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Sleep Disordered Breathing and Cardiac Autonomic Modulation in Children

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Abstract

Objectives—To investigate the adverse cardiac autonomic effects of sleep-disordered breathing (SDB) in a large population-based sample and a clinical sample of children.

Methods—Subjects were based a population-based sample of 700 and a clinically diagnosed sample of 43 SDB children. SDB was defined based on the Apnea Hyponea Index (AHI) hour over one night of polysomnography. Cardiac autonomic modulation was measured by heart rate variability (HRV) analysis of the beat-to-beat RR interval data collected during the polysomnography.

Results—The mean (SD) age was 112 (21) months, with 49% male and 25% non-white. 73.0% had AHI < 1 (No SDB), 25.8% had 1–5 AHI (Mild SDB), and 1.2% had ≥ 5 AHI (Moderate SDB). Among individuals with moderate SDB in the population-based sample and the clinically diagnosed SDB patients, the mean (SE) of HRV-high frequency power (HF) were significantly lower compared to children without SDB [6.00 (0.32) and 6.24 (0.14), respectively, vs. 6.68 (0.04) ms², $p < 0.05$ and $p < 0.01$, respectively], whereas the low frequency power to high frequency power ratio (LF/HF) were significantly higher [1.62 (0.20) and 1.74 (0.09), respectively, vs. 0.99 (0.02), both $p < 0.01$].

Conclusions—SDB in healthy young children and in clinical patients is significantly associated with impaired cardiac autonomic modulation, i.e., sympathetic overflow and weaker parasympathetic modulation, which may contribute to increased risk of acute cardiac events in persons with SDB, even before reaching the “high risk age.”

Keywords

Sleep Disordered Breathing; Sleep Apnea; Cardiac Autonomic Modulation; Heart Rate Variability; Population-based Study

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Introduction

It is well-known that an episode of apnea is accompanied by a typical pattern of heart rate fluctuations – bradycardia during the apnoeic phase and tachycardia at the restoration of breathing. Several studies in adults have shown that sleep-disordered breathing (SDB) is significantly associated with lower heart rate variability (HRV), indicating impaired cardiac autonomic modulation among persons with apnea [1–4]. Baharav et al reported a significant association between SDB and sleep stage specific shift of HRV in 10 SDB and 10 normal control children [5]. In the cardiac disease literature, analysis of beat-to-beat HRV has emerged as a clinically and epidemiologically useful non-invasive method to quantitatively assess cardiac autonomic activity [6–21]. Most importantly, lower HRV has been consistently associated with the risk of incident cardiovascular disease [9–12,20–21,22–26]. However, little is known about the impact of SDB on cardiac autonomic control in population-based sample of children. This study was designed to investigate whether SDB is associated with impaired HRV indices, indicating impairment of cardiac autonomic modulation in a population-based and a clinically based sample of young children.

Methods

Population

The study population was from the Penn State Child Cohort (PSCC). The PSCC is a population-based study of the prevalence and correlates of SDB in children. The study sample was selected through a two-phase sampling process, with the first phase collecting general information from the parents about their child's sleep and behavioral patterns, and the second phase collecting more detailed data from a one night sleep study in our General Clinical Research Center (GCRC). The study was reviewed and approved by Penn State University College of Medicine Institutional Review Board as well as the GCRC review board. All participants and their parents provided informed consent prior to the initiation of the study. Briefly, in the first phase, a questionnaire was sent home to the parents of all elementary school (grade K-5) children in three school districts in Dauphin county, central Pennsylvania. In the first phase, we sent home 7,312 questionnaires and 5,740 were returned, with a response rate of 79%. In the second phase of sampling, each year we randomly selected 200 children from those who returned our questionnaires in phase I to participate in our GCRC sleep study. We stratified this sampling based on the severity of risk for SDB as reported by parents in the Phase I questionnaire and by grade and gender. A total of 700 children enrolled in our Phase II study, with a response rate of 70%.

Because of the small sample size in the group with moderate SDB in the population-based sample, we included a group of 43 children with clinically diagnosed SDB to enhance our comparison with the non-SDB and mild-SDB groups. These individuals were consecutive patients seen in our sleep clinic during the same time period of the population-based sample. These individuals had a similar age range (grade K-5) as the population-based sample.

Methods

During the Phase II, a detailed physical examination and a 9-hour fixed protocol polysomnogram (PSG) recording were performed in our GCRC. The physical examination, completed in the evening prior to the PSG recording, included height, weight, hip and waist circumferences, neck measurement, blood pressure, and a visual evaluation of the nose and throat by an ENT specialist and an evaluation of the respiratory function by a pediatric pulmonologist. All measurements were based on standardized procedures and protocols, and were subject to established quality control procedures.

For the sleep evaluation, all subjects, in the presence of a parent, spent one night in sound-attenuated, temperature- and light-controlled rooms in our GCRC. During this time the child's sleep was continuously monitored for nine hours (24 analog channel and 10 dc channel TS amplifier using Gamma software, Grass-Telefactor Inc). A four-channel electroencephalogram, a two-channel electro-oculogram, and a single-channel electromyogram were recorded. A single-channel electrocardiograph (ECG) was also recorded as the voltage at a continuously sampling rate of 100 Hz. The sleep records were subsequently scored independently according to standardized criteria [2]. Respiration was monitored throughout the night by use of thermocouple at the nose and mouth (model TCT R, Grass-Telefactor, Inc), nasal pressure (MP 45–871 $\pm$ 2 cm H₂O, Validyne Engineering Corp) and thoracic and abdominal strain gauges (model 1312 Sleepmate Technologies Midlothian, VA). A subjective estimate of snoring was obtained from parental report. In addition, we obtained an objective estimate of snoring during the PSG by monitoring breathing sounds with a microphone attached to the throat (model 1250 Sleepmate Technologies Midlothian, VA)) as well as a separate room microphone. All night hemoglobin oxygen saturation (SaO₂) was obtained from the finger (model 8800, Nonin Medical).

SDB definition—We defined sleep apnea and hypopnea using criteria that are currently used in clinical practice [27–28]. All records were double scored. An *apnea* was defined as a cessation of airflow with a minimum duration of five seconds and an out of phase strain gauge movement. A *hypopnea* was defined as a reduction of airflow of approximately 50% with an associated decrease in oxygen saturation (SaO₂) of at least 3% or an associated arousal. We then combined the total number of apnea and hypopnea episodes and divided it by the total duration of sleep to form the Apnea Hypopnea Index (AHI) [Episodes / hour of sleep]. We further defined individuals as “without SDB” if AHI is < 1, as “mild SDB” if AHI $\geq$ 1 but < 5, and as “moderate SDB” if AHI $\geq$ 5.

HRV variability indices—From the 1-channel ECG voltage data, we first converted the voltage file form into a wave form file. Then we identified the peak of each QRS complex as the R wave point. We then calculated beat-to-beat RR interval data from the entire night of ECG recording. A potential artifact identification and removal algorithm was applied to the entire RR interval data. This algorithm identified and removed as artifacts any RR interval < 375 ms, any RR interval > 1200 ms, or RR interval ratio from two adjacent RR intervals < 0.8 or > 1.2. We also excluded the segment where an episode of apnea or hypopnea occurred.

We used the HRV Analysis Software [29] to complete the HRV analysis to the above described “artifact free” RR interval files if the total length of the “artifact free” RR interval file was more than 6.5 hours (corresponding to approximately 75% of the total recording time). When performing frequency domain HRV analysis, we used Fast Fourier Transformation (FFT). Briefly, the adjacent RR interval data were interpolated using a piecewise cubic spline interpolation approach, with a 2 Hz sampling rate. The FFT was performed on the equidistantly interpolated RR time series. We used 2nd order polynomial model to remove the slow nonstationary trends of the HRV signal. As a result, we have HRV data for this study from 616 participants (88% of total sample size of 700) of the population-based sample, and from 43 patients with clinically diagnosed SDB.

From the HRV analysis, we calculated the following frequency domain HRV indices for this study: Low Frequency Power (**LF**) – the power in the low frequency range (0.04 – 0.15 Hz), High Frequency Power (**HF**) – the power in the high frequency range (0.15 – 0.40 Hz), and **LF/HF** Ratio. We also calculated the following time domain HRV indices for this study: **SDNN** – the Standard deviation of all RR intervals (ms), **RMSSD** – the square root of the

mean of the sum of the squares of differences between adjacent RR intervals (ms), and **Mean HR** – the Mean heart rate (BPM). In general, LF represents a mixture of sympathetic and parasympathetic modulation, HF represents the parasympathetic modulation, and LF/HF Ratio represents the balance of sympathetic and parasympathetic modulation. Lower HF and higher LF/HF ratio are used as an indicator of an autonomic balance of more sympathetic and less parasympathetic modulation. The time domain measures are used to represent the overall variability of RR intervals, with SDNN being highly correlated with the total power of the frequency domain analysis, and RMSSD highly correlated with the HF of the frequency domain analysis [22].

Other covariables—The covariables we investigated included age, race, sex, BMI, percent REM sleep, snore status, and sleep efficiency. All covariables were collected during the Phase II physical examination, and subject to standardized protocols. The BMI percentile was used, which was calculated as the percentile of BMI distribution for age and gender of the US population. Percent REM sleep was defined as the proportion of sleep time spent in the REM stage. Sleep efficiency was defined as the proportion of the recorded time that the participant was asleep. The minimum oxygen saturation (SaO₂) and the average arousal index were obtained from the PSG.

Statistical Methods—Means and proportions of the main variables were calculated for the entire study population, as well as stratified according to the SDB status. Four mutually exclusive groups, namely population-based no-SDB, mild-SDB, and moderate SDB, and clinical SDB patients were compared by means of analysis of covariance (ANCOVAR), simultaneously adjusting for major potential confounders. Comparisons of the mean HRV indices from the moderate SDB and clinical SDB to non-SDB and mild-SDB groups were obtained and the multivariable adjusted means and the standard errors (SE) of HRV indices were presented. Following the convention of HRV analysis [22], HF and LF values were log-transformed when analyzed. We accounted for the sampling probability from Phase I to Phase II enrollments in all of the analyses in order to generate population level estimates and to make inference back to the population from which the Phase II study participants were selected from. SAS 9.1 was used for our analysis.

Results

The population characteristics are presented in Table 1, as mean levels for continuous variables and as proportions for categorical variables. The mean (SD) age of participants was 9 (1.75) years, with 49% male and 25% non-white. The average AHI (SD) was 0.79 (1.03) during the entire sleep, while 73.0% had No SDB, 25.8% had mild SDB, and 1.2% had Moderate SDB. For 7 children with moderate SDB, the average AHI is 5.79, ranging from 5.02 to 7.47. In this population, both systolic and diastolic blood pressures were higher among children with higher levels of AHI. Children who snored during the sleep period were also more likely to have higher levels of AHI. For the 43 children with clinically diagnosed SDB, the mean age was 9 (SD 2.17) years, with 47% male and 42% non-white. Their average AHI was 26 (SD=27, range 5.00 to 125). They had significantly higher BMI percentile and HR than the population-based moderate SDB group (both $p < 0.01$). They also had lower, but not statistically significant, systolic blood pressure than the population-based moderate SDB group ($p = 0.06$). None of the SDB children had any significant chronic conditions.

The age, race, sex, BMI percentile, percent REM sleep, snore status, and sleep efficiency adjusted mean levels of HRV indices and their standard errors according to SDB categories are presented in Table 2. In general, children with moderate SDB have significantly impaired HRV indices compared to children without SDB, or children with mild SDB,

indicative of sympathetic overflow unopposed by parasympathetic modulation. Also as presented in Table 2 in the last column, the clinically diagnosed SDB group, after adjusting for major potential confounders, had significantly lower HF, RMSSD, SDNN, and significantly higher LF-HF ratio and HR than the population-based no-SDB and mild-SDB groups. Clinically diagnosed SDB group was not significantly different from the population-based moderate SDB group in any HRV indices, except for the clinically diagnosed SDB group had faster HR ($p < 0.01$). The population-based mild and no-SDB group were not statistically different in any of the HRV indices.

We also tested interactions between SDB and several covariables, such as gender, race, snore status, percent REM sleep, and sleep efficiency, and none of them were statistically significant at the $p < 0.10$ level. We also analyzed the relationship between HRV indices and the covariables adjusted in the models to generate the results for Table 2, and the results suggest that older age, being non-white, female, and higher BMI percentile are associated with lower levels of HRV, whereas, percent REM sleep, snore status, sleep efficiency, minimum SaO₂, and arousal Index were not associated with HRV indices in the population-based sample (data not shown).

Discussion

In this population-based sample of young children, the prevalence of moderate SDB, defined as AHI ≥ 5 , is relatively low, at about 1.2%, and the prevalence of mild SDB, defined as 1–5 AHI is 25.8%. The most important finding from this study is the significant decrease of HRV indices among young children with even moderate SDB, as compared to children without SDB. This finding is further substantiated by the significantly lower HF, SDNN, RMSSD and higher LF-HF ratio and HR in the clinically diagnosed SDB group, as compared to the non-SDB and mild-SDB groups. Our findings are supportive of our *a priori* hypothesis that moderate SDB is significantly associated with impaired HRV profile in the direction of sympathetic overflow and weaker parasympathetic modulation. This finding is especially relevant considering the study participants were either randomly selected from school-aged children or similar aged children with clinically diagnosed SDB but without any chronic conditions that can impair their cardiac autonomic modulation.

Studies on adult patients have found that lower HRV is associated with a higher risk of all-cause mortality in survivors of acute myocardial infarction (AMI) [9,11–12,16] and sudden cardiac death (SCD) [13]. Results from population-based follow-up studies also suggest that lower HRV is associated with the risk of developing coronary heart disease [9–12,20–21,22–23,25–26], and that lower HRV is associated with other cardiovascular related comorbidity and risk factors [24,30–35]. HRV has since been proposed as a marker of cardiac vulnerability for arrhythmia and acute cardiac events [22]. In adult patients, SDB was significantly associated with lower HRV, indicating impaired cardiac autonomic modulation [1–4]. In a small group of children, SDB children had lower HRV than the normal controls [5].

Therefore, biologically, it is likely that SDB can lead to an imbalance of the cardiac autonomic modulation, and such an imbalance is presented as sympathetic over flow unopposed by parasympathetic modulation. This can be observed as lower HRV HF, lower HRV time domain variables, and increased LF/HF ratio. However, little is known about the SDB-HRV association in population-based samples, or among young children. Our study results are supportive of a significant shifting of cardiac autonomic modulation towards sympathetic overflow unopposed by parasympathetic modulation among young children with moderate SDB. The significant association observed in our data remained after multivariable adjustment of several factors that were associated with SDB and HRV, such as

age, race, sex, BMI percentile, percent REM sleep, snore status, and sleep efficiency. This interpretation is further supported by significantly lower HRV observed in clinically diagnosed SDB group, as compared to the non-SDB or mild-SDB populations. It is important to emphasize that the definition of “moderate SDB” in our population-based sample is only $AHI \geq 5$ and the actual overall burden of SDB on cardiac regulatory system should have been relatively light at such young age. Therefore, our data, if confirmed by other studies, suggest that the SDB and HRV association contribute to increased risk of acute cardiac event in persons with SDB, even before they reach the traditional “high risk age.” On the other hand, it should be noted that the lower HRV and higher risk of acute cardiac events literatures were all based on adults, and no data to date has been published relating childhood HRV and the future development of acute cardiac events. Our interpretation of the impact of SDB related impairment on cardiac autonomic modulation in children is based on the premise of adult literature. Thus, it is possible that lower HRV in children may or may not represent higher risk of future acute cardiac events, which requires further studies. Contrary to our expectation, the mild SDB group had slightly lower LF/HF ratio and higher values on all other HRV variables than the non-SDB group, although none was statistically significant. One possible explanation is that the lack of effects in the mild SDB group may be due to the fact that this is a population-based sample of healthy young children, and as a result, the severity and the duration of SDB may not yet be sufficient enough to impact the sympathetic-parasympathetic modulation among the mild-SDB group.

There are several limitations in this study. The ECG data were collected digitally at a sampling rate of 100 Hz from one-ECG channel. At such a sampling frequency, it is possible that some degree of systematic misclassification of R wave due to a jitter (1–3 ms inaccuracy) of R wave identification. Such misclassification of R waves can lead to inaccuracy of the HRV estimation, especially the frequency domain HRV indices. To overcome this inherited limitation, we analyzed long duration of RR data (9 hours). Additionally, if the R waves were systematically misclassified due to the 100 Hz sampling frequency (non-differential misclassification), the association between SDB and HRV would have been biased toward null. Thus, our findings are more conservative in this perspective. Since there was only ECG data from one channel, when artifacts occurred, we cannot make judgments/adjudications from other ECG channels. Instead, we applied a set of statistical criteria (RR interval < 375 ms, RR interval > 1200 ms, or RR interval ratio from two adjacent RR intervals < 0.8 or > 1.2) to identify and remove such RR intervals from the analysis of HRV. This approach was at the expense of shortening the duration of RR interval data for HRV analysis. However, this limitation is offset by the major strengths of this study - large population, and long-duration of continuous ECG. For example, we successfully performed HRV analysis on 88% of the original PSCC sample (616 out of 700) based on at least 5 hours of RR interval data. To avoid major bias introduced by different duration of RR data in the final analysis, we only performed statistical analysis excluding participants whose total RR interval data after artifacts elimination were 6.5 hours or longer. Another limitation is that the ECG data were collected from the sleep study at night. It is well recognized that there exist a circadian shift of the cardiac autonomic modulation. Thus, the HRV profile at evening/night while sleeping may not be representative of day-time HRV file. However, this is offset by a supine, quiet, and no-interference data collection environment.

In summary, in the population-based sample of K-5 school-aged children and in the clinically diagnosed SDB patients, SDB is significantly associated with impaired cardiac autonomic modulation indicative of sympathetic overflow unopposed by parasympathetic modulation. If these results are confirmed by other studies, this association may contribute to increased risk of acute cardiac event in persons with SDB, even before they reach the traditional “high risk age.”

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Table 1

Characteristics of the Study Population

	All	SDB Status				p-value
	Population-based sample (N=616)	No SDB AHI < 1 (N=450)	Mild SDB AHI 1 – 5 (N=159)	Moderate SDB AHI ≥ 5 (N=7)	Clinically Diagnosed SDB (N=43)	
Age (Months)	112 (21)	110 (21)	112 (19)	117 (17)	107 (26)	NS
Male (%)	49	48	52	15	46.5	< 0.05
Race (% non-Caucasian)	25	20	36	0	42	< 0.05
BMI Percentile	61 (29)	59 (30)	66 (28)	59 (41)	87 (26)	< 0.01
REM Sleep (%)	20 (5.6)	20 (5.9)	20 (4.9)	18 (6.8)	16 (6.7)	NS
Sleep Efficiency (%)	86 (8.5)	85 (8.6)	87 (7.9)	80 (7.8)	85 (8.4)	NS
Snore (%)	24	20	34	65	95	< 0.05
AHI (# / hr sleep)	0.79 (1.03)	0.29 (0.27)	1.98 (0.80)	5.79 (0.93)	26.0 (28.5)	< 0.01
Systolic BP (mmHg)	111 (12)	110 (12)	113 (11)	128 (11)	117 (15)	< 0.01
Diastolic BP (mmHg)	65 (8)	65 (8)	65 (7)	72 (5.3)	68 (8.7)	NS
One night (9 hours) HRV						
Log-HF (ms ²)	6.70 (0.84)	6.67 (0.86)	6.83 (0.77)	5.91 (0.73)	6.14 (0.90)	< 0.01
Log-LF (ms ²)	6.57 (0.66)	6.55 (0.66)	6.65 (0.64)	6.37 (0.71)	6.51 (0.88)	NS
LF/HF Ratio	0.98 (0.53)	1.00 (0.55)	0.91 (0.42)	1.69 (0.62)	1.75 (1.14)	< 0.01
RMSSD (ms)	73 (34.0)	72 (34.2)	78 (33.3)	45 (15.5)	53 (27.1)	< 0.01
SDNN (ms)	94 (27.4)	93 (27.1)	98 (28.2)	85 (23.1)	77 (26.7)	NS
Heart Rate (bpm)	77 (8.2)	77 (8.2)	76 (8.4)	79 (6.8)	92 (12.9)	< 0.01

NS Not significant (p > 0.05)

Log-LF Log transformed low frequency power

Log-HF Log transformed high frequency power

LF/HF The ratio of LF and HF

SDNN The standard deviation of all RR intervals (ms)

RMSSD The square root of the mean of the squares of differences between adjacent RR intervals (ms)

Table 2

Multivariable Adjusted Means (SE) of HRV Indices calculated from overnight EKG, according to SDB categories

	SDB Status and Source of Subjects			
	No SDB AHI < 1 (N=450)	Mild SDB AHI 1 – 5 (N=159)	Moderate SDB AHI ≥ 5 (N=7)	Clinically Diagnosed SDB (N=43)
Log-HF (ms ²)	6.68 (0.04)	6.87 (0.07)	6.00 (0.32)	6.24 (0.14)
			p = 0.025, vs. No SDB p = 0.007, vs. Mild SDB	p= 0.01 vs. No SDB p< 0.0001 vs. Mild SDB
Log-LF (ms ²)	6.55 (0.03)	6.70 (0.05)	6.38 (0.25)	6.64 (0.11)
			p NS, vs. No SDB p NS, vs. Mild SDB	p NS, vs. No SDB p NS, vs. Mild SDB
LF/HF Ratio	0.99 (0.02)	0.92 (0.04)	1.62 (0.20)	1.74 (0.09)
			p< 0.01, vs. No SDB p< 0.01, vs. Mild SDB	p< 0.0001 vs. No SDB p< 0.0001 vs. Mild SDB
RMSSD (ms)	72 (1.55)	79 (2.70)	50 (6.91)	58 (5.51)
			p NS, vs. No SDB p < 0.01, vs. Mild SDB	p=0.01 vs. No SDB p= 0.001 vs. Mild SDB
SDNN (ms)	93 (1.24)	100 (2.16)	85 (10.37)	83 (4.45)
			p NS, vs. No SDB p NS, vs. Mild SDB	p= 0.04 vs. No SDB p= 0.002 vs. Mild SDB
HR (bpm)	77 (0.36)	76 (0.63)	78 (3.00)	89 (1.32)
			p NS, vs. No SDB p NS, vs. Mild SDB	p< 0.001 vs. No SDB p< 0.001 vs. Mild SDB

Adjusted for age, race, sex, BMI percentile, percentage of REM sleep, snore statue, and sleep efficiency.