovascular system is not only due to hypertension but also to earlier stages of abnormal BP control, such as increased BP variability and decreased nocturnal dipping (8–16). Because children with OSA, in comparison with children with primary snoring, are at greater risk for developing end-organ damage in the form of left ventricular hypertrophy (17), we hypothesized that children with OSA will demonstrate the earlier stages of abnormal BP control in the form of elevation and decreased dipping of nocturnal BP and an increase in BP variability. Some of the results of these studies have been reported previously in the form of an abstract (18).

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METHODS

Study Design

Pediatric subjects who were referred for evaluation of obstructive breathing disorder during sleep underwent polysomnography (PSG) with continuous BP recording, followed by a 24-hour recording of ambulatory blood pressure (AMBP). Evaluation at the time of enrollment consisted of a history and physical examination, BP, and body mass index (BMI). All subjects presented with a history of snoring 7 nights per week. PSG results were used to divide subjects into those with OSA and those with primary snoring. Subjects were classified as having primary snoring when they had no evidence of nocturnal hypoventilation and had an obstructive apnea–hypopnea index (AHI) between 0 and 1 per hour of sleep (Group 1). Subjects with AHI greater than 1 per hour of sleep were classified as having OSA and were further subdivided into two groups: those with AHI from 1 to 5 (Group 2) and those with AHI greater than 5 per hour of sleep (Group 3). Informed consent was obtained from the parents/legal guardian of each child, and assent was obtained from children older than 11 years of age. The Institutional Review Board of Cincinnati Children's Hospital Medical Center, Ohio, approved the study.

Study Group

Subjects aged 5 to 17 years, who were referred to the pediatric Sleep Disorder Clinic at Cincinnati Children's Hospital Medical Center for evaluation of obstructive breathing during sleep, were recruited sequentially. Children with genetic syndromes, children with chronic medical conditions including psychiatric conditions and attention deficit/hyperactivity disorders, children with conditions that might alter BP, and children who receive daily medications were excluded from the study.

PSG

PSG studies were performed overnight according to the American Thoracic Society standards (19, 20) using computerized systems (Grass; Telefactor, West Warwick, RI). The following parameters were recorded during the study: (*1*) EEG, (*2*) right and left electrooculogram, (*3*) submental and tibial EMG, (*4*) ECG, (*5*) nasal/oral airflow measured by thermocouple, (*6*) end-tidal Pco_2 measured at the nose by infrared capnometry and Sa_{O_2} using the Nelcor N1000 (Nelcor, Van Nuys, CA) and oximeter pulse waveform, (*7*) snoring microphone, (*8*) video monitoring using an infrared video camera, and (*9*) chest and abdominal wall motion by computer-assisted respiratory inductance plethysmograph (Somnostar; Noninvasive Monitoring System Inc., Miami Beach, FL).

The following parameters were measured.

Sleep staging was scored according to published standards (21). Arousals were defined as recommended by the American Sleep Disorders Association (22). Awakening from sleep was defined as an increase in the frequency of the EEG for more than 15 seconds.

Obstructive apnea was defined as the presence of chest/abdominal wall motion in the absence or decrease of airflow and/or the sum channel from the inductive plethysmography by more than 80% of the preceding breath. All obstructive events greater than or equal to two breaths duration were counted.

Obstructive hypopnea was defined as a reduction in airflow and/or the sum channel from the inductive plethysmography between 20 to 50% in the presence of chest/abdominal wall motion, associated with oxyhemoglobin desaturation greater than/or equal to 4% and or followed by an arousal.

AHI was defined as the number of obstructive apneas and obstructive hypopneas per hour of sleep.

Oxyhemoglobin desaturation index (DI) was defined as the number of events per hour of sleep when Sa_{O_2} decreased by 4% or greater.

The average end-tidal Pco_2 was calculated as an average of the maximum values per 30-second epoch. Maximum carbon dioxide (CO_2) level and time spent during sleep with an end-tidal CO_2 level above 45 and 50 mm Hg were calculated. The diagnosis of alveolar hypoventilation during sleep was made when two-thirds of the sleep time was spent with an end-tidal CO_2 higher than 45 mm Hg and/or 10% of the time was spent with level above 50 mm Hg.

BP Recording

BP was recorded with a SpaceLab monitor (Spacelabs Medical, Redmond, WA). The reproducibility and validity of Spacelabs monitors have been extensively studied (23–28). Subjects were asked to keep a sleep diary and report their wake and sleep time. We ensured that sleep–wake time was clearly documented before an AMBP study was considered acceptable. When in doubt, the research coordinator contacted the child's parent to confirm the reported data. The monitor was programmed to cycle every 15 minutes, giving a maximum number of measurements of 96 per 24 hours. The readings were divided into BP during wakefulness and BP during sleep on the basis of the information acquired from the sleep diary. The study was considered adequate when a minimum of 70% of the measurements were obtained without errors both for sleep and/or wake BP. The effect of BP recording on sleep was derived from the BP data acquired during PSG from 41 subjects. The percentage of BP measurements associated with an arousal or awakening in the 30-second epoch that preceded the measurement and the 30 seconds during the measurement was calculated. The BP cuff was placed around the same arm as the pulse oximeter. The timing of BP measurement could therefore be accurately determined because cuff inflation was associated with gradual loss of the pulse amplitude waveform obtained from the oximeter. The following parameters were obtained and/or calculated from the continuous BP recording.

Measures of BP variability. BP variability was derived from the 24-hour AMBP by calculating the average SD of awake and sleep systolic, diastolic, and mean BP.

Measures of nocturnal BP dipping. The degree of systolic, diastolic, and mean BP dipping during sleep was derived by calculating the difference between awake and sleep BP obtained from 24-hour AMBP and expressed as a percentage of BP during wakefulness. To determine whether the change in the degree of BP dipping is stage specific, the difference between mean awake BP derived from the 24-hour AMBP and BP obtained during the PSG while awake in bed and during each stage of sleep was also calculated. A comparison between groups for night-to-day systolic BP ratio was performed, given its prognostic value in predicting future cardiovascular events (14, 15).

Average BP during wakefulness and sleep. Average systolic, diastolic, and mean arterial BP during wakefulness and sleep was calculated. Pressure load was measured by calculating the percentage of systolic and diastolic BP measurements above the 95th percentile for awake BP. Published age-appropriate values for the 95th percentile for BP according to age and sex were used to determine the percentage of BP greater than the 95th percentile (29).

Statistical Analysis

All results are expressed as mean ± SD. Log transformation of BMI, AHI, BP SDs and night-to-day systolic BP ratio was performed to achieve normal distribution. BP measurements were expressed as a mean of awake and sleep BP. To control for the effect of the wide age range on BP, we calculated the difference between measured BP and the published systolic and diastolic 95th percentile for each subject (30). We indexed this value to the 95th percentile using the following formula:

$$\text{BP index} = \frac{(\text{Measured BP} - \text{BP at 95th percentile})}{\text{BP at 95th percentile}} \times 100$$

The average of this index was compared between groups. BP results were also expressed as a percentage of the 95th percentile and compared between groups. The BMI was converted into a Z score according to the standards published by the CDC (Z BMI) (31). For comparison of means, a one-factor analysis of variance was performed. An orthogonal contrast for a linear trend was used to determine if a linear trend existed across the mean of the groups: primary snorers, children with an AHI between 1 and 5, and children with an AHI greater than 5. Pearson correlation was performed between log-transformed BP measurements and log-transformed polysomnographic and demographic variables. Multiple regression analysis was performed to identify demographic and polysomnographic factors that might predict measures of BP variability and nocturnal BP dipping. The following independent variables were entered in a backward elimination regression analysis: age, sex, race, Z BMI, AHI, arousal index, DI, lowest Sa_{O_2}, and maximum end-tidal CO_2. Variables with a p value less than or equal to 0.05 were kept in the model. To control for possible effect of BMI on nocturnal BP dipping, this variable was forced into the model despite a p value greater than 0.05. Race was also forced into the model to control for ethnicity.

RESULTS

Study Population

Seventy-two subjects consented to participate in the study. Twelve subjects requested the discontinuation of BP recording during the night and refused to complete the 24-hour AMBP recording. Subjects who withdrew from the study were: 41% females, 11.6 ± 2.6 years old with a BMI of 28.7 ± 9.7. Sixty subjects completed the 24-hour AMBP monitoring. Forty-nine subjects completed the BP recording during the PSG and 24-hour AMBP monitoring. Eleven subjects refused to complete BP monitoring during PSG but adequately completed the 24-hour study. The demographic and polysomnographic characteristics are shown in Tables 1 and 2.

Effect of BP Recording on Sleep

The effect of BP recording on sleep efficiency and frequency of arousals was determined by calculating the percentage of BP

TABLE 1. DEMOGRAPHIC AND POLYSOMNOGRAPHIC CHARACTERISTICS OF 60 SUBJECTS WHO COMPLETED 24-HOUR AMBULATORY BLOOD PRESSURE RECORDING

	24-h AMBP (*n* = 60)			
	Group 1	Group 2	Group 3	p Value
n	21	17	22	
Age, yr	10.1 ± 3	10.7 ± 4	11.6 ± 3	NS
Male, %	57	53	68	NS
White, %	90	53	64	0.03
BMI	23 ± 8	24 ± 8.7	31 ± 9	0.01
AHI	0.17 ± 0.2	2.7 ± 0.9	26.8 ± 28	< 0.001
DI	0.75 ± 0.7	1.7 ± 1.6	19.9 ± 25	0.002
Lowest saturation	91 ± 2.3	90 ± 2.9	80 ± 10	< 0.001
Maximum carbon dioxide	49 ± 1.9	51 ± 3.5	54 ± 7.8	0.003
Arousal index	11 ± 7	10 ± 4	25 ± 25	0.003

Definition of abbreviations: AHI = apnea–hypopnea index; AMBP = ambulatory blood pressure; BMI = body mass index; DI = desaturation index; NS = not significant.

Group 1 = AHI less than 1 per hour of sleep; Group 2 = AHI 1 to 5 per hour of sleep; Group 3 = AHI greater than 5 per hour of sleep.

TABLE 2. DEMOGRAPHIC AND POLYSOMNOGRAPHIC CHARACTERISTICS OF 49 SUBJECTS WHO COMPLETED BLOOD PRESSURE RECORDING DURING POLYSOMNOGRAPHY FOLLOWED BY 24-HOUR AMBULATORY BLOOD PRESSURE MONITORING

	24-h AMBP and BP-PSG (*n* = 49)			
	Group 1	Group 2	Group 3	p Value
n	14	17	18	
Age	10.6 ± 3	10.7 ± 4	12 ± 3	NS
Male, %	57	58	66	NS
White, %	86	47	61	NS
BMI	23.9 ± 8.4	24.1 ± 8.7	31.7 ± 9	0.03
AHI	0.15 ± 0.16	2.7 ± 0.9	34 ± 34	< 0.001
DI	0.5 ± 0.5	1.7 ± 1.6	21 ± 27	0.005
Lowest saturation	91 ± 2.1	90 ± 2.9	79 ± 11	< 0.001
Maximum carbon dioxide	49 ± 2	51 ± 3.5	56 ± 8	0.01
Arousal index	12 ± 9	10 ± 4	28 ± 27	0.004

Definition of abbreviations: AHI = apnea–hypopnea index; AMBP = ambulatory blood pressure; BMI = body mass index; BP = blood pressure; DI = desaturation index; NS = not significant; PSG = polysomnography.

Group 1 = AHI less than 1 per hour of sleep; Group 2 = AHI 1 to 5 per hour of sleep; Group 3 = AHI greater than 5 per hour of sleep.

TABLE 3. TWENTY-FOUR–HOUR AMBULATORY SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE (mm Hg) OBTAINED FROM 60 SUBJECTS DURING WAKEFULNESS AND DURING SLEEP*

	Group 1	Group 2	Group 3	p Value
Mean wake SBP	115 ± 7	116 ± 10	116 ± 8	NS
Mean sleep SBP	102 ± 6	106 ± 10	107 ± 9	NS
Mean wake DBP	70 ± 5	70 ± 7	66 ± 5	0.014
Mean sleep DBP	58 ± 4	60 ± 6	58 ± 6	NS
Mean wake MAP	86 ± 4	85 ± 6	83 ± 4	NS
Mean sleep MAP	74 ± 4	76 ± 6	76 ± 6	NS
% SBP > 95th	22. ± 15	21 ± 25	26 ± 22	NS
% DBP > 95th	13 ± 10	13 ± 15	11 ± 14	NS

Definition of abbreviations: AHI = apnea–hypopnea index; DBP = diastolic blood pressure; % DBP > 95th = percentage of diastolic blood pressure measurements above the 95th percentile; MAP = mean arterial pressure; NS = not significant; SBP = systolic blood pressure; % SBP > 95th = percentage of systolic blood pressure measurements above the 95th percentile.

Group 1 = AHI less than 1 per hour of sleep; Group 2 = AHI 1 to 5 per hour of sleep; Group 3 = AHI greater than 5 per hour of sleep.

* Also shown are the systolic and diastolic BP load expressed as the percentage of BP measurements above the 95th percentile across the three groups.

measurements obtained during the PSG that were associated with arousals and those associated with full awakening. Forty-one of the 49 subjects who completed BP recording during PSG had data that could be accurately analyzed. The remaining eight subjects requested that the BP monitor be placed on the opposite arm from the oximeter; therefore, the exact timing of the measurement could not be estimated and the relationship between cuff inflation and arousals could not be determined. The percentage of measurements associated with arousals was 18% ± 6, 16% ± 10, and 20% ± 11 for Groups 1, 2, and 3, respectively (p = not significant). The percentage of measurements associated with arousals that led to awakenings was 5% ± 5, 4% ± 4, and 4% ± 5, respectively. These results show that more than 80% of the measurements do not affect sleep and that a very small number of measurements lead to full awakening. Total sleep time was similar for all three groups. Sleep time was 390 ± 55, 381 ± 49, and 391 ± 77 minutes for Groups 1, 2, and 3, respectively. Sleep efficiency after sleep onset as a percentage of total sleep time was 89% ± 7, 89% ± 6, and 85% ± 10 for Groups 1, 2, and 3, respectively.

For subjects who completed 24-hour AMBP recording and BP monitoring during PSG, there was no significant difference found between nocturnal BP obtained in the sleep laboratory and nocturnal BP obtained at home. Mean sleep systolic BP at home was 104 ± 6, 106 ± 10, and 107 ± 10 mm Hg, whereas mean systolic BP during PSG was 101 ± 8, 104 ± 10, and 110 ± 11 mm Hg for Groups 1, 2, and 3, respectively. Mean sleep diastolic BP at home was 58 ± 5, 60 ± 6, and 59 ± 6 mm Hg, whereas mean sleep diastolic BP during PSG was 58 ± 5, 59 ± 5, and 60 ± 8 for Groups 1, 2, and 3, respectively.

Systolic, Diastolic, and Mean Arterial BP

For daytime BP, a significant difference in diastolic BP was observed among the three groups with the lowest pressure seen in Group 3. There was no difference measured among groups for systolic or mean arterial BP. Similarly, there was no significant difference detected among groups for systolic, diastolic, and mean arterial BP during sleep. A trend toward a higher systolic BP during sleep was observed with increased severity of OSA but did not reach statistical significance (Table 3). When BP index was used to normalize for the effect of age and growth on BP, a trend similar to the one seen with absolute BP was observed (Figure 1). A significant trend for diastolic BP index during wakefulness was demonstrated. There was no change in the trend of systolic and diastolic BP across groups when BP was expressed as a percentage of the 95th percentile (data not shown). There was also no significant difference in pressure load for systolic or diastolic BP among the three groups (Table 3).

BP Variability

A dose-dependent increase in BP variability was observed across the three groups with the largest SD seen in subjects with AHI greater than 5 per hour of sleep. A significant linear trend was found for the variability of awake systolic and mean arterial BP and for sleep systolic, diastolic, and mean BP (Figures 1 and 2). This observation demonstrates that increased BP variability with

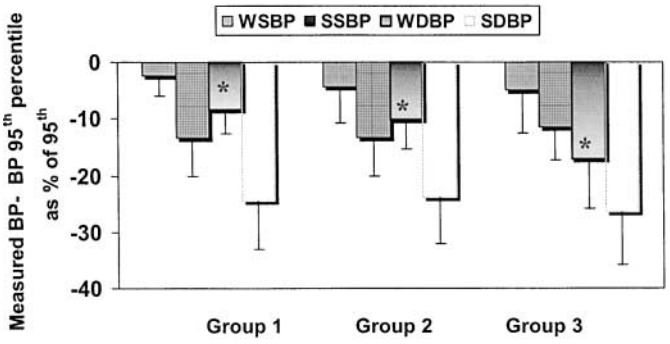

Figure 1. Trend for blood pressure (BP) index for systolic and diastolic BP during wakefulness and during sleep across the three groups. Diastolic BP index showed a significant trend across the three groups with the larger difference seen in Group 3 (*p = 0.005). Group 1 = apnea–hypopnea index (AHI) less than 1 per hour of sleep; Group 2 = AHI 1 to 5 per hour of sleep; Group 3 = AHI greater than 5 per hour of sleep. SDBP = sleep diastolic blood pressure; SSBP = sleep systolic blood pressure; WDBP = awake diastolic blood pressure; WSBP = awake systolic blood pressure.

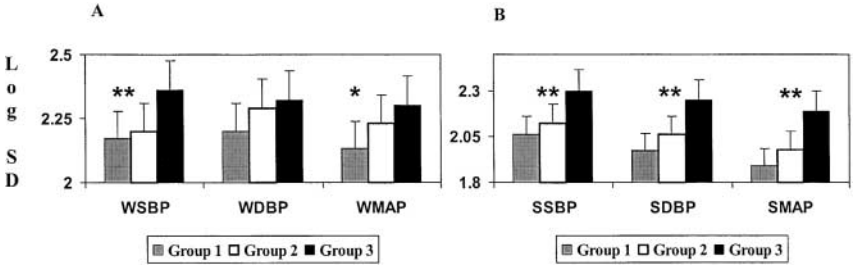

Figure 2. BP variability during wakefulness and sleep. (*A*) Log-transformed SD across the three groups of systolic (**p < 0.01), diastolic, and mean arterial BP (*p = 0.014) during wakefulness. (*B*) Log-transformed SD across the three groups of systolic (**p < 0.01), diastolic (**p < 0.01), and mean arterial BP (**p < 0.01) during sleep. Group 1 = AHI less than 1 per hour of sleep; Group 2 = AHI 1 to 5 per hour of sleep; Group 3 = AHI greater than 5 per hour of sleep. WMAP = awake mean arterial blood pressure; SMAP = sleep mean arterial blood pressure.

an increased severity of OSA is not limited to nighttime BP but persists during wakefulness.

Nocturnal BP Dipping

A significant linear trend for the difference between awake and sleep BP expressed as a percentage of awake BP was observed for systolic, diastolic, and mean arterial BP from Groups 1 to 3. The trend from Group 1 to Group 3 was 11.5% ± 4.2, 8.6% ± 4.9, 7.4% ± 7.3 for systolic BP (p = 0.01); 17.5% ± 5, 14% ± 8, 11% ± 9 for diastolic BP (p = 0.01); and 13.4% ± 4.3, 10.6% ± 5.9, 8.4% ± 6.7 for mean arterial pressure (p = 0.002). The ratio of night-to-day systolic BP was 0.88 ± 0.04, 0.90 ± 0.04, and 0.93 ± 0.07 for Groups 1, 2, and 3, respectively (p = 0.02). These results indicate that children with OSA have a night-to-day systolic BP ratio that surpasses the cutoff ratio of 0.899 for females and 0.9009 for males that is known to increase the risk for cardiovascular morbidity in adults (14, 15). The difference between awake BP and BP during different stages of sleep demonstrates that BP dipping during sleep is not stage specific and that the effect of OSA on nocturnal BP is similar during REM and non–REM sleep (Figure 3).

Bivariate Correlations

Diastolic BP during wakefulness correlated negatively with AHI and DI and positively with Z BMI. BP variability during wakefulness correlated positively with log AHI, DI, and Z BMI, whereas BP variability during sleep correlated positively with log AHI, maximum end-tidal CO_2, and Z BMI. The degree of nocturnal BP dipping correlated negatively with measures of severity of OSA, namely, log AHI, DI, and maximum end-tidal CO_2 (Table 4). These results show that there is an association between the degree of BP dysregulation and increased severity of OSA in children with sleep-disordered breathing.

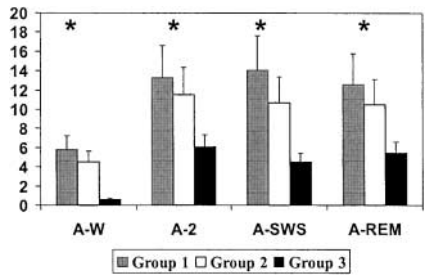

Figure 3. Difference between mean arterial BP obtained from 24-hour ambulatory BP recording during daytime wakefulness, and BP during wakefulness in bed, and BP during different stages of sleep. A significant linear trend was observed for the difference in mean arterial BP across the three groups, with the largest difference seen in Group 1 and the smallest in Group 3 (*p = < 0.05). Group 1 = AHI less than 1 per hour of sleep; Group 2 = AHI 1 to 5 per hour of sleep; Group 3 = AHI greater than 5 per hour of sleep. A−W = difference in mean arterial BP when active awake and awake in bed; A−2 = difference in mean BP when active awake and Stage 2 sleep; A−SWS = difference in mean BP when active awake and slow wave sleep (SWS); A−REM = difference in mean BP when active awake and REM sleep.

Multiple Regression Analysis

BP variability. Variability of mean arterial pressure during wakefulness was predicted by a model (p = < 0.0001) that included DI (p = 0.002), Z BMI (p = 0.005), and arousal index (p = 0.006). Variability of mean arterial pressure during sleep was predicted by a model (p = < 0.0001) that included AHI (p = 0.001) and Z BMI (p = 0.003). Models for BP variability and the dependent variables remained significant after controlling for ethnicity.

Nocturnal dipping of BP. Nocturnal BP dipping was predicted by a model (p = 0.015) that only included DI. The model and the dependent variable remained significant after controlling for Z BMI and ethnicity.

These results suggest that sleep-related factors that affect BP variability during sleep differ from factors affecting variability during wakefulness and that intermittent oxygen desaturation contributes to BP dysregulation in children with OSA both during wakefulness and sleep.

Diastolic BP. Diastolic BP index during wakefulness was predicted by a model (p = < 0.001) that included age (p = < 0.001), AHI (p = 0.014), race (p = 0.03), and Z BMI (p = 0.04).

DISCUSSION

This study demonstrates that children with OSA show evidence of dysregulation of systemic BP in the form of increased BP variability and a decreased degree of nocturnal dipping and that BP dysregulation correlates with measures of severity of OSA.

Previous studies have demonstrated that children with OSA tend to have higher systolic and/or diastolic BP compared with control subjects; however, the prevalence of systemic hypertension remained insignificant between the two groups (27, 32–35). In our study, we have shown that the early stages of BP dysregulation in children do not present with sustained elevation of BP but rather with an alteration in the circadian rhythm of BP profile and an increase in BP variability. Although this study concurs with previous observations as to the lack of significant difference in the prevalence of hypertension in children with OSA compared with control subjects, it differs regarding the trend of diastolic BP during sleep and during wakefulness. Marcus and coworkers (34) have shown that children with OSA tend to have a higher diastolic BP during sleep compared with children with primary snoring. We, on the contrary, showed no difference among groups in diastolic BP during sleep. The discrepancy between the two studies raises an important ques-

TABLE 4. PEARSON CORRELATION BETWEEN BLOOD PRESSURE PARAMETERS AND POLYSOMNOGRAPHIC VARIABLES*

	Wake Diastolic BP index	Wake–Sleep MAP	Log SD WMAP	Log SD SMAP
Log AHI	−0.37 (p = 0.0037)	−0.3 (p = 0.019)	0.29 (p = 0.02)	0.47 (p = 0.0002)
DI	−0.38 (p = 0.0023)	−0.31 (p = 0.013)	0.30 (p = 0.01)	NS
Maximum carbon dioxide	NS	−0.29 (p = 0.024)	NS	0.31 (p = 0.013)
Z BMI	0.28 (p = 0.03)	NS	−0.45 (p ⩽ 0.0001)	−0.46 (p = 0.0002)

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; BP = blood pressure; DI = desaturation index; NS = not significant; SMAP = sleep mean arterial pressure; Wake–sleep MAP = difference between wake to sleep mean arterial pressure; WMAP = wake mean arterial pressure; Z BMI = Z score for BMI.

* Four BP parameters, namely, diastolic BP index, difference between wake-to-sleep mean arterial BP as a measure of nocturnal BP dipping, and log-transformed SD of awake and asleep BP as a measure of variability were correlated with polysomnographic variables and Z BMI.

tion as to whether the cardiovascular morbidity of OSA in children is age dependent, given the younger age of the population in Marcus's study. Future studies are needed to determine if young age increases the susceptibility to cardiovascular morbidity from OSA. This study is the first to characterize the diurnal and nocturnal BP profile in children with OSA. We have observed in this study a lower diastolic BP during wakefulness in children with severe OSA compared with children with a milder degree of sleep apnea and children with simple snoring. Low diastolic BP during wakefulness seen in children with more severe OSA suggests abnormal elastic recoil of blood vessels during diastole. This finding, in addition to increased BP variability, could represent the early stages of autonomic and/or endothelial dysfunction in children with OSA (36–38).

In hypertensive and normotensive adults, increased BP variability and decreased nocturnal BP dipping are associated with end-organ damage and increased risk for cardiovascular diseases (1, 2, 11, 12, 14–16, 22). In a prospective study that examined prognostic significance of BP variability in 1,542 subjects 40 years or older, Kikuya and coworkers (39) showed a significant linear relationship between daytime systolic AMBP variability and relative risk for cardiovascular mortality. In a study of 1,433 subjects, the variance of systolic BP was significantly associated with coronary artery disease after adjustment for mean systolic pressure (40). The relationship between BP variability and cerebrovascular diseases has been examined in several studies. Havlik and coworkers (10) demonstrated in a prospective study that systolic BP variability in midlife is associated with increased risk for white matter lesions in the brain later in life and that subjects who were in the highest category of systolic BP variability had significantly more brain atrophy. The importance of this observation stems from the knowledge that the presence of periventricular white matter lesions, which are thought to be caused by small-vessel disease, strongly correlates with progressive loss of cognitive function (18, 41, 42). Knowledge about the association between BP variability and adverse cardiovascular outcomes in children is limited. Because evidence is growing that children with symptoms of obstructive breathing during sleep are at an increased risk for low academic performance (43–46), further studies are needed to determine whether OSA-associated neurocognitive morbidity in children is related to BP dysregulation and small-vessel disease.

Several studies have examined the relationship between 24-hour BP profile and end-organ damage and have demonstrated that AMBP is superior prognostically to office BP (47, 48). Verdecchia and coworkers (14, 15) studied a group of 1,187 hypertensive subjects and 205 normotensive control subjects and found that a night-to-day systolic BP ratio greater than 0.899 for men and greater than 0.9009 for women was associated with significantly higher risk for cardiovascular events after adjusting for risk factors and 24-hour systolic BP. In our study, we demonstrate that children with OSA have a higher night-to-day systolic BP ratio compared with children with simple snoring. More recently, Hoshide and coworkers (49) examined the association between nondipping of nocturnal BP and left ventricular geometry in normotensive subjects. They demonstrated that left ventricular mass index and relative wall thickness were greater in nondippers than in dippers, suggesting that even in the absence of sustained diurnal or nocturnal hypertension, nondipping of BP increases the risk for myocardial damage. It is therefore plausible that the BP profile we described in children with sleep-disordered breathing could lead to future cardiovascular morbidity.

We observed in this study that increased BP variability in subjects with OSA is present both during sleep and wakefulness, suggesting that the hemodynamic and blood gas abnormalities associated with OSA have a tonic effect on the cardiovascular system. In subjects with OSA, the repeated fall in intrathoracic pressure and the marked increase in left ventricular transmural pressure and afterload contribute largely to BP variability during sleep. In addition to the mechanical effects of OSA on the systemic circulation, there is also repeated activation of the central and peripheral chemoreceptors, which elicit both hyperventilation and increased sympathetic traffic to peripheral blood vessels. Simultaneously, the enhanced chemoreceptor response elicits an inhibitory response from the baroreceptors and pulmonary stretch receptors. Therefore, the final BP response and variability are the product of this intricate interaction among the chemoreceptors, baroreceptors, pulmonary stretch receptors, and the mechanical effect of OSA on cardiac dynamics and function (50, 51). This study has shown that the AHI is a strong predictor of BP variability during sleep, whereas the frequency of oxygen desaturation is a strong predictor for daytime variability. A plausible explanation of these findings is that during wakefulness, when the mechanical effect of OSA is not affecting BP variability, there is a residual perturbing effect of intermittent hypoxia on the balance between chemoreceptor and baroreceptor function. We have also demonstrated that the DI is the best predictor of the degree of BP dipping. This suggests that intermittent hypoxia plays an important role in BP dysregulation in children with OSA.

This study shows the independent effects of obesity and OSA on BP variability. This study has shown that BMI contributes to increased BP variability both during wakefulness and sleep. Studies that examined the changes in the autonomic nervous system among obese subjects showed that obesity is associated with decreased sympathetic and parasympathetic tone, altered ratio of sympathetic to parasympathetic tone, and decreased baroreceptor sensitivity. Both the duration of obesity and the fat distribution contribute to these autonomic changes (52–56). It is likely that obesity and OSA contribute to dysregulation of

BP by different mechanisms and independently contribute to cardiovascular morbidity.

There are several limitations to this study. The control group consisted of children with primary snoring. It is possible that with normal control subjects a significant trend for mean BP across the three groups would have been identified. It is also likely that the small sample size provided limited power to detect a significant difference in nocturnal BP among the three groups. Although this study showed an independent effect of OSA on BP regulation, it does not address the possibility that OSA might have a differential effect on BP control in lean versus obese children.

In summary, this study shows that children with OSA have evidence of BP dysregulation that manifests during sleep and wakefulness. These findings could represent the early stages of BP dysregulation, which could ultimately lead to sustained hypertension if OSA is left untreated or if additional risk factors for hypertension develop over time. Lack of nocturnal dipping and increased BP variability may also be useful in determining a subset of patients for whom more aggressive management of OSA is indicated.

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