I, Lisa A Burns, hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:
Ambulatory Blood Pressure And Cardiac Remodeling After Adenotonsillectomy In Pediatric Sleep Apnea

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This work and its defense approved by:

Committee chair: Erin Nicole Haynes, Ph.D.
Ambulatory Blood Pressure And Cardiac Remodeling After Adenotonsillectomy In Pediatric Sleep Apnea

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ABSTRACT

Rationale: There is limited knowledge about the effects of obstructive sleep apnea on cardiovascular outcomes in children.

Objectives: Determine the effects of adenotonsillectomy on 24-hour ambulatory blood pressure and left ventricular remodeling six months after treatment.

Methods: In children with obstructive sleep apnea, polysomnography, ambulatory blood pressure monitoring, and echocardiography were measured at baseline and six months after adenotonsillectomy. Findings were compared to those from healthy controls. Linear mixed effects models were applied to blood pressure and echocardiography parameters.

Measurements and Main Results: The study included 36 healthy controls, 22 with mild, and 23 with severe apnea. Six months following adenotonsillectomy, children with severe apnea had a decrease in nocturnal systolic index (p=0.027), diastolic blood pressure (p=0.002), diastolic index (p<0.001), diastolic variability (p=0.034), mean arterial blood pressure (p=0.008), heart rate (p=0.003), rate pressure product (p=0.005) and increase in nocturnal blood pressure dipping. A regression of left ventricular remodeling was measured by a significant decrease in left ventricular mass index (p=0.012) and relative wall thickness (p=0.014). Similar changes were not found in controls or children with mild sleep apnea. Interval changes in sleep diastolic and mean arterial blood pressure predicted left ventricular mass index.

Conclusions: Children with obstructive sleep apnea have evidence of blood pressure dysregulation and left ventricular remodeling which improves post-adenotonsillectomy. These findings support a causal relationship between obstructive sleep apnea, and cardiovascular morbidity in children. Furthermore, ambulatory blood pressure and left ventricular geometry are valid measures of cardiovascular outcomes in children with obstructive sleep apnea.
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INTRODUCTION:

The early reports of the relationship between obstructive sleep apnea (OSA) in adults and cardiovascular morbidity were described close to two decades ago showing an independent association between the breathing disorder and hypertension (1). Further, studies which described the efficacy of treatment of OSA in lowering blood pressure (BP) provided an even stronger argument for the potential causal relationship between OSA and BP dysregulation (2). As a result, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) now considers sleep apnea as an identifiable cause of hypertension (3).

Hypertension is a well known risk factor for cardiovascular morbidity, including left ventricular hypertrophy and failure, and is likely to be one of the mechanistic links between OSA and heart failure (4-7). In children, the evidence of a similar association between OSA and BP dysregulation is growing. Twenty-four hour ambulatory BP parameters which are known to cause end organ injury in adults have been observed to be abnormal in children with OSA. A significantly higher BP in children with OSA compared to healthy controls as well as to children with primary snoring has been described in multiple studies (8-10). In addition, other clinically significant BP parameters such as BP load, a measure that reflects the number of measurements that exceed the 95th percentile for age and gender, as well as BP variability and nocturnal BP dipping have all been shown to deviate from normal ranges (8-9). These BP changes, although small in magnitude were closely associated with remodeling of the left ventricle. As such, these observations made in children provide a mechanistic explanation for the observed link between OSA and heart failure observed in adults with the same disorder.
Although many pediatric studies have demonstrated the association between OSA and BP dysregulation, there have been no studies to evaluate the effect of treatment on BP control and left ventricular remodeling. The goal of our current study is to further delineate this relationship by examining the effect of adenotonsillectomy on 24-hour ambulatory BP parameters and left ventricular geometry. We hypothesized that treatment of OSA through adenotonsillectomy will lead to improvement in 24-hour ambulatory BP parameters and a decrease in left ventricular mass index and relative wall thickness six months after treatment. This hypothesis is based on our previous observations which demonstrated that OSA in children is associated with an increase in BP, BP load and morning BP surge which correlated with left ventricular remodeling (8).

METHODS

Subjects

Children age 7 to 13 with symptoms of OSA were recruited from pulmonary and otolaryngology clinics at Cincinnati Children’s Hospital Medical Center. Children were classified as mild OSA if they had an obstructive apnea-hypopnea index (AHI) > 1 and < 5 per hour of sleep and as severe if they had an obstructive AHI ≥ 5 per hour of sleep. Age and gender matched healthy controls without symptoms of obstructive breathing during sleep in the previous two years and normal polysomnogram were recruited from the community. Children were excluded if they had chronic medical conditions, genetic syndromes, or if they were on chronic medications that could not be temporarily discontinued. All children completed 24-hour ambulatory BP monitoring, polysomnography, and echocardiography at baseline and at six months. The evaluations of children with OSA were performed before and six months after
adenotonsillectomy. Informed consent was obtained from the parents or legal guardian of each child, and assent was obtained from all children. The study was approved by the Institutional Review Board.

**Polysomnography**

Overnight polysomnography was performed according to the American Thoracic Society standards (11) using computerized systems (Grass, Telefactor). All subjects were studied at baseline. Healthy controls were studied six months after baseline and OSA subjects were studied six months post-adenotonsillectomy. All studies were interpreted by the primary investigator, RA, who was blinded to each subject’s study group and the results of the 24-hour ambulatory BP monitoring.

**Twenty-Four Hour Ambulatory BP Monitoring and Actigraphy**

Noninvasive 24-hour ambulatory BP monitoring was performed with an automatic BP monitor (SpaceLabs 90207), which recorded BP and heart rate every 15 minutes. BP recordings were obtained within two weeks of polysomnography. Each subject wore a wrist actigraph (Ambulatory Monitoring Inc.) during the 24-hour BP recording period. Activity was recorded in 10-second epochs throughout the 24-hour period and weighted as previously described (8) to provide an activity score corresponding to each 15 minute BP and heart rate measurement.

*Average BP during sleep and wakefulness.* Data was synchronized at the point of sleep onset, as determined by actigraphy readings. 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 continued to indicate wakefulness. Data from the 9th hour after sleep onset often included a mix of wake and sleep and therefore was excluded.

**Blood Pressure Load.** The 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 (12).

**Blood Pressure Index.** In order to control for the variation in age across our study population, we calculated the BP index using following formula:

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

**Variability.** Measures of variability were determined by calculating the average standard deviation of wake and sleep BP and heart rate.

**Nocturnal Dipping.** The degree of nocturnal dipping was derived by calculating the difference between awake and sleep BP expressed as a percentage of BP during wakefulness.

**Morning Surge.** The morning surge for each variable of interest was defined as the slope of the systolic BP, diastolic BP, mean arterial BP, or heart rate from the beginning of the last hour of sleep to the end of the second hour of awakening.

**Rate Pressure Product (RPP).** The RPP, a marker of cardiac work load, was calculated by multiplying the systolic BP by the corresponding heart rate measured at the same time point.

**Echocardiography**

Left ventricular geometry was measured with two-dimensional and two-dimensionally directed M-mode echocardiography images to determine relative wall thickness and left ventricular mass index as previously described (13).
Statistical Methods

Gender and race were compared across groups using the likelihood ratio chi-square test. Continuous demographic and polysomnographic variables were compared across groups at the baseline visit using the Kruskal-Wallis test. Within-group comparisons of baseline and follow-up visits for these variables were made using the Wilcoxon signed-rank test. Treatment effect was assessed by comparing baseline and follow-up visits for each group. OSA groups were compared to healthy controls at the follow-up visit to examine potential normalization of each variable.

Linear mixed effects models, conducted separately for diurnal and nocturnal periods, were used to model BP index measures, BP variability, and monitored heart rate, RPP, and BP responses. Predictor variables included a three-way interaction of group, visit, and hour; age; race; gender; BMI z score; and actigraphy. For BP load, a repeated measures logistic regression model was used to estimate the probability of being above the 95th percentile. Key comparisons were made using odds ratios.

To determine whether change in AHI, arousal index, or desaturation index is predictive of changes in BP, heart rate or RPP, values for each response variable at six months were modeled with covariate adjustment for age, race, gender, and BMI z score, along with the baseline value of the response variable to mitigate regression to the mean (14). A similar model was used to determine whether changes in BP measures were predictive of changes in left ventricular mass index and relative wall thickness. Sleep and wake periods were analyzed separately.

Values are reported as least square means or fixed effect estimates ± SE unless otherwise noted. Simulation based multiple comparison adjustments were applied where appropriate. Significance for all tests was set a priori at \( \alpha < 0.05 \). Both R (R Foundation for Statistical
Computing, version 2.8.0, Vienna, Austria) and SAS software (SAS Institute, version 9.2, Cary, NC) were used for analyses.

RESULTS

Study Population

The cohort consisted of 36 healthy controls, 22 children with mild OSA, and 23 with severe OSA. Demographic and polysomnographic characteristics at baseline and six months are shown in Table 1. There were no to nominal changes in ambulatory BP parameters for the control and mild OSA groups. Therefore, the results will focus initially on changes seen in the severe OSA group.

Group Differences in 24-hour Ambulatory Blood Pressure after Adenotonsillectomy

Systolic, Diastolic, and Mean Arterial BP

The severe OSA group had significant improvements in many of the 24-hour ambulatory BP parameters during sleep at six months post-treatment of OSA with adenotonsillectomy. Changes in systolic and diastolic BP are shown in Figure 1. There was a significant decrease in the sleep systolic BP index from -14.9 ± 1.2 to -17.7% ± 1.3 (-2.8 ± 1.0, p = 0.027). The sleep diastolic BP decreased from 59 ± 1 to 55 ± 1 (-4 ± 1, p = 0.002), and there was a significant decrease in the sleep diastolic BP index from -24.4% ± 1.4 to -29.7% ± 1.5 (-5.2 ± 1.3, p < 0.001). There was also a significant improvement in mean arterial BP after adenotonsillectomy in the severe OSA group, Figure 2. Although we found significant improvements in sleep systolic and diastolic BP, there were no significant changes in sleep BP load in the severe OSA group.
When examining the contribution of BMI to changes in sleep diastolic BP, there was a
decrease independent of a change in BMI z score. In the group who increased BMI z score over
six months, sleep diastolic BP decreased from 60 ± 1 to 56 ± 1 (-3.6 ± 1.3, \( p = 0.027 \)). However,
in the group who maintained or decreased BMI z score the estimates for sleep diastolic BP
decreased from 58 ± 2 to 54 ± 2 (-3.9 ± 1.6, \( p = 0.054 \)).

_Nocturnal Dipping_

The severe OSA group also had significant improvements in nocturnal dipping of systolic
BP, diastolic BP, mean arterial BP, and heart rate at six months post-adenotonsillectomy.
Systolic BP dipping increased from 9.6% ± 1.1 to 13.3% ± 1.0 (3.7 ± 1.1, \( p = 0.009 \)). Diastolic
BP dipping increased from 14.3% ± 1.5 to 20.1% ± 1.6 (5.8 ± 1.8, \( p = 0.011 \)). Mean arterial BP
dipping increased from 9.8% ± 1.2 to 14.5% ± 1.2 (4.6 ± 1.3, \( p = 0.007 \)). Heart rate dipping
increased from 13.9% ± 1.5 to 19.0% ± 1.4 (5.1 ± 1.3, \( p = 0.002 \)).

_BP Variability_

There was significant improvement in the sleep diastolic BP variability, with a decrease
in the standard deviation from 8.3 ± 0.5 at baseline to 6.8 ± 0.4 at six months (-1.4 ± 0.5, \( p =
0.034 \)). Changes in variability, however, were only seen in the subjects who maintained or
decreased their BMI z score over the study period. In this group, sleep diastolic BP variability
decreased from 9.8 ± 0.9 to 6.8 ± 0.7, (-3.0 ± 0.6, \( p = 0.003 \)), and sleep mean arterial BP
variability decreased from 8.4 ± 0.8 to 6.5 ± 0.8 (-1.9 ± 0.4, \( p = 0.007 \)).

_Morning BP Surge_
Despite significant improvements in nocturnal dipping, adjusted estimates for morning surge in systolic BP, diastolic BP, mean arterial BP, and heart rate did not significantly change following adenotonsillectomy in the severe OSA group.

Heart Rate

There was a significant decrease in sleep heart rate after adenotonsillectomy in the severe OSA group, as shown in Figure 2.

Rate Pressure Product

There was a significant decrease in the sleep RPP after adenotonsillectomy in the severe OSA group, from 8179 ± 240 to 7518 ± 274 (-661 ± 208, p = 0.005). The change in RPP was only seen in children with severe OSA who maintained or decreased their BMI z score throughout the study period. The RPP during sleep decreased from 8048 ± 469 to 7180 ± 441 (-867 ± 294, p = 0.010) in this group, but there was no significant change in RPP for the severe OSA subjects who had an increase in BMI z score throughout the study period.

Normalization of 24-hour Ambulatory Blood Pressure after Adenotonsillectomy

Normalization of ambulatory BP parameters was assessed by comparing the OSA groups to healthy controls at the follow-up visit. Following treatment with adenotonsillectomy, there were no differences in sleep BP, heart rate, BP index, BP load, nocturnal dipping, surge, or RPP between the severe OSA group and healthy controls, indicating normalization among the severe OSA group. The wake ambulatory BP parameters were also assessed for improvement and normalization. There were no significant improvements in the wake ambulatory BP parameters.
for the severe OSA group after adenotonsillectomy. There were also no significant differences in the wake ambulatory BP parameters between the control group and the severe OSA group at six months, indicating that these values were already normalized. The only exception to this was for wake systolic BP load. The wake systolic BP load was 25.1% in controls and 41.1% in the severe OSA group, OR 1.64 (1.17, 2.29).

The control group had an increase in wake diastolic BP from 67 ± 1 to 70 ± 1 (2 ± 1, p = 0.046) at the end of the study, as well as an increase in wake diastolic BP load from 10.6% to 17.1% OR 1.6 (1.16, 2.27). Controls also showed an increase in diastolic BP dipping from 17.3% ± 1.3 to 20.7% ± 1.3 (3.4 ± 1.4, p = 0.036). Even with such change in BP dipping in the control group, however, the severe OSA group showed no differences from controls in BP dipping after adenotonsillectomy. The mild OSA group did not have any change in ambulatory BP parameters after adenotonsillectomy, except for a decrease in systolic BP surge from 3.7 ± 0.8 to 0.5 ± 0.8 (-3.3 ± 1.1, p = 0.020). There was no difference between the mild OSA group and the control group at six months, indicating the values were already normalized.

**Group Differences in Echocardiography after Adenotonsillectomy**

There was a significant decrease in the left ventricular mass index (LVMI) in the severe OSA group six months after adenotonsillectomy from 35.9 ± 1.7 to 32.5 ± 1.3 (-3.4 ± 1.1, p = 0.012). There were no significant changes in LVMI in the control group or mild OSA group, and there were no differences between healthy controls and either OSA group at 6 months, indicating normalization of LVMI among the severe OSA group. In a mixed model analysis predicting change in LVMI, the change in sleep diastolic BP (F = 4.17, p = 0.045) and mean arterial BP (F = 5.20, p = 0.003) were significant predictors of the LVMI at six months.
There was a significant decrease in relative wall thickness (RWT) in the severe OSA group at six months, from $0.35 \pm 0.01$ to $0.30 \pm 0.01$ ($-0.05 \pm 0.02$, $p = 0.014$), and there was no difference between the control group and those with severe OSA at six months, indicating normalization of RWT. There were no significant changes in RWT in the control group or mild OSA group from baseline to six months although there was a significant difference between the control group and those with mild OSA at six months, $0.28 \pm 0.01$ and $0.32 \pm 0.01$ ($0.04 \pm 0.01$, $p = 0.006$) respectively. In a mixed model analysis predicting change in RWT, the change in sleep and wake systolic BP, diastolic BP, mean arterial BP, heart rate, and RPP were not significant predictors of RWT at six months.

**Polysomnography Predictors of 24-hour Ambulatory BP Parameters and Echocardiography**

The mixed model analyses with arousal index as a continuous variable showed that change in arousal index was a significant predictor of sleep systolic BP variability ($p < 0.0001$) and sleep mean arterial BP variability ($p = 0.01$). The change in 3% desaturation index was a significant predictor of change in RWT ($p = 0.015$). The change in AHI was not a significant predictor of change in any of the ambulatory BP parameters or echocardiography variables.

**DISCUSSION**

The results of this study indicate that treatment of children with OSA who have an AHI \(\geq \) 5 per hour with adenotonsillectomy leads to a reversal of systemic BP dysregulation which in turn contributes to decrease in left ventricular mass and relative wall thickness. These findings advance our understanding of the effect of dysregulation of BP in normotensive children with
OSA. As such, these observations made in children may provide a mechanistic explanation for the observed link between OSA and myocardial disease observed in adults with the same disorder. Further, these findings provide evidence to support the use of 24-hour ambulatory BP monitors and echocardiography as a validated measure of cardiovascular outcomes in children with OSA.

Several studies in children with OSA have focused on the noncardiovascular consequences of OSA, including neurobehavioral problems, excessive daytime sleepiness, and metabolic abnormalities. However, population based studies have shown that OSA in children has cardiovascular consequences as well. Although children often remain normotensive, children with sleep apnea have been shown to have higher BP measurements than healthy controls (8, 10, 15-16). Furthermore, children with OSA have evidence of end organ involvement with significant changes in left ventricular geometry and function (13, 17-18). These findings illustrate the importance of treating OSA in children in order to halt the progression of cardiovascular morbidity.

The use of 24-hour ambulatory BP monitors in children with OSA provides an assessment of the normal circadian variation in BP that cannot be assessed by casual BP measurements. Studies conducted in both children and adults have found a stronger correlation between ambulatory BP and end organ damage compared to casual BP measurements or self-measurement of BP (19). Cuspidi et al, found that recently diagnosed hypertensive adults with a < 10% dip in nocturnal BP had a greater prevalence of left ventricular hypertrophy (20). We have previously reported that children with sleep apnea had less nocturnal dipping in BP (9). We now show an increase in nocturnal dipping of systolic BP, diastolic BP, mean arterial BP, and HR in children with severe OSA who were treated with adenotonsillectomy.
Subjects with OSA have been found to have changes in both diurnal and nocturnal BP. We found that improvement in nocturnal BP parameters alone, without any significant changes in diurnal variables was enough to influence changes in end organ involvement. There have been several studies in adults and children demonstrating the effects of sleep disordered breathing on left ventricular function. Chan et al. showed that subjects with sleep disordered breathing had an increase in the prevalence of diastolic heart failure despite no significant difference in BMI or prevalence of hypertension between the groups (5). Arias et al. showed that abnormalities in left ventricular diastolic function can be reversed after treating OSA in normotensive adult men with nasal continuous positive airway pressure (4). We have previously shown a negative correlation between OSA severity and LV diastolic function independent of obesity, blood pressure, and left ventricular mass (17). Our current study shows improvement in LVMI and RWT after treatment of severe OSA with adenotonsillectomy. Furthermore, the changes in sleep diastolic BP and mean arterial BP predicted changes in LVMI, providing further evidence to support changes in BP as a mechanistic link between OSA and heart failure.

In addition to heart failure, the prevalence of ischemic heart disease is greater in adults with OSA than the general population. The RPP has been shown to correlate with myocardial oxygen consumption and can be used as a measure of cardiac workload (21-22). This increase in cardiac workload may be an additional mechanism of cardiovascular morbidity in adults with OSA. In the current study, we found that subjects with severe OSA had a decrease in the RPP during sleep after adenotonsillectomy.

Obesity is also a risk factor for hypertension and other cardiovascular diseases. Therefore in evaluating the effect of adenotonsillectomy on ambulatory BP and left ventricular geometry, we controlled for obesity by including BMI z score in the linear mixed effects models. We also
evaluated subjects who had an increase in BMI z score from baseline to follow-up visit separately from those who maintained or decreased their BMI z score. Our results show a trend toward significant changes in sleep diastolic BP regardless of whether the subjects had an increase or decrease in BMI z score, indicating that OSA may have more of an effect on diastolic BP than other ambulatory BP parameters.

We have previously shown that AHI had a greater contribution than BMI to changes in sleep diastolic BP in children with OSA (9). Our current study confirms these findings with significant changes in sleep diastolic BP, diastolic BP index, and diastolic BP variability after treatment of OSA with adenotonsillectomy among children with severe disease. Although we found significant changes in sleep systolic BP, diastolic BP, mean arterial BP, and HR, the changes in diastolic BP and mean arterial BP predicted changes in LVMI, indicating a more profound effect of adenotonsillectomy on these parameters.

Although we found significant changes in systemic BP regulation and left ventricular size with treatment of OSA, we do not know if these improvements are long-lasting, that is, beyond six months post-surgery. This represents a potential limitation to our study in its duration of follow-up. Future longitudinal studies should follow cardiovascular outcomes with 24-hour ambulatory BP monitoring and echocardiography in order to determine the long-term effects of adenotonsillectomy.

Still, the results of our study fill the current gap in knowledge by showing that diastolic BP and its influence on LVMI and RWT are important cardiovascular outcomes in children with OSA. Children with OSA have evidence of BP dysregulation and end organ involvement despite remaining normotensive. The more prominent changes in sleep diastolic BP and its influence on
LVMI after treatment of OSA support the use of 24-hour ambulatory BP monitoring and echocardiography in monitoring cardiovascular outcomes in children.
TABLE LEGENDS

Table 1. Demographic and Polysomnographic Characteristics

Definitions of abbreviations: OSA = Obstructive Sleep Apnea, BMI = Body Mass Index, ETCO2 = End-tidal Carbon Dioxide Level, REM = Rapid Eye Movement

* Comparisons of Baseline and 6 months within each group, p < 0.05
† Comparisons of Baseline and 6 months within each group, p < 0.01
‡ Comparisons of Control and OSA Group at the same visit, p < 0.05
§ Comparisons of Control and OSA Group at the same visit, p < 0.01
FIGURE LEGENDS

Figure 1. Systolic BP and Diastolic BP synchronized at sleep onset
* Differences between Baseline and 6 months for sleep mean
† Differences between Baseline and 6 months for wake mean

Figure 2. Mean Arterial BP and HR synchronized at sleep onset
* Differences between Baseline and 6 months for sleep mean
† Differences between Baseline and 6 months for wake mean
Table 1.

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<th>Control (n = 36)</th>
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Figure 1.
Figure 2.
REFERENCES


