Baroreflex Gain in Children with Obstructive Sleep Apnea

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***Rationale*: We previously demonstrated that children with obstructive sleep apnea have increased blood pressure associated with changes in left ventricular mass index. Others have shown in adults that blood pressure variability is an important predictor of changes in left ventricular mass. The baroreflex system buffers blood pressure changes by varying heart rate. We have thus hypothesized that (*1*) baroreflex system gain is increased during sleep, improving blood pressure buffering; (*2*) children with obstructive sleep apnea lack this baroreflex gain increase; and (*3*) reduced blood pressure buffering results in exaggerated blood pressure variability that is associated with end-organ damage.**

***Objectives*: Compare measures of left ventricular mass index and nighttime baroreflex gain of healthy children to those of children with obstructive sleep apnea.**

***Methods*: A total of 169 children (50 control subjects, 63 with mild obstructive sleep apnea, and 56 with severe obstructive sleep apnea) with a mean age of 9.9 years (±2.2) underwent echocardiography followed by polysomnography with continuous blood pressure measurement. Baroreflex gain was calculated in time and frequency domains.**

***Measurements and Main Results*: Healthy children demonstrated a nighttime pattern of increasing baroreflex gain. Children with obstructive sleep apnea had decreased nighttime baroreflex gain compared with control subjects. Nighttime blood pressure and blood pressure variability were significantly correlated with left ventricular mass index.**

***Conclusions*: Obstructive sleep apnea is associated with a decrease in nighttime baroreflex gain and an increase in blood pressure variability. This increase is correlated with changes in left ventricular mass index.**

Keywords: sleep; apnea; baroreceptor; blood pressure

Numerous studies show that adults with obstructive sleep apnea (OSA) commonly have associated impairment of cardiovascular autonomic control (1–5). Beat-to-beat heart rate variability is diminished while sympathetic nerve activity and blood pressure (BP) are increased. Although the mechanisms linking OSA to cardiovascular pathology remain unclear, OSA is an identified cause of hypertension in adults (6, 7).

Recently, as part of an ongoing National Institutes of Health protocol, we showed that children with OSA have elevated nighttime and diurnal BP (8). Other studies have shown that children with OSA have left ventricular remodeling (9), altered heart rate variability (10), and increased sympathetic activity (11). Together, these findings suggest that children with OSA may likewise suffer from cardiovascular autonomic control impairment.

A critical component of cardiovascular autonomic control is the baroreflex system. This system provides the negative feedback control necessary to buffer BP fluctuations with accelerating or decelerating heart rate by changing the R-wave interval. The feedback is transmitted via the arterial baroreceptors, which are nerve fiber endings that respond to pressure-induced changes in circumferential stress of the major arteries that they innervate. Activation of the baroreceptors alters their efferent discharge to the medulla oblongata, which in turn triggers changes in afferent parasympathetic and sympathetic activity. Subsequently, vascular resistance, cardiac contractility, and heart rate are modulated to maintain cardiovascular homeostasis.

The sensitivity of the baroreflex system, referred to as baroreflex gain, is calculated by relating changes in the R-wave interval to changes in BP in open loop analysis. Techniques for noninvasive analysis of baroreflex gain include frequency domain analyses of oscillations of R-wave interval and BP during steady-state conditions (12) and time domain analyses of sequential increases or decreases in BP and R-wave interval (13). Studies using these techniques in adults demonstrate changes in cardiovascular autonomic control during sleep (14–17). To date, investigators have also used these techniques to analyze baroreflex gain in children during brief daytime studies (18–23); however, overnight studies have not yet been reported.

In view of these collective findings, we hypothesized that (*1*) baroreflex gain in control subjects would increase during sleep, (*2*) nighttime baroreflex gain would be lower in children with OSA compared with control subjects, and (*3*) changes in nighttime blood pressure parameters would be related to left ventricular mass index. In the present study, we tested these hypotheses as part of our ongoing National Institutes of Health protocol and in the same patient population.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The autonomic control of the cardiovascular system during sleep in children with sleep apnea has not been investigated. The associations between altered baroreceptor gain with abnormal control of blood pressure and with changes in cardiac geometry are not known.

What This Study Adds to the Field

Healthy children with obstructive sleep apnea have decreased baroreceptor gain. Blood pressure and blood pressure variability are directly related to increase in left ventricular mass.

METHODS

Subjects

Children ranging in age from 7 to 13 years who were being treated by adenotonsillectomy for nightly snoring and hypertrophy of the tonsils

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and adenoids were recruited by the institution's otolaryngology and community pediatric clinics. Children had to be without chronic medical conditions or genetic syndromes and able to temporarily discontinue any chronic medications. All of these children underwent echocardiographic evaluation and overnight polysomnography (PSG). The children were subsequently divided into two subgroups: (*1*) those with mild OSA (PSG showing an obstructive index [OI]: $1 < OI < 5$), and (*2*) those with moderate to severe OSA, (PSG showing $OI \geq 5$). Age- and sex-matched healthy children recruited from our institution and local pediatric practices composed a control group. Control group inclusion criteria were the absence of a history of OSA and the absence of any sleep-disordered breathing or alveolar hypoventilation on PSG. Parents signed an informed consent prior to enrolling their children in the study. Children 7 years of age or older signed an assent form. This study was approved by the Cincinnati Children's Hospital Medical Center institutional review board.

Study Design

A medical history was taken and a physical examination was performed on all children. Next, all children underwent overnight PSG studies performed according to standards set by the American Thoracic Society (24) using computerized systems (Grass Telefactor, Astro-Med Inc., West Warwick, RI). Simultaneous continuous BP monitoring was obtained by finger arterial photoplethysmography (Portapres; TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). The ECG was recorded using a Grass Telefactor System (Grass Telefactor) with standard ECG electrodes. Respiratory cycles were monitored by inductive plethysmography (Somnostar; SensorMedics Corp. Yorba Linda, CA). All signals were recorded using the Grass Heritage System and Gamma software. The data were acquired at 500 Hz per channel.

PSG interpretation was performed by the principal investigator (R.A.), who was blinded from subject grouping. Sleep stages were scored according to Rechtschaffen and Kales (25). PSG recordings included a period of wakefulness prior to sleep onset. The R-waves were manually calculated from the ECG R-waves, identified signal using custom software using a derivative and peak detection algorithm. The R-wave interval data were manually reviewed to identify and remove artifact and ectopic beats. The systolic blood pressure (SBP) was calculated as the maximum pressure during each heartbeat.

Echocardiography

Relative wall thickness and left ventricular mass index were determined from two-dimensional and two-dimensionally directed M-mode echocardiography as previously described (9).

Data Analysis

Blood pressure variability was defined as the periodicity of the beat-to-beat systolic pressure measured by spectral analysis within the low-frequency band (0.04–0.15 Hz) and high-frequency band (0.15–0.5 Hz).

Instantaneous baroreflex gain was analyzed in the time domain using the sequence method. The sequence method is based on the assumption that concurrent linearly related increases in SBP and R-wave interval are indications of baroreflex gain. This method involved an open loop computer analysis to identify spontaneously occurring sequences of three or four heartbeats in which SBP increased by at least 1 mm Hg, and R-wave interval increased by at least 5 milliseconds. Spontaneous sequences of heartbeats in which SBP and R-wave interval decreased were also identified and analyzed separately (13, 26). The slope of the regression of SBP against R-wave interval describes baroreflex gain. Additionally, we have used the initial SBP change in each sequence to describe the triggering pressure associated with baroreflex activation.

The oscillatory characteristics of the baroreflex system were analyzed in the frequency domain using the α method. The α method of baroreflex gain analysis is based on the finding that variability in SBP and R-wave interval has a high degree of linear correlation at the respiratory frequency and at approximately 0.1 Hz (12). The α method involved Fourier analysis of beat-to-beat SBP and R-wave interval data as follows: for each sleep study the complete recordings of SBP and R-wave interval were separated into 300-second time series with a single heartbeat offset. Uniformly sampled data sets were created from each 300-second time series segment by cubic spline interpolation at 2 Hz. These data sets were then de-trended (using a fifth order polynomial) and Hanning filtered. Finally, the power spectrum of each data set was calculated as the square of the Fourier transform. Coherence between the signals was calculated. The α calculation is the square root ratio of the integration of the SBP and R-wave interval power spectra where the signal coherence is greater than 0.5. We calculated this ratio within a low-frequency band of 0.04 to 0.15 Hz and within a high-frequency band of 0.15 to 0.5 Hz.

Cardiovascular data that coincided with respiratory events were omitted from the time domain and spectral analyses. Such an approach ensured that comparison of baroreflex data between control subjects and children with OSA could be performed without the confounding effect of respiratory events.

Statistical Analysis

The differences in sex and race frequencies were analyzed using the Pearson chi-square exact test. Differences of means in demographic, sleep, and echocardiographic variables were analyzed using the large-sample Kruskal-Wallis nonparametric test. Baroreflex data were synchronized to sleep onset. The spectral data distribution was normalized by log transformation and results are reported as log values. Baroreflex parameters were modeled by repeated-measures analysis controlling for age, body mass index *z* score (BMIZ), sex, and race. The impact of sleep stage was analyzed by including sleep stage as a time-varying covariate in repeated-measures analysis. Group differences for a given sleep stage were analyzed by repeated-measures analysis of covariance (ANCOVA) with a step-down simulation adjustment for multiple comparisons (27). The monotonic behavior of the baroreceptor gain parameters was determined using isotonic contrasts for ordered alternatives (28). Results were obtained by treating hour as a class variable in the previously described repeated-measures model. Additional detail on the BP standard deviation variability between groups is provided in the online supplement.

A separate time-series autoregressive variance/covariance structure was modeled for each group. Significance level for all tests was set as $P < 0.05$.

Spearman correlation was performed to measure the association between BP and baroreceptor parameters and left ventricular remodeling.

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND OVERNIGHT POLYSOMNOGRAPH PARAMETERS

Variable	Control (*n* = 50)	Mild (*n* = 63)	Severe (*n* = 56)
	Demographics		
Male, %	54	51	43
White, %	74	56*	48*
Age, years	10.2 (2)	9.9 (2.3)	9.6 (2.2)*
BMI	18.6 (3.9)	23.2 (7.7)†	23.8 (6.1)†
BMIZ	0.3 (1)	1.2 (1.1)†	1.5 (1.1)‡
	Sleep Parameters		
Sleep efficiency	82.8 (10.4)	81.6 (7.6)	79.7 (11.3)
Obstructive index	0.3 (0.3)	2.5 (1.1)‡	13.7 (11.2)‡
Total sleep time, min	398.3 (51.1)	402.3 (46.6)	390.4 (51.5)
% Time in stage 1	3.1 (1.7)	2.8 (1.3)	3.3 (2.2)
% Time in stage 2	49.6 (6.1)	49.3 (6.7)	49.5 (7.5)
% Time in stage 3 and 4	29 (5.9)	28.6 (6.2)	28.8 (4.8)
% Time in REM	18.3 (4.4)	19.3 (6.2)	18.4 (5.6)
SBP, mm Hg	92 (0.8)	97 (0.7)‡	100 (0.6)‡§
DBP, mm Hg	48 (0.8)	52 (0.6)†	53 (0.5)‡
Relative wall thickness	0.30 (0.06)	0.31 (0.04)	0.34 (0.06)*
Left ventricular mass index	30 (5.5)	33 (5.8)†	35 (8.9)†

Definition of abbreviations: BMI = body mass index; BMIZ = BMI *z* score; DBP = diastolic blood pressure; OSA = obstructive sleep apnea; REM = rapid eye movement; SBP = systolic blood pressure.

Means (SD) and frequencies for groups (control, mild, and severe).

* $P < 0.05$ compared with control subjects.

† $P < 0.005$ compared with control subjects.

‡ $P < 0.001$ compared with control subjects.

§ $P < 0.005$, comparison between mild and severe OSA.

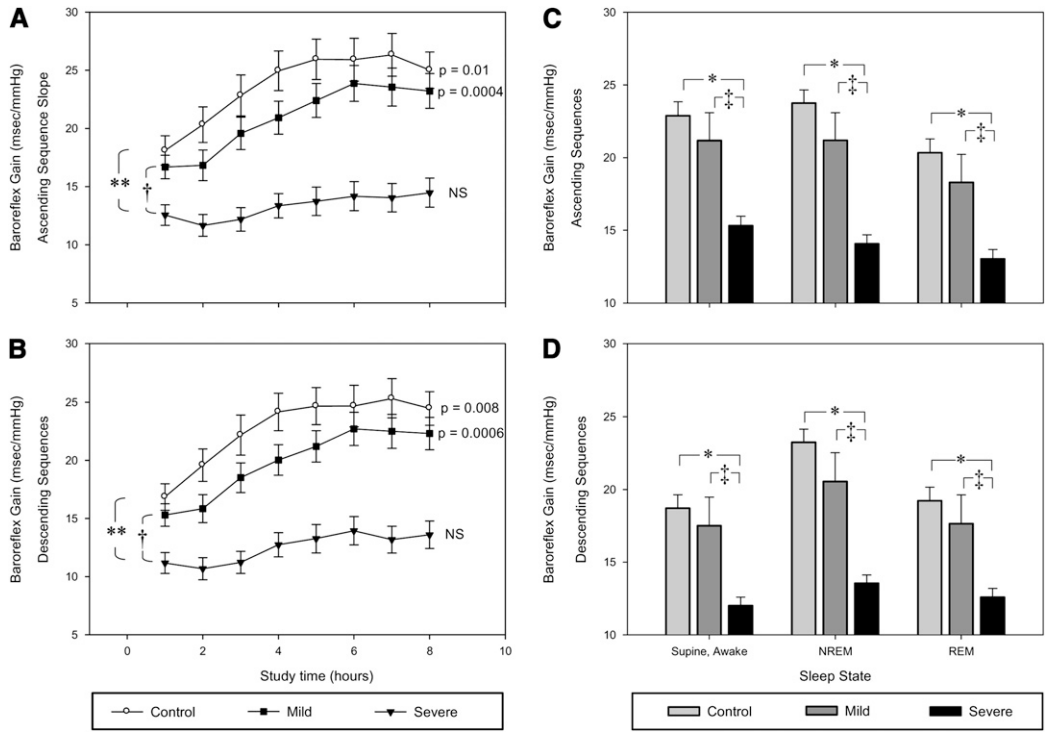

Figure 1. Nighttime baroreflex gain in the time domain. Data are hourly means ± SEM. *P* values on the graph reflect the results of monotonic increase during the sleep period. The symbols reflect the *P* values for the differences in overall least-squares means between groups. **P* < 0.05, mild versus control subjects; †*P* < 0.05 mild versus severe; ‡*P* < 0.0001 mild versus severe; ***P* < 0.0001, severe versus control subjects.

SAS software (SAS Institute, version 9.1.3, Cary, NC) was used for all analyses. SAS procedures were executed using an eight core HP ProLiant DL585 server with 4 Opteron 8,218 2.6 GHz dual core processors, 32 GB RAM, and 500 GB storage.

RESULTS

The demographic characteristics and overnight PSG results of the study participants are reported in Table 1. A total of 119 children with mild and severe OSA had significantly higher body mass index (BMI) and BMIZ compared with 50 age- and sex-matched healthy control subjects. Sleep efficiency was not significantly different among the three groups. Likewise, total sleep time and the percentage of time in each specific sleep stage were not significantly different among the groups. According to study design, children with mild or severe OSA had a higher OI than control subjects. Both the mild and severe OSA groups had significantly higher overnight SBP and diastolic BP than control subjects. Subjects with severe OSA had significantly higher SBP that those with mild OSA (Table 1).

During the first 7 hours of sleep instantaneous baroreflex gain exhibited a monotonic increase in children with mild OSA and in control subjects for ascending and descending sequences. In contrast, instantaneous baroreflex gain in children with severe OSA remained relatively constant (Figures 1A and 1B). Instantaneous baroreflex gain among the groups is compared in Figures 1C and 1D. Children with mild OSA had consistently lower instantaneous baroreflex gain across the sleep states compared with control subjects; however, this difference was not statistically significant. Children with severe OSA had significantly lower instantaneous baroreflex gain compared with control subjects and mild OSA prior to sleep and during both non–rapid eye movement (NREM) and REM sleep. Repeated-measures ANCOVA indicated that OI (as categorically grouped in our study design), sex, age, and BMIZ all contributed significantly to the variability of instantaneous baroreflex activity (Table 2).

The initial pressure change in baroreflex events in children with mild and severe OSA was significantly greater in magni-

TABLE 2. REPEATED-MEASURES ANALYSIS OF COVARIANCE PREDICTING BAROREFLEX GAIN (INCREASING AND DECREASING SEQUENCE SLOPES), LOG LOW-FREQUENCY α AND LOG HIGH-FREQUENCY α

	Baroreflex Gain Ascending Seq. Slope		Baroreflex Gain Descending Seq. Slope		Log L_f α		Log H_f α	
Variables	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
Group	*	<0.0001	*	<0.0001	*	<0.0001	*	<0.0001
Stage	*	<0.0001	*	<0.0001	*	0.0470	*	<0.0001
Group*Stage	*	<0.0001	*	<0.0001	*	0.0368	*	0.0002
Female	−2.27	0.0192	−1.92	0.0383	−0.18	<0.0001	−0.06	0.0877
Nonwhite	1.02	0.2942	0.35	0.7081	−0.028	0.1981	0.14	0.0004
Age	−0.64	0.0024	−0.43	0.0316	−0.05	<0.0001	−0.05	<0.0001
BMIZ	−1.24	0.0036	−1.19	0.0032	−0.07	<0.0001	−0.15	<0.0001
Hour	0.39	0.0005	0.15	0.1108	−0.002	0.4971	0.01	0.0102

Definition of abbreviations: BMIZ = body mass index *z* score; H_f = high frequency; L_f = low frequency; Seq = sequence.

* Separate estimates (β) were produced for each level of Group, Stage, and Stage*Group, and are therefore not included in this table. The *P* values for these variables are for the overall Type III tests.

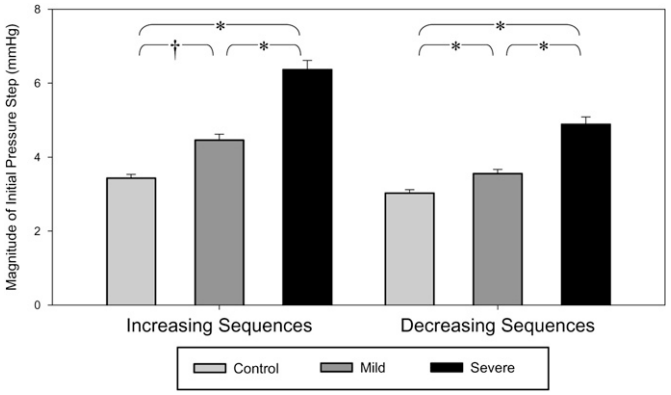

Figure 2. Initial baroreflex event pressure step. Data are means ± SEM. Tests for differences between groups are for overall least-squares means. *$P < 0.0001$; †$P = 0.0018$.

tude and more variable over the course of the night compared with this measure in control subjects. In control subjects, however, the initial pressure change in baroreflex events remained relatively constant. A significantly greater pressure change in subjects with severe OSA was observed compared with the mild group (Figure 2).

The high-frequency log α was monotonically increasing during the first 6 hours of sleep in children with mild OSA and for the first 5 hours of sleep in control subjects. In contrast, the high-frequency log α in children with severe OSA did not demonstrate a monotonic increase during sleep. There was no measurable monotonic increase in the low-frequency α for the three groups (Figures 3A and 3B). Spectral analysis of the baroreflex gain showed that there was not a significant difference in the low-frequency log α of children with mild OSA compared with control subjects during periods of supine wakefulness, NREM sleep, and REM sleep. However, there were significant differences in the low-frequency α in children with severe OSA compared with the mild group and with the control subjects. There was a decrease of the high-frequency log α in children with severe OSA compared with control subjects and the mild groups across all sleep states. Children with mild OSA had significantly decreased high-frequency log α during supine wakefulness and NREM sleep compared with control subjects (Figures 3C and 3D). Repeated-measures ANCOVA of the log α parameters indicated that age and BMIZ contributed significantly to both the low- and high-frequency log α parameters (Table 2). When we controlled for SBP differences in the statistical model, the log α parameters in both frequency ranges were significantly lower in children with severe OSA compared with control subjects.

The specific BP and R-wave interval components of the α calculations are reported in Table 3. The overnight BP and BP variability measures are displayed in Figure 4. In both high- and low-frequency ranges, SBP variability was significantly higher in children with mild and severe OSA compared with control subjects. Furthermore, subjects with severe OSA had higher variability in both frequency bands compared with mild OSA. In the high-frequency range, R-wave interval variability was higher only in children with mild OSA compared with control subjects. In the low-frequency range, R-wave interval variability was significantly higher in children with mild OSA and significantly lower in children with severe OSA, compared with control subjects. R-wave interval variability differed between mild and severe OSA in both frequency bands.

Spearman correlation between baroreceptor gain and BP parameters showed that high-frequency α correlated negatively with mean SBP (-0.22, $P = 0.005$) and with SBP in the high frequency (-0.4, $P < 0.0001$). The low-frequency α correlated negatively with mean SBP (-0.23, $P = 0.003$) and with SBP in the low frequency (-0.33, $P < 0.0001$).

Spearman correlations demonstrated an association between BP parameters and left ventricular parameters (Table 4). Mean SBP was significantly associated with relative wall thickness and with left ventricular mass index. SBP low frequency and SD correlated with relative wall thickness, whereas SBP high frequency correlated with left ventricular mass index. There was no direct linear association between baroreceptor gain and left ventricular mass index.

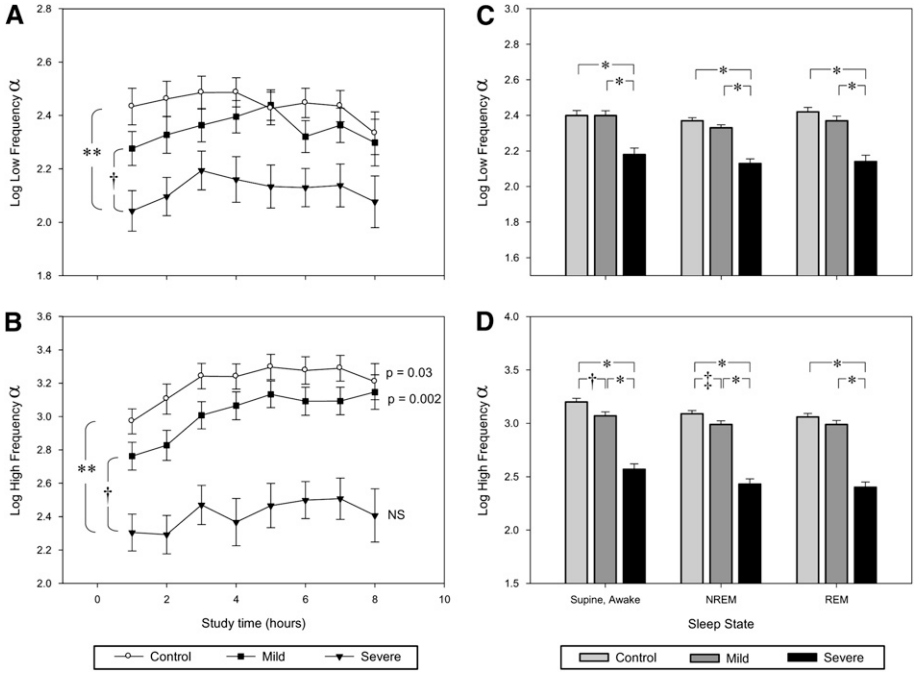

Figure 3. Nighttime baroreflex gain in the spectral domain. Data are hourly means ± SEM. *P* values on the graph reflect the results of monotonic increase during the sleep period. The symbols reflect the *P* values for the differences in overall least-squares means between groups. *$P < 0.0001$; †$P < 0.01$; ‡$P < 0.05$.

TABLE 3. SYSTOLIC BLOOD PRESSURE AND R-WAVE INTERVAL SPECTRAL MEASURES

Variable	Control ($n = 50$)	Mild ($n = 63$)	Severe ($n = 56$)
Log SBP L_f	2.4 (0.03)	2.5 (0.03)*	2.6 (0.04)†‡
Log SBP H_f	1.8 (0.04)	2.3 (0.04)†	3 (0.06)†§
Log RR L_f	7.5 (0.04)	7.6 (0.04)‖	7.3 (0.06)*§
Log RR H_f	8 (0.06)	8.3 (0.06)*	8 (0.06)§

Definition of abbreviations: BMIZ = body mass index *z* score; H_f = high frequency; L_f = low frequency; RR = R-wave interval; SBP = systolic blood pressure.

Comparison of least-squares means (SEM) for groups (control, mild, and severe) from a repeated-measures model (including stage, age, race, BMIZ, sex, and hour during sleep as covariates).

* $P < 0.005$ compared with control subjects.

† $P < 0.0001$ compared with control subjects.

‡ $P < 0.005$, comparison between mild and severe OSA.

§ $P < 0.0001$, comparison between mild and severe OSA.

‖ $P < 0.05$ compared with control subjects.

DISCUSSION

We report baroreflex gain during supine wakefulness and during the entire sleep period in children with OSA and in control subjects. We found that overnight baroreflex gain increases in healthy children during sleep and that nighttime baroreflex gain is lower in children with OSA compared with control subjects. Furthermore, we found that nighttime SBP and SBP variability were significantly correlated with left ventricular mass index. Together, these findings may help in understanding the links between OSA and cardiovascular disease.

Nighttime Patterns of Baroreflex Gain

Over the course of the night, control subjects exhibited increasing baroreflex gain as measured by both time and frequency domain techniques. These findings indicate a shift during sleep toward parasympathetic dominance in cardiovascular autonomic control. Because we found no significant group differences in sleep architecture (Table 1), the net trend of increasing nighttime baroreflex gain demonstrates a predominance of control due to ultradian rhythms over and against perturbations due to changing sleep stages. Other studies show similar trends in healthy adults (14, 15).

This interpretation of our findings is supported by a previous study by Legramante and colleagues (26). These authors show that baroreflex gain in healthy adults is significantly higher in late REM sleep stages compared with early REM sleep stages.

Nighttime Baroreflex Gain in Children with OSA

Nighttime baroreflex gain in children with OSA was lower than nighttime baroreflex gain in control subjects. These results are consistent with published reports of decreased daytime baroreflex gain in children with conditions that impair cardiovascular autonomic control (22, 23). In children with mild and severe OSA, the initial pressure change in baroreflex events over the course of the night was both greater in magnitude and more variable than this measure in control subjects. This finding indicates that the source of increase in baroreflex gain in healthy control subjects is a greater heart rate response to BP variability. Conversely, our findings in children with mild and severe OSA indicate a reduced heart rate response to BP variability. Reduced heart rate variability in response to BP variability in children with OSA is consistent with observations made in adults with OSA (29).

Nighttime instantaneous baroreflex gain increased both in children with mild OSA and in control subjects. In contrast, instantaneous baroreflex gain in children with severe OSA remained relatively constant. Moreover, instantaneous baroreflex gain was consistently lower throughout the night both in children with mild OSA and in those with severe OSA when compared with control subjects (Figures 2A and 2B). The finding of an inverse relationship between nighttime baroreflex gain increase and OSA severity suggests that it is not prudent to consider even mild OSA in children as a benign condition.

Although a consistent difference in baroreceptor parameters between healthy control subjects and subjects with mild OSA has been observed, the lack of statistical significance could in part be due to type II error.

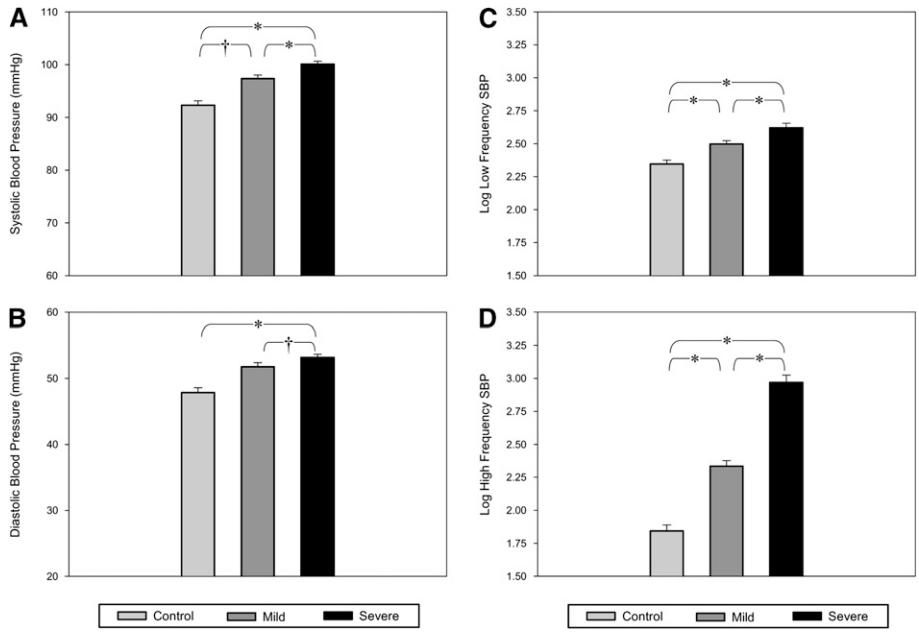

Figure 4. Overnight blood pressure profile. Data are means ± SEM. Tests for differences between groups are for overall least-squares means. *$P < 0.0001$; †$P < 0.002$.

TABLE 4. SPEARMAN CORRELATION *R*, (*P*) BETWEEN ECHOCARDIOGRAPHY PARAMETERS AND BARORECEPTOR GAIN PARAMETERS AND NOCTURNAL BLOOD PRESSURE PARAMETERS

	RWT	LVMI
Mean SBP	0.19 (0.016)	0.22 (0.004)
SBP H_f	0.09 (NS)	0.22 (0.004)
SBP L_f	0.16 (0.04)	0.06 (NS)
SBP SD	0.15 (0.048)	0.14 (0.07)
H_f α	−0.05 (0.5)	−0.05 (0.5)
L_f α	−0.1 (0.2)	0.02 (0.8)
Slope[a]	−0.06 (0.4)	−0.03 (0.6)

Definition of abbreviations: H_f = high frequency band; L_f = low frequency band; LVMI = left ventricular mass index; NS = not significant; RWT = relative wall thickness; SBP = systolic blood pressure; slope[a] = slope for ascending sequences; SD = standard deviation.

Echocardiography parameters are RWT and LVMI. Baroreceptor gain parameters and nocturnal blood pressure parameters include mean SBP, blood pressure variability in the H_f and L_f bands, and SBP SD.

Association between SBP, SBP Variability, and Left Ventricular Mass Index

SBP was significantly correlated with left ventricular mass index. This finding corroborates our earlier study, which demonstrates that children with OSA have significant left ventricular mass index that is correlated with SBP (8). Furthermore, we found that SBP variability correlated significantly with left ventricular mass index. Maule and colleagues hypothesize that the development of left ventricular mass index depends on high BP variability (30). Indeed, recent studies in adults show that daytime SBP variability is an important predictor of left ventricular remodeling independent of SBP levels (31). In the present study our findings indicate that in children with OSA, nighttime SBP variability is also significantly correlated with left ventricular mass index.

Conflict of Interest Statement: K.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. V.K.S. has served as a consultant for ResMed, Respironics, GlaxoSmithKline, Sepracor, and Cardiac Concepts, as a principal investigator or coinvestigator on grants from the ResMed Foundation, the Respironics Sleep and Respiratory Research Foundation, Sorin, Inc., and Select Research, Inc., and works with Mayo Health Solutions and iLife on intellectual property related to sleep and to obesity. T.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.A. received funding from Proctor and Gamble to study noninvasive monitoring of physical activity during sleep.

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