Activity-Adjusted 24-Hour Ambulatory Blood Pressure and Cardiac Remodeling in Children with Sleep Disordered Breathing

Raouf Amin, Virend K. Somers, Keith McConnell, Paul Willging, Charles Myer, Marc Sherman, Gary McPhail, Ashley Morgenthal, Matthew Fenchel, Judy Bean, Thomas Kimball, Stephen Daniels

Abstract—Questions remain as to whether pediatric sleep disordered breathing increases the risk for elevated blood pressure and blood pressure–dependent cardiac remodeling. We tested the hypothesis that activity-adjusted morning blood pressure surge, blood pressure load, and diurnal and nocturnal blood pressure are significantly higher in children with sleep disordered breathing than in healthy controls and that these blood pressure parameters relate to left ventricular remodeling. 24-hour ambulatory blood pressure parameters were compared between groups. The associations between blood pressure and left ventricular relative wall thickness and mass were measured. 140 children met the inclusion criteria. In children with apnea hypopnea index <5 per hour, a significant difference from controls was the morning blood surge. Significant increases in blood pressure surge, blood pressure load, and in 24-hour ambulatory blood pressure were evident in those whom the apnea hypopnea index exceeded 5 per hour. Sleep disordered breathing and body mass index had similar effect on blood pressure parameters except for nocturnal diastolic blood pressure, where sleep disordered breathing had a significantly greater effect than body mass index. Diurnal and nocturnal systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure predicted the changes in left ventricular relative wall thickness. Therefore, sleep disordered breathing in children who are otherwise healthy is independently associated with an increase in morning blood pressure surge, blood pressure load, and 24-hour ambulatory blood pressure. The association between left ventricular remodeling and 24-hour blood pressure highlights the role of sleep disordered breathing in increasing cardiovascular morbidity. (Hypertension. 2008;51:84-91.)

Key Words: sleep apnea ■ children ■ ambulatory blood pressure ■ blood pressure surge ■ blood pressure load ■ cardiac remodeling ■ hypertrophy

The association between sleep disordered breathing (SDB) and cardiovascular morbidity in adults has become an important consideration in the management of patients with SDB. Results from numerous cross-sectional and prospective studies of blood pressure (BP) control in adults support the concept that hypertension is an intermediate end point between SDB and cardiovascular disease.1,2 Further support of this concept is derived from studies linking SDB to atherosclerotic pathways.3–6 These studies provide insight into the mechanisms of vascular injury secondary to SDB. Although the impact of duration of this disorder on the development of risk factors for cardiovascular disease is difficult to estimate, morbidity secondary to SDB seems to manifest gradually, often taking decades. As such, with the exception of isolated cases of heart failure, children with SDB rarely show evidence of cardiovascular disease. Thus far, studies addressing whether children with SDB acquire risk factors for the early development of cardiovascular disease are inconclusive.

Findings from several pediatric studies suggest that BP dysregulation is associated with the presence of SDB. We have previously demonstrated that in a group of children with SDB, the severity of the disorder was associated with increased BP variability and decreased nocturnal dipping.7 Additionally, several cross-sectional studies have described trends of increasing BP with greater frequency of apnea and hypopneas index (AHI) during sleep.8–10 To date, however, the level of SDB severity at which BP in pediatric SDB patients begins to diverge from that of healthy controls is not known. Furthermore, the relationship between 24-hour ambulatory BP in children with SDB and changes in left ventricular geometry has not yet been evaluated.

Twenty-four–hour ambulatory BP monitoring provides a window through which several measures of BP control can be examined. Among these measures are the rate of BP rise during the transition from sleep to wakefulness (referred to as morning BP surge), BP load, and diurnal and nocturnal BP measurements, all of which are important predictors of cardiovascular disease.11–15 These parameters are known to be influenced by physical activity, degree of adiposity, and...
demographic characteristics. A rigorous comparison of these parameters in children with SDB and healthy controls that adjusts for these confounding factors has not, however, been performed. We thus designed the current study to test the hypothesis that the morning BP surge, BP load, and diurnal and nocturnal BP are significantly higher in children with SDB than in healthy controls. We also endeavored to determine the level of SDB severity in children at which these specific BP measures significantly differ from healthy controls and how these measures relate to measures of left ventricular remodeling. The knowledge gained will provide an insight into the early cardiovascular changes associated with SDB in children and serve as a useful guideline for the management of children with the disorder.

Methods

Subjects

Children ranging in age from 7 to 13 years with nightly snoring and hypertrophy of the tonsils and adenoids were recruited for this study. The inclusion criteria for the SDB group consisted of absence of chronic medical conditions and genetic syndromes, a polysomnogram consistent with the diagnosis of SDB which was defined as obstructive AHI greater than 1 per hour of sleep. Age- and gender-matched healthy children comprised a control group. Additional inclusion criteria for the control group were: (1) absence of history of obstructive breathing during sleep; and (2) absence of SDB or alveolar hypoventilation on polysomnography. Children receiving chronic medications were excluded if they were unable to temporally discontinue their use. The duration of discontinuation of medications was recommended by the hospital pharmacists based on the pharmacokinetics of the drug. Children enrolled in this study were newly recruited and were not part of any of our prior studies.

Polysomnography

Polysomnography studies were performed overnight according to the American Thoracic Society standards using computerized systems (Grass, Telefactor). The interpretation of polysomnography was performed by the investigator RA who was blinded as to which group subjects were enrolled in and to the results of 24-hour ambulatory BP monitoring. The interpretations of BP and actigraphy were performed by a coordinator who was also blinded to the results of polysomnography.

Twenty-Four-Hour Ambulatory BP Monitoring

Noninvasive ambulatory BP was performed with an automatic BP monitor (SpaceLabs 90207), which recorded BP and heart rate (HR) every 15 minutes during the awake period and during sleep. BP recording was obtained approximately 2 weeks after the polysomnography studies. For the purpose of calculating average BP during wakefulness and sleep, data were synchronized at the point of sleep onset, as determined by the actigraphy readings. The 15-minute BP and HR readings were then averaged into 1-hour epochs for each subject. Sleep data were defined as Time ≤8 hours, where the actigraphy continued to indicate sleep. Wake data were defined as Time ≥10 hours, where the actigraphy indicated wake. Data from the 9th hour from sleep onset included varying periods of wakefulness and sleep and, therefore, were not used. For the purpose of calculating morning BP surge, data were synchronized at the point of wake onset, as determined by the actigraphy readings. The morning BP surge was defined as the slope of BP from the beginning of the last hour of sleep to the end of the first hour of awakening. BP load was measured by calculating the percentage of systolic and diastolic measurements above the 95th percentile according to published age and gender-appropriate values.

Assessment of Physical Activity by Actigraphy

Subjects wore an actigraph (Ambulatory Monitoring Inc) on their wrist during wakefulness and sleep. Activity was recorded in 10-second epochs throughout the 24-hour period. A weighted activity per subject was calculated by weighting by 5 the actigraphy reading corresponding to the 15-minute BP measurement, adding the previous 5 actigraphy readings, and then calculating the average. The square root transformation was applied to all activity measures to reduce the positive skew of the distribution and to improve normality.

Echocardiography

Two-dimensional and two-dimensionally directed M-mode echocardiographic images were recorded to determine relative wall thickness and left ventricular mass as previously described.

Statistical Analysis

All results are expressed as mean±SD, except where noted as mean±SEM. Log transformation of AHI was performed to achieve normal distribution. The body mass index (BMI) was converted into a Z score according to the standard published by the CDC. For comparison of means, a 1-way analysis of variance was performed for Age, BMI, and BMIZ; differences in other continuous variables were tested with the Kruskal-Wallis nonparametric test. Pearson chi-square tests were used to measure differences between groups for gender, race, and BP load variables. A significance level of α<0.05 was used for all tests.

Inferential Analysis

Three-step analyses were performed to determine the independent effect of SDB on BP parameters. The first step aimed at determining whether a difference in BP and HR existed between the control and the SDB groups by performing a repeated measures analysis and modeling within subject variance/covariance over time. The following independent variables were used: group, time defined as the hourly BP measurements, age, BMI Z score, gender, activity, and race. SDB groups were compared with controls, using Dunnett adjustment. The second step consisted of subgrouping the study population into lean and obese children and performing a repeated measures analysis comparing the LS-means of 4 groups: lean-control, lean-SDB, obese-control, and obese-SDB. Such approach was taken to further discern the influence of SDB from that of obesity in predicting BP. The third step aimed at determining the overall effect of polysomnographic parameters; namely AHI, lowest oxygen saturation, and arousal index on BP. A mixed model analysis was performed with polysomnographic parameters used as continuous variables. A null-model chi-square likelihood ratio test was used to determine goodness-of-fit (P<0.0001) for all models.

The relative predictive contributions of BMI and AHI were tested for a significant difference as follows: both were standardized to unit SD before entry into repeated measures models predicting BP. Their 2 coefficients from a model were then compared using a t test.

The relationship between BP parameters and left ventricular relative wall thickness and mass was measured by partial Pearson correlation adjusted for age and BMI Z score and linear regression analysis. The linear regression controlled for gender and ethnicity in addition to age and BMI Z score.

Initial analyses focused on comparing healthy controls to all SDB subjects. We considered the possibility that a significant divergence of BP parameters in SDB subjects may not occur in mild cases, but does occur in children with higher levels of AHI. Based on descriptive statistics and the distribution of subjects available in our study, we hypothesized that children with AHI ≥5 may exhibit a significant difference in BP parameters from healthy controls. Whereas the primary analyses focused on comparing the control group to the severe group, we also compared the control group to the mild (AHI <5) group.

Informed consent was obtained from the parents/legal guardian of each child, and assent was obtained from children older than 7 years.
of age. The study was approved by the Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

**Results**

Of the 210 recruited children, 140 met the inclusion criteria. Valid sleep BP data were obtained from 134 of the 140 subjects and wake BP data were obtained from 131 subjects. BP morning surge was obtained from 125 subjects. (Demographic and polysomnographic characteristics of those with valid data are shown in Table 1).

**Polysomnography**

Fifty-three percent of subjects with SDB had an AHI between 1.1 and 5 per hour of sleep (mild SDB), whereas 47% of subjects had an AHI >5 (severe SDB). In subjects with severe SDB, the obstructive AHI were more frequent and lasted longer than in those with mild SDB and also were associated with lower oxygen desaturation compared with those with mild SDB and healthy controls (Table 1).

**Group Differences in Blood Pressure Parameters and Heart Rate**

For BP surge, BP load, and diurnal and nocturnal BP, significant differences from healthy controls were measured after adjusting for all covariates when AHI exceeded 5 per hour. A difference from healthy controls in systolic BP surge was also measured at AHI <5 per hour.

**BP Surge**

The adjusted least square estimates±SEM for systolic BP surge were 0.4±0.9, 2.8±0.9, and 3.5±0.9 for healthy controls and mild and severe SDB groups, respectively. Significant differences were measured between healthy controls and subjects with mild SDB (−2.3±0.9, P=0.01) and between controls and those with severe SDB (−3.1±1.0, P=0.002). The estimates for diastolic BP surge were 0.8±0.8, 2±0.9, and 2.7±0.9 for the 3 groups, respectively. Significant difference was measured between controls and subjects with severe SDB (−1.9±0.9, P=0.04). The estimates for mean arterial BP were 0.6±0.7, 2.1±0.8, and 2.9±0.8, for the 3 groups, respectively. Significant difference was measured between controls and subjects with severe SDB (−2.3±0.8, P=0.004).

The difference between the lowest systolic BP in the preceding 3 hours to awakening and BP at the time of awakening was significantly different between children with mild and severe SDB (results not shown).

### Table 1. Demographic and Polysomnographic Characteristics of Children with SDB and Healthy Controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Mild</th>
<th>Severe</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>10.2 (2.1)</td>
<td>9.6 (2.1)</td>
<td>9.8 (2.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Male gender</td>
<td>52%</td>
<td>64%</td>
<td>53%</td>
<td>0.4</td>
</tr>
<tr>
<td>White</td>
<td>79%</td>
<td>52%†</td>
<td>50%†</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI</td>
<td>18.4 (3.6)</td>
<td>20.6 (5.3)†</td>
<td>23.2 (6.2)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>0.3 (1.0)</td>
<td>1.0 (1.0)†</td>
<td>1.4 (1.2)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apnea hypopnea index, #/h</td>
<td>0.3 (0.3)</td>
<td>2.5 (1.2)*</td>
<td>16.6 (16.8)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average end tidal CO2, mm Hg</td>
<td>43.4 (3.0)</td>
<td>43.6 (4.6)</td>
<td>41.3 (8.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>Maximum end tidal CO2, mm Hg</td>
<td>50.3 (3.9)</td>
<td>51.2 (4.1)</td>
<td>53.8 (5.9)†</td>
<td>0.013</td>
</tr>
<tr>
<td>Duration with end tidal CO2&gt;50, s</td>
<td>2.4 (5.7)</td>
<td>6.9 (12.3)‡</td>
<td>15.9 (26.9)†</td>
<td>0.003</td>
</tr>
<tr>
<td># obstructive apnea/night, #/h</td>
<td>0.5 (1.0)</td>
<td>8.4 (6.5)*</td>
<td>58.1 (53.4)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obstructive apnea -lowest desaturation, %</td>
<td>94.5 (0.7)</td>
<td>91.8 (3.7)</td>
<td>87.7 (7.5)‡</td>
<td>0.035</td>
</tr>
<tr>
<td>Obstructive apnea average duration, s</td>
<td>3.1 (5.1)</td>
<td>10.3 (4.0)*</td>
<td>12.1 (2.4)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obstructive apnea longest duration, s</td>
<td>3.4 (5.5)</td>
<td>14.6 (7.1)*</td>
<td>22.6 (7.0)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td># obstructive hypopnea/night, #/h</td>
<td>1.2 (1.5)</td>
<td>7.3 (5.6)*</td>
<td>46.2 (53.4)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obstructive hypopnea -lowest desaturation, %</td>
<td>94.0 (1.0)</td>
<td>92.3 (2.6)</td>
<td>89.1 (7.4)‡</td>
<td>0.046</td>
</tr>
<tr>
<td>Obstructive hypopnea average duration, s</td>
<td>6.2 (6.9)</td>
<td>12.9 (3.5)*</td>
<td>13.2 (2.9)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obstructive hypopnea longest duration, s</td>
<td>7.7 (8.7)</td>
<td>19.5 (6.3)*</td>
<td>24.5 (6.6)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% sleep time in stage 1</td>
<td>3.5 (5.5)</td>
<td>2.9 (1.5)</td>
<td>4.5 (4.6)</td>
<td>0.1</td>
</tr>
<tr>
<td>% sleep time in stage 2</td>
<td>48.3 (9.7)</td>
<td>50.4 (7.6)</td>
<td>51.9 (8.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>% sleep time in stage 3</td>
<td>3.1 (4.6)</td>
<td>3.1 (1.6)</td>
<td>3.1 (2.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>% sleep time in stage 4</td>
<td>26.5 (6.0)</td>
<td>26.7 (6.0)</td>
<td>23.1 (7.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>% sleep time in rapid eye movement sleep</td>
<td>18.9 (4.9)</td>
<td>17.0 (6.1)</td>
<td>17.3 (6.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Arousal index, #/hr</td>
<td>8.9 (3.5)</td>
<td>9.4 (2.6)</td>
<td>17.9 (13.7)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>82.1 (11.4)</td>
<td>81.7 (8.3)</td>
<td>80.2 (13.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>Sleep efficiency after sleep onset, %</td>
<td>89.5 (8.9)</td>
<td>89.9 (6.9)</td>
<td>90.8 (6.2)</td>
<td>0.9</td>
</tr>
<tr>
<td>Total sleep time, minutes</td>
<td>394.6 (55.1)</td>
<td>398.7 (43.4)</td>
<td>387.5 (76.9)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Pairwise comparisons are performed with Control group as a comparator.

*P<0.0001; †0.0001<P<0.01; ‡0.01<P<0.05.

BMI indicates body mass index.
Systolic BP, Diastolic BP, and Mean Arterial BP

**Systolic BP**
The adjusted estimates for wake systolic BP measurements were 109 ± 0.7, 110 ± 0.7, and 113 ± 0.7 for healthy controls and subjects with mild and severe SDB respectively. A significant difference was measured between controls and those with severe SDB (3.4 ± 1.0, \( P = 0.002 \)). Sleep systolic BP measurements did not differ between the three groups (Figure).

**Diastolic BP**
The adjusted estimates for wake diastolic BP measurements were 67 ± 0.5, 69 ± 0.5, and 71 ± 0.6 for the 3 groups, respectively. A significant difference was measured between controls and those with severe SDB (3.5 ± 0.8, \( P = 0.0001 \)). Sleep diastolic BP measurements were 56 ± 0.6, 57 ± 0.6, and 59 ± 0.6 for the 3 groups, respectively. A significant difference was measured between controls and subjects with severe SDB (3.4 ± 0.9, \( P = 0.0003 \); Figure).

**Mean Arterial BP**
The adjusted estimates for wake mean arterial BP measurements were 82 ± 0.5, 83 ± 0.5, and 85 ± 0.5 for the 3 groups, respectively. A significant difference was measured between controls and those with severe SDB (3.1 ± 0.8, \( P = 0.0001 \)). Sleep mean arterial BP measurements were 72 ± 0.6, 73 ± 0.6, and 74 ± 0.6 for these groups, respectively. A significant difference was measured between controls and subjects with severe SDB (2.3 ± 0.9, \( P = 0.01 \); Figure).

**BP Load**
The percentage of systolic and diastolic BP measurements exceeding the 95th percentile for age and gender was significantly greater in subjects with an AHI >5 than in healthy controls (Table 2). Subjects with an AHI >5 had twice as many BP measurements >95th percentile as compared with healthy controls. As a result, 3 (6%) healthy controls, 6 (15%) children with mild SDB, and 10 (29%) children with severe SDB had mean 24-hour systolic BP >95th percentile.

### Table 2. Percentages of BP Measurements Exceeding the 95th Percentile

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Mild</th>
<th>Severe</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>% SBP &gt; 95th during 24-hour period</td>
<td>10.4 (15.0)</td>
<td>13.0 (17.0)</td>
<td>22.4 (22.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% DBP &gt; 95th during 24-hour period</td>
<td>6.1 (8.9)</td>
<td>7.4 (9.1)</td>
<td>9.7 (8.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>% SBP &gt; 95th during wake only</td>
<td>15.5 (21.0)</td>
<td>19.7 (25.2)</td>
<td>32.2 (28.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% DBP &gt; 95th during wake only</td>
<td>9.4 (13.3)</td>
<td>12.4 (15.9)</td>
<td>16.2 (14.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>% SBP &gt; 95th during sleep only</td>
<td>1.3 (7.9)</td>
<td>2.3 (7.8)</td>
<td>5.3 (17.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>% DBP &gt; 95th during sleep only</td>
<td>0.9 (6.2)</td>
<td>0.7 (3.4)</td>
<td>1.2 (4.3)</td>
<td>0.641</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD. \( P = \) overall \( P \) for the trend.
A similar trend was observed for diastolic BP but did not reach statistical significance.

**Heart Rate**

The adjusted estimates for wake mean HR measurements were 92 ± 0.8, 92 ± 0.8, and 97 ± 0.9 for the 3 groups, respectively. A significant difference was measured between controls and those with severe SDB (−5.0 ± 1.3, \( P = 0.0002 \)). Sleep HR measurements were 76 ± 1.1, 76 ± 1.1 and 81 ± 1.2 for the 3 groups, respectively. A significant difference was measured between controls and those with severe SDB (−4.5 ± 1.7, \( P = 0.02 \)).

**Mixed Model Analysis**

Because of the small number of obese controls, there was no difference measured in any of BP parameters between the 2 obese groups. In comparison to lean children with SDB, obese children with SDB had a higher wake systolic BP 114 ± 0.8 versus 110 ± 0.7 (\( P < 0.001 \)) and sleep systolic BP 102 ± 1 versus 98 ± 0.9 (\( P = 0.02 \)) after adjusting for the severity of SDB. There were no significant differences in diastolic or mean arterial pressures between the two SDB groups.

**Subgroup Analysis of Lean and Obese Children**

To further discern the effect of SDB from that of obesity on BP, the study population was divided into lean and obese controls and lean and obese children with SDB. 47 were lean controls (BMI = 17.7 ± 2.5), 48 were lean children with SDB (BMI = 18 ± 2.4), 5 were obese controls (BMI = 26 ± 4), and 34 were obese children with SDB (BMI = 27 ± 4.8). Differences between left least square means adjusted for age, gender, race, and activity were measured between lean controls and lean children with SDB for wake systolic BP 108 ± 0.7 versus 111 ± 0.7 (\( P = 0.01 \)), wake diastolic BP 67 ± 0.5 versus 70 ± 0.5 (\( P = 0.001 \)), wake mean arterial BP 81 ± 0.5 versus 84 ± 0.5 (\( P = 0.0002 \)), and wake HR 91 ± 0.9 versus 95 ± 0.8 (\( P = 0.003 \)). Differences in the sleep parameters were measured for diastolic BP 56 ± 0.6 versus 58 ± 0.6 (\( P = 0.007 \)) and mean arterial BP 72 ± 0.6 versus 74 ± 0.6 (\( P = 0.04 \)).

## Table 3. Mixed Model Analysis Predicting Systolic, Diastolic, and Mean Arterial Blood Pressure Surge

<table>
<thead>
<tr>
<th>Variables</th>
<th>( \beta )</th>
<th>( F )</th>
<th>( P )</th>
<th>( \beta )</th>
<th>( F )</th>
<th>( P )</th>
<th>( \beta )</th>
<th>( F )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log AHI</td>
<td>0.9</td>
<td>11</td>
<td>0.001</td>
<td>0.5</td>
<td>7.7</td>
<td>0.006</td>
<td>0.6</td>
<td>11.7</td>
<td>0.0009</td>
</tr>
<tr>
<td>Time</td>
<td>2.0</td>
<td>8.2</td>
<td>0.004</td>
<td>1.6</td>
<td>5.9</td>
<td>0.02</td>
<td>1.7</td>
<td>8.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Age</td>
<td>1.9</td>
<td>42</td>
<td>&lt;0.0001</td>
<td>0.5</td>
<td>4.9</td>
<td>0.03</td>
<td>1</td>
<td>23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI Z</td>
<td>0.6</td>
<td>1</td>
<td>0.3</td>
<td>0.4</td>
<td>0.9</td>
<td>0.3</td>
<td>0.7</td>
<td>3</td>
<td>0.08</td>
</tr>
<tr>
<td>Activity</td>
<td>0.18</td>
<td>48</td>
<td>&lt;0.0001</td>
<td>0.2</td>
<td>68</td>
<td>&lt;0.0001</td>
<td>0.2</td>
<td>56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>-2.5</td>
<td>4</td>
<td>0.04</td>
<td>-1.6</td>
<td>3.1</td>
<td>0.07</td>
<td>-1.8</td>
<td>4</td>
<td>0.04</td>
</tr>
<tr>
<td>Race NC</td>
<td>0.7</td>
<td>0.3</td>
<td>0.5</td>
<td>0.4</td>
<td>0.2</td>
<td>0.7</td>
<td>0.8</td>
<td>0.7</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Results of mixed model analyses with log AHI as a continuous variable.

TIME indicates hourly BP measurements; AHI, apnea hypopnea index; NC, non-white.

## Table 4. Mixed Model Analysis Predicting Wake and Sleep Systolic and Diastolic Blood Pressure

<table>
<thead>
<tr>
<th>Variables</th>
<th>( \beta )</th>
<th>( F )</th>
<th>( P )</th>
<th>( \beta )</th>
<th>( F )</th>
<th>( P )</th>
<th>( \beta )</th>
<th>( F )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log AHI</td>
<td>0.5</td>
<td>4.6</td>
<td>0.03</td>
<td>0.5</td>
<td>3.6</td>
<td>0.06</td>
<td>0.5</td>
<td>7.05</td>
<td>0.009</td>
</tr>
<tr>
<td>Time</td>
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<td>12</td>
<td>0.0007</td>
<td>-0.3</td>
<td>16.5</td>
<td>&lt;0.0001</td>
<td>0.03</td>
<td>0.65</td>
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<td>46</td>
<td>&lt;0.0001</td>
<td>1.7</td>
<td>30</td>
<td>&lt;0.0001</td>
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<td>0.9</td>
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<td>1.86</td>
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<td>0.0002</td>
<td>0.2</td>
<td>247.20</td>
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<td>Female gender</td>
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<td>0.02</td>
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<td>1</td>
<td>0.2</td>
<td>0.19</td>
<td>0.04</td>
<td>0.8</td>
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Results of mixed model analyses with log AHI as a continuous variable.

AHI indicates apnea hypopnea index; NC, non-white.
Relative Contributions of Obesity and SDB to 24-Hour Ambulatory BP

The relative predictive contributions of AHI and BMI were significantly different for nocturnal diastolic BP with parameter estimates of 0.16 and 0.01, respectively (0.15 ± 0.08, \( P = 0.03 \)). However, there was no significant difference in the predictive contributions of Log AHI and BMI Z score of diurnal systolic BP, diastolic BP, and sleep systolic BP. These results demonstrate that SDB severity and BMI have similar effect on BP parameters except for nocturnal diastolic BP where SDB has a significantly greater effect than BMI.

Echocardiography

Relative Wall Thickness

The adjusted least square means estimates for relative wall thickness were 0.3 ± 0.009, 0.31 ± 0.009, and 0.34 ± 0.01 for control, mild, and severe groups, respectively. A significant difference between control and severe was measured (−0.04, \( P = 0.01 \)). In a model which in addition to individual BP measurements included BMI Z score, age, gender, and race as independent variables, wake systolic BP (F = 9.58, \( P = 0.002 \)), diastolic BP (F = 5.74, \( P = 0.018 \)), and mean BP (F = 10.43, \( P = 0.002 \)) were significant predictors of relative wall thickness. Sleep systolic BP (F = 9.01, \( P = 0.003 \)), diastolic BP (F = 8.61, \( P = 0.004 \)), and mean arterial BP (F = 12.32, \( P = 0.0006 \)) were also significant predictors of relative wall thickness.

Left Ventricular Mass Index

The adjusted least square estimates for left ventricular mass index were 31 ± 1, 32 ± 1, and 34 ± 1. A difference between control and severe groups was observed but did not reach statistical significance (−2.9, \( P = 0.09 \)).

Partial correlation between left ventricular mass index and wake systolic, diastolic, and mean arterial pressure adjusted for BMI Z score and age were 0.19 (\( P = 0.03 \)), 0.15 (\( P = 0.08 \)), and 0.2 (\( P = 0.01 \)) respectively.

Discussion

Our results clearly indicate that after adjusting for physical activity and controlling for confounding factors, children with SDB exhibit a significantly higher 24-hour BP and faster HR than age- and gender-matched healthy controls. The study adopted a rigorous and novel approach in discerning the effect of obesity from that of SDB on BP in children. The differences in BP parameters observed in the whole study population were clearly evident when the same analyses were applied to lean controls and lean children with SDB. Also, we have found that differences in BP parameters are associated with end organ changes, namely left ventricular remodeling. Additionally, for the first time, we have described the level of SDB associated with elevation of BP and have demonstrated that the AHI threshold associated with BP dysregulation falls within the range thought to represent the mildest level of SDB. These collective findings provide new insights into the early stages of BP dysregulation associated with SDB and provide evidence supporting a rationale for treating children with even a mild degree of SDB.

The study examined 3 BP parameters: morning BP surge, BP load, and mean nocturnal and diurnal BP. We have showed that children with mild SDB exhibited an exaggerated morning systolic BP surge in the absence of significant elevation in nocturnal and diurnal BP. However, those with an AHI greater than 5 exhibited both a significantly greater morning BP surge and elevation of nocturnal and diurnal BP as compared with healthy controls. Several investigators have proposed that an exaggerated morning BP surge may advance vascular remodeling from the larger arteries to the small resistance vessel because of the shear stress of an exaggerated fluctuations of blood flow on the vessel wall.22–24 Indeed, various cardiovascular morbidities have been described in patients with an exaggerated morning BP surge. These studies, conducted primarily in adults, consistently indicate that morning BP surge is an important predictor of the development of risk markers such as increased carotid intima thickness14 myocardial hypertrophy and infarction25 and cardiovascular events, such as stroke.26,12 Morning BP surge is a normal phenomenon attributed to enhanced \( \alpha \)-adrenergic vasoconstrictor response,27 increased activity of the rennin-angiotensin-aldosterone system, and reduced early morning endothelial function. The mechanisms of exaggerated morning BP surge in children with SDB have not yet been studied.

As with the morning BP surge, increased BP load is also known to trigger myocardial and vascular remodeling. Mitsnefes and colleagues have reported that in children who have undergone renal transplants, systolic BP load was associated with decreased carotid artery distensibility.14

The clinical significance of the differences in BP parameters between children with SDB and healthy controls is highlighted by the observed independent association between BP and left ventricular remodeling. We have previously demonstrated a greater relative wall thickness and left ventricular mass index in children with SDB as compared with children with simple snoring.20 However, casual BP measurements were not significantly different between groups. This study adds to the previous knowledge showing that changes in ambulatory BP, although small in magnitude, correlate with measures of end organ damage.

Understanding the causal relationship between BP dysregulation and SDB in children requires reevaluation of BP after resolution of SDB. To accurately predict the reversibility of BP dysregulation after treatment, it is essential to determine which BP parameter(s) is/are differentially affected by obesity versus SDB. We have shown that there was no significant difference between the effects of BMI and AHI on wake systolic and diastolic BP and sleep systolic BP. However, a greater contribution by SDB to changes in nocturnal diastolic BP was observed. Thus, in future studies that examine the effect of treatment on BP regulation in children with SDB, we anticipate observing a greater change in nocturnal diastolic BP than in BP measurements that seem to be equally influenced by obesity and SDB.
Additionally, children with SDB exhibit a faster HR during wakefulness and during sleep even after controlling for confounding variables. Diurnal and nocturnal BP and HR are thus independently associated with measures of severity of SDB. A normal physiological response to increasing BP is a slowing of HR through a baroreceptor loop. The presence of a significant elevation of BP simultaneously with an increase in HR may be an indicator of baroreflex dysfunction in children with SDB. Exaggerated sympathetic tone or elevation in blood volume might be possible pathways overriding tight baroreceptor control.

An important limitation to the study is the cutoff we have used to define the 95th percentile for systolic and diastolic BP. The study referenced the data to distributions of casual BP published in the Report of the Second Task Force on Blood Pressure Control in Children. Applying casual BP cutoffs to ambulatory BP measurements to set threshold limits for defining BP pressure load and hypertension does, however, introduce an important error. This error is derived from the fact that ambulatory BP normative data tend to provide higher BP limits for age and gender compared with casual BP. We have elected to use casual BP cutoffs because the age and height of our study population fell outside the ranges previously published in ambulatory BP literature. In an effort to minimize the error derived from the discrepancy between the 2 methods, we applied the same cutoff to children with SDB and healthy controls. We also avoided categorizing subjects as hypertensive based on a casual BP cutoff.

Despite these limitations, our study clearly demonstrates a significant trend of an increasing number of measurements exceeding the cutoff for casual BP with increasing severity of SDB.

The findings from this study broaden our knowledge of BP control in children with SDB by demonstrating that in the prehypertensive stage, a cluster of ambulatory BP parameters reflect a dysregulation of BP control. These parameters include increases in both BP surge and BP load, as well as the previously described changes in BP variability and nocturnal BP dipping.

Perspectives
This study describes the complex interaction between physical activity, adiposity, and SDB in modifying diurnal and nocturnal BP parameters in otherwise healthy children. The detection of a significant difference in systolic BP surge at a mild level of SDB suggests that exaggerated rise in morning BP might be one of the earliest changes in BP control in children with SDB. The linear relationship between 24-hour BP and left ventricular wall thickness provides a mechanism for cardiac remodeling in children with SDB. The findings also suggest that children with SDB who are left untreated may be at increasing risk for left ventricular hypertrophy, itself an independent risk factor for cardiovascular disease. With the widespread availability of 24-hour ambulatory, and because of the relationship found in our study between parameters of BP with end-organ damage, such test could guide the management of children with SDB.

Sources of Funding
This work was supported by grants RO1-HL70907-02A1 and MO1 RR 08084-08.

Disclosures
None.

References


Activity-Adjusted 24-Hour Ambulatory Blood Pressure and Cardiac Remodeling in Children with Sleep Disordered Breathing

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Hypertension. 2008;51:84-91; originally published online December 10, 2007; doi: 10.1161/HYPERTENSIONAHA.107.099762

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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