

# Left Ventricular Hypertrophy and Abnormal Ventricular Geometry in Children and Adolescents with Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) has been shown to be an independent risk factor for cardiovascular disease in adults. However, there are severe limitations in the extent to which the cardiovascular consequences of OSA are being studied in children. To investigate the echocardiographic changes in children with OSA, right and left ventricular (RV, LV) dimensions and LV mass index and geometry were measured in 28 children with OSA and 19 children with primary snoring (PS). The study showed that LV mass index and relative wall thickness were greater in the OSA group compared with those with PS ( $p = 0.012$  and  $p < 0.0001$ , respectively). An apnea-hypopnea index of more than 10 per hour was significantly associated with RV dimension above the 95th percentile (odds ratios, 6.7; 95% confidence interval, 1.4–32) and LV mass index above the 95th percentile (odds ratios, 11.2; confidence interval, 1.9–64). Abnormality of LV geometry was present in 15% of children with PS compared with 39% of children with OSA. We conclude that OSA in children is associated with increased LV mass.

**Keywords:** obstructive sleep apnea; children; adolescents; left ventricular hypertrophy; cardiovascular morbidity

Adult patients with obstructive sleep apnea (OSA) have higher morbidity and mortality due to cardiovascular disease compared with the general population (1–6). Cardiac dysfunction, nocturnal hypertension, and myocardial and cerebral ischemia during obstructive apnea have been documented in adults (7–10). Several epidemiologic studies have demonstrated that OSA in adults is associated with high prevalence of sustained systemic hypertension, which is an independent risk factor for cardiovascular morbidity (11–13). In pediatric patients, severe OSA can lead to congestive heart failure. However, neither the early stages of the pathophysiologic changes that link OSA to cardiovascular disease nor the long-term impact of milder degrees of the disorder on the cardiovascular system are well understood. The goal of this study is to evaluate cardiac structure in children with OSA. We hypothesized that the intermittent increase in systemic and pulmonary vascular resistance that occurs with OSA leads to elevation of systemic and pulmonary pressures and subsequent remodeling and hypertrophy of the left and right ventricles (LV, RV).

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## METHODS

### Study Design

Pediatric patients who were referred for evaluation of obstructive breathing disorder during sleep underwent a polysomnography followed by echocardiography. The evaluation at the time of enrollment consisted of a history and physical examination, resting blood pressure, and body mass index (BMI). BMI was expressed as a percentage of the 50th percentile for age and sex (14). In the history, snoring was quantified as less than 1, 1–2, 3–5, or 7 nights/week (15). All subjects presented with a history of snoring 7 nights/week. Polysomnography results were used to subdivide subjects into those with OSA and those with primary snoring (PS). Subjects classified as having PS presented with a history of snoring nightly, snored during the polysomnogram, and had an obstructive apnea-hypopnea index (AHI) between 0 and 1 per hour of sleep. Children with an obstructive AHI higher than 1 per hour of sleep were classified as having OSA. 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 Children's Hospital Medical Center in Cincinnati, Ohio, approved the study.

### Study Group

Patients aged 2–18 years who were referred to the pediatric Sleep Disorder Clinic at Children's Hospital Medical Center for evaluation for obstructive breathing during sleep were recruited sequentially. Children with genetic syndromes or congenital or acquired cardiac diseases were excluded from the study.

### Polysomnography

Polysomnography studies were performed overnight according to the American Thoracic Society Standards (16) using computerized systems (Grass; Telefactor, West Warwick, RI). The following parameters were recorded during the study: (1) electroencephalogram, (2) right and left electrooculogram, (3) submental and tibial electromyogram, (4) electrocardiography, (5) nasal/oral airflow measured by thermocouple, (6) end-tidal CO<sub>2</sub> tension measured at the nose by infrared capnometry and oxygen saturation using the Nelcor N1000 (Van Nuys, CA) and oximeter pulse waveform, (7) snoring microphone, (8) video monitoring using an infrared video camera, (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. (1) Sleep architecture—sleep staging was scored according to published standards (17). Arousals were defined as recommended by the American Sleep Disorders Association (18). (2) OSA 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. (3) Obstructive hypopnea was defined as reduction in airflow and/or the sum channel from the inductive plethysmography between 20 and 50%, in the presence of chest/abdominal wall motion, associated with oxyhemoglobin desaturation 4% or less and/or followed by arousal. (4) Apnea index was defined as the number of obstructive apnea per hour of sleep. (5) AHI was defined as the number of obstructive apnea and obstructive hypopnea per hour of sleep. (6) Oxyhemoglobin

desaturation index was defined as the number of events per hour of sleep where oxygen saturation decreased by 4% or greater. (7) Peak end-tidal CO<sub>2</sub> tension during sleep was determined.

### Echocardiography

Echocardiographic examinations were performed using the Sonos 5,500 Ultrasound Imaging System (Agilent, Andover, MA) and Vivid 5 (General Electric, Milwaukee, WI). Two-dimensional and two-dimensionally directed M-mode echocardiographic images were recorded to determine LV mass and relative wall thickness. Echocardiographic measurements were made on three or more cardiac cycles according to the recommendations of the American Society of Echocardiography (19). All measurements were made under standardized resting conditions with the subjects in the supine position after a minimum rest period of 5 minutes in a quiet, darkened examination room. The sonographer was blinded to the results of the polysomnography. The correlation for intraobserver and interobserver has been 0.96 and 0.84, respectively (20).

### Left Ventricular Structure

The primary measure of LV structure is the LV mass. This was calculated from M-mode measurements of the LV end-diastolic dimension, the thickness of the interventricular septum, and the thickness of the LV posterior wall. End-diastole was defined as the onset of the QRS complex.

LV mass was calculated using the equation described by Devereux and colleagues (21).

LV mass (g) = 0.8 (1.04[IVS + PWT + LVED]<sup>3</sup> - [LVED]<sup>3</sup>) + 0.06, where LVED is LV end-diastolic dimension, IVS is interventricular septum, and PWT is LV posterior wall. Relative wall thickness was calculated by RWT = 2(PWT)/(LVED), where RWT is relative wall thickness, PWT is LV posterior wall, and LVED is LV end-diastolic dimension. To minimize the impact of variation of body size on heart size, LV mass was divided by the subject's height raised to the power of 2.7 as described by de Simone and colleagues (22) to provide LV mass index.

### Left Ventricular Geometry

The LV geometry was categorized as normal, concentric remodeling, eccentric hypertrophy, or concentric hypertrophy on the basis of LV mass and relative wall thickness as described by Ganau and colleagues (23).

### Right Ventricular Structure

The RV end-diastolic dimension was calculated from the M-mode echocardiographic images. RV dimension was indexed to height by dividing the dimension by the subject's height. RV dimension was also indexed to body surface area by dividing the dimension by the square root of the body surface area (19).

### Statistical Analysis

Demographic and polysomnographic differences between OSA and PS subjects were compared using Student's *t* test. All results are ex-

pressed as mean ± SD. All variables except age and blood pressure were log-transformed to improve normality, and the log-transformed values were used in the analyses. Pearson correlation was performed between log-transformed echocardiographic measurements and log-transformed polysomnographic and demographic variables. Multiple regression analysis was performed to identify demographic and polysomnographic factors that might predict LV mass index, relative wall thickness, and RV dimension. The following independent variables were entered in a stepwise regression analysis: age, race, sex, BMI as a percentage of 50th percentile for age and sex, AHI, desaturation index, maximum end-tidal CO<sub>2</sub>, arousal index, and systolic and diastolic blood pressure. Variables with a *p* value of 0.05 or less were kept in the model. To control for possible effects of age, sex, and BMI on the echocardiographic measurements, we forced these three variables in the model generated by stepwise regression. Logistic regression analysis was performed to determine the odds ratios for having RV dimension or LV mass index above the 95th percentile if AHI was greater than 10 per hour relative to AHI below 10 per hour while controlling for age, sex, and BMI. A value of 38.6 was used as the cutoff point for the 95th percentile for LV mass index (24). Published age-appropriate values for the 95th percentile for RV dimension were used in calculating the odds ratios (19). Chi-square analysis was performed to examine the differences between groups regarding presence or absence of abnormal LV geometry.

## RESULTS

### Study Population

The total number of study participants was 47 (Table 1). There was no difference between the two groups regarding age, race, BMI, and systolic and diastolic blood pressure. Patients with OSA were more likely than those with PS to be males.

### Polysomnographic Variables and Cardiac Structure

Of the subjects with OSA, 13 had an AHI of 1.1–10 per hour, and 15 had an AHI greater than 10 per hour. Children with OSA had a statistically significant increased LV mass index and LV relative thickness compared with children with PS. There was no difference in the RV dimension adjusted for height or for body surface area between the two groups (Table 2).

### Bivariate Correlations

LV mass index and relative wall thickness of the LV correlated with measures of severity of the disorder, namely AHI and desaturation index, and with lowest oxygen saturation (Table 3). LV mass index correlated negatively with age, suggesting a differential effect of OSA on LV mass in younger compared with older children. RV dimension adjusted for height correlated with AHI, maximum end-tidal CO<sub>2</sub>, and with frequency of arousals from sleep (Table 3).

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF CHILDREN WITH SNORING AND CHILDREN WITH OBSTRUCTIVE SLEEP APNEA

	All Patients	Primary Snoring	OSA
Number	47	19	28
Age, years	8.8 ± 4.2	9.5 ± 3.6	8.4 ± 4.6
Females, n, %	17 (36)	11 (58)	6 (21)
Black, n, %	17 (36)	6 (32)	11 (39)
Height, m	1.3 ± 0.24	1.29 ± 0.26	1.32 ± 0.21
BMI, kg/m <sup>2</sup>	23.2 ± 8.8	22.2 ± 8.8	23.9 ± 8.9
BMI as % of median	138 ± 50	130 ± 43	143 ± 55
SBP, mm Hg	111 ± 14	110 ± 12	112 ± 16
DBP, mm Hg	57 ± 10	57 ± 9	58 ± 11
Subjects with SBP above the 95th percentile, n, %	111 (23%)	2 (10)	9 (32%)
Subjects with DBP above the 95th percentile, n, %	1 (2%)	0	1 (3.5%)

Definition of abbreviations: BMI = body mass index; BMI as % of median = body mass index expressed as percentage of the 50th percentile for age and sex; DBP = diastolic blood pressure; OSA = obstructive sleep apnea; SBP = systolic blood pressure.

**TABLE 2. POLYSOMNOGRAPHIC VARIABLES AND CARDIAC STRUCTURE OF CHILDREN WITH PRIMARY SNORING AND CHILDREN WITH OBSTRUCTIVE SLEEP APNEA**

	Primary Snoring	OSA
n	19	28
Polysomnographic variables		
AHI	0.15 ± 0.31	18.2 ± 21.0*
Desaturation index	1.07 ± 1.96	13.6 ± 17.3*
Lowest O <sub>2</sub> saturation	93.4 ± 2.6	73.6 ± 19*
Maximum ETCO <sub>2</sub> , mm Hg	49.5 ± 3.6	55.3 ± 9.1†
Arousal index	9.25 ± 3.6	16.8 ± 11†
Cardiac structure		
Left ventricular mass index, g/ht <sup>2.7</sup>	30.1 ± 6.5	36.8 ± 10.8‡
Relative wall thickness	0.28 ± 0.05	0.346 ± 0.07§
RV dimension adjusted for body surface area, cm/m	1.43 ± 0.45	1.52 ± 0.52
RV dimension adjusted for height, cm/m	1.21 ± 0.26	1.39 ± 0.34
Number of subjects with RV dimension above the 95th percentile, n (%)	5 (26)	14 (50)

Definition of abbreviations: AHI = apnea-hypopnea index; ETCO<sub>2</sub> = end-tidal CO<sub>2</sub>; ht = height in m; OSA = obstructive sleep apnea; RV = right ventricle.

All data displayed as mean ± SD unless otherwise specified.

\* p Value < 0.001.

† p = 0.002–0.005.

‡ p = 0.012.

§ p = 0.001.

### Multiple Regression Analysis

**LV Parameters.** Multiple regression analysis showed that 19% of the variability of LV mass index (squared correlation = 0.19) was predicted by a model that only included AHI. ( $p < 0.0027$ ). When age, sex, and BMI were forced in the model, AHI remained the only significant variable ( $p = 0.048$ ). AHI and systolic blood pressure predicted 30% of the variability of relative wall thickness ( $p = < 0.0001$ ) (squared correlation = 0.3). When age, sex, and BMI were forced in the model, AHI remained the only significant variable ( $p = 0.0004$ ). The addition of age, sex, and BMI to either regression equation increased the squared correlation by only 7%, which demonstrates that most of the LV mass index and relative wall thickness variability is explained by the AHI.

**RV Dimension.** RV dimension adjusted for height was predicted by arousal index ( $p = 0.01$ ). The model, however, loses its statistical significance when age, sex, and BMI are forced in the model.

### Logistic Regression

Out of 47 subjects, 20 had RV dimension above the 95th percentile, 12 had an LV mass index above the 95th percentile, and eight had both RV and LV masses above the 95th percentile. After controlling for age, sex, and BMI, subjects with AHI more than 10 per hour compared with subjects with AHI of less than 10 per hour had an odds ratios of 6.7 for the presence of RV dimension above the 95th percentile (confidence interval, 1.4–32) or of 11.2 for LV mass index above the 95th percentile (confidence interval, 1.9–64).

The results of logistic regression indicate that patients with OSA are more likely to have RV and LV abnormalities than patients with PS.

### Left Ventricular Geometry

A total of 14 subjects (29%) had abnormal geometry of the LV. Three subjects had an AHI between 0 and 1 (PS group), and 11 subjects had an AHI more than 1 (OSA group). Thirteen subjects had LV hypertrophy and one subject had LV re-

**TABLE 3. PEARSON CORRELATION BETWEEN ECHOCARDIOGRAPHIC MEASUREMENTS AND DEMOGRAPHIC AND POLYSOMNOGRAPHIC VARIABLES**

	LV Mass Index	Relative Wall Thickness	RV Dimension/HT
Age	-0.30 ( $p = 0.039$ )	NS	NS
AHI	0.41 ( $p = 0.003$ )	0.49 ( $p = 0.0004$ )	0.34 ( $p = 0.02$ )
DI	0.41 ( $p = 0.005$ )	0.32 ( $p = 0.026$ )	NS
Lowest saturation	0.4 ( $p = 0.004$ )	0.37 ( $p = 0.009$ )	NS
AI	NS	0.33 ( $p = 0.02$ )	0.36 ( $p = 0.012$ )
Max ETCO <sub>2</sub>	NS	NS	0.31 ( $p = 0.031$ )
SBP	NS	0.33 ( $p = 0.019$ )	NS

Definition of abbreviations: AHI = apnea-hypopnea index; AI = arousal index; DI = desaturation index; HT = height in m; LV = left ventricle; Max. ETCO<sub>2</sub> = maximum end-tidal CO<sub>2</sub>; NS = not significant; RV = right ventricle; SBP = systolic blood pressure.

All variables were log-transformed except for age and systolic blood pressure.

modeling. Eleven subjects had eccentric hypertrophy, and two had concentric hypertrophy. There was a trend toward increased prevalence of abnormal LV geometry with increased severity of OSA. Three subjects (15%) in the PS group, two subjects (16%) in the group with apnea index less than 10 per hour, and nine subjects (60%) in the group with apnea index more than 10 per hour had abnormal LV geometry. However, this trend did not reach statistical significance due to the small sample size.

### Blood Pressure

Neither resting systolic blood pressure nor diastolic blood pressure was a statistically significant predictor for LV mass index or RV dimension adjusted for height in patients with OSA. This suggests that the effects of OSA on the heart do not operate through elevation of daytime blood pressure. There was a tendency toward higher blood pressures in the OSA group compared with the snoring group. Two out of 19 subjects in the PS group had systolic blood pressure above the 95th percentile, whereas 9 out of 28 subjects in the OSA group had systolic blood pressure above the 95th percentile ( $p = NS$ ). One patient in the OSA group had diastolic blood pressure above the 95th percentile.

### DISCUSSION

This study has shown for the first time that OSA in children is associated with cardiac remodeling and hypertrophy involving both RV and LV and that the degree of LV hypertrophy is related to the degree of severity of OSA. In contrast, most previous studies that have examined the structural changes of the heart in children with OSA have focused on the changes in the dimension of the RV (25–28). The importance of this observation stems from the knowledge that LV hypertrophy is an independent risk factor for future cardiovascular disease (29, 30).

The relationship between LV hypertrophy and adverse cardiovascular outcomes has been investigated in the context of systemic hypertension. Investigators in the Framingham study have demonstrated the relationship between hypertension, LV hypertrophy, and the development of congestive heart failure. Adults with longstanding hypertension and electrocardiographic evidence of LV hypertrophy had a risk of developing congestive heart failure 10 times greater than that of those without hypertrophy (31). The Framingham study demonstrated a significant association between LV mass and cardiovascular mortality (32). Koren and colleagues have shown that LV mass stratifies risk of morbidity and mortality of adult patients with hypertension independently and more strongly

than do blood pressure and other modifiable risk factors (33). The association between OSA and LV hypertrophy in children is therefore likely to increase their risks for cardiovascular morbidity and mortality at an older age.

This study has shown that OSA in children is associated with an at least 11-fold increase in the risk for LV hypertrophy. The mechanism whereby OSA leads to changes in cardiac structure remains to be further investigated. Hedner and colleagues showed that adult normotensive patients with OSA had a higher LV mass index compared with normotensive control patients (34). Ventricular hypertrophy may either be eccentric, which occurs primarily in response to volume overload, or concentric, which occurs primarily in response to pressure overload. Among the 12 patients with LV hypertrophy in our study, 10 had eccentric hypertrophy, whereas 2 had concentric hypertrophy. Finding a majority of patients with eccentric hypertrophy among patients with OSA and abnormal LV geometry suggests that, at least in the initial phase of the disease, sustained pressure overload is probably not the main mechanism of LV hypertrophy.

Several animal studies have examined the relationship between chronic episodic hypoxia and LV mass. Studies have demonstrated that exposure to chronic episodic hypoxia in a rat model was associated with an increase in the ratio of LV weight to total body weight compared with control subjects (35). The same studies have also demonstrated that animals exposed to episodic hypoxia develop persistent elevation of mean arterial pressure (36). In an attempt to separate the effect of hypertension on LV from the effect of hypoxia, Fletcher and associates performed the same experiments on animals that had chemical sympathectomy. These studies show that, although mean arterial pressure was not different from baseline values after a period of episodic hypoxia, the animals still showed evidence of LV hypertrophy (35). These observations, like those from the present study, suggest that LV hypertrophy secondary to episodic hypoxia may develop independent of persistent elevation of blood pressure, suggesting that more than one mechanism could be implicated in the development of LV hypertrophy in patients with OSA.

The role of humoral factors and cytokines in mediating myocardial hypertrophy has also been examined in animal models. Animal studies have shown that continuous intravenous infusion of norepinephrine induces LV hypertrophy in rats even when the LV afterload is maintained within a normal range. LV hypertrophy seems to be mediated through a series of cytokines such as interleukin 6 and interleukin 1 $\beta$ . The use of adrenergic receptor blockers prevents the release of these cytokines and the development of LV hypertrophy (37). Therefore, several mechanisms could contribute to LV hypertrophy in patients with OSA besides persistent elevation of systemic blood pressure.

Our study has arrived at a different conclusion from that of Niroumand and colleagues (38), which did not detect a relationship between OSA in adults and LV mass after adjusting for age, sex, and BMI. A possible explanation for the difference between the two studies could be due to the different methods used to index LV mass to body size. Whereas we indexed LV mass to height raised to power 2.7, Niroumand and associates indexed LV mass to height. There has been much research on determining the best method for standardizing LV mass for body size so that comparisons among individuals of different sizes can be made. One suggestion has been to use height as a method for indexing. Although this method would not allow for the effect of obesity on LV mass, de Simone and colleagues have suggested that it is more appropriate to use a higher power of height because it would be expected that the

relationship of mass of LV to other measures of body size would reflect the geometric relationships between variables with different dimensions (22). Height, which is one dimension, would be a poor variable with which to standardize LV mass, which is three-dimensional. Research into these allometric relationships across the age range from childhood to adulthood has determined that height raised to the power of 2.7 provides the best method for standardizing LV mass for body size.

There are several limitations to this study. Although a larger number of subjects in the OSA group had RV dimension above the 95th percentile compared with the PS group and more subjects with severe OSA had abnormal LV geometry compared with subjects with mild OSA and the PS group, these trends did not reach statistical significance. It is likely that the small sample size provided limited scope to detect a significant difference among these variables. It is also possible that a significant difference could have been identified if a group of normal children without evidence of obstructive breathing during sleep had been used as the control group rather than children with PS. This study did not show an association between increase in LV mass, altered LV geometry, and elevation of systemic blood pressure. Without 24-hour ambulatory blood pressure recording, it is not possible to examine the association between abnormalities in nocturnal blood pressure, increased blood pressure load, and variability and end organ damage in the form of LV hypertrophy.

In summary, this study demonstrates that OSA in children causes structural changes involving both RV and LV, independent of body weight and blood pressure elevation. These cardiac changes are helpful in understanding better the effects of OSA on the cardiovascular system over time. The presence of LV hypertrophy may also be useful in determining a subset of patients for whom more aggressive management of OSA is indicated.

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