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Evaluation of cardiac modulation in children in response to apnea/hypopnea using the phone oximeter™

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Abstract

Individuals with sleep disordered breathing (SDB) can experience changes in automatic cardiac regulation as a result of frequent sleep fragmentation and disturbance in normal respiration and oxygenation that accompany most apnea/hypopnea events. In adults, these changes are reflected in enhanced sympathetic and reduced parasympathetic activity. In this study, we examined the autonomic cardiac regulation in children with and without SDB, through spectral and detrended fluctuation analysis (DFA) of pulse rate variability (PRV). PRV was measured from pulse-to-pulse intervals (PPIs) of the photoplethysmogram (PPG) recorded from 160 children using the Phone Oximeter™in the standard setting of overnight polysomnography. Spectral analysis of PRV showed the cardiac parasympathetic index (high frequency, HF) was lower ($p < 0.01$) and cardiac sympathetic indices (low frequency, LF and LF/HF ratio) were higher ($p < 0.01$) during apnea/hypopnea events for more than 95% of children with SDB. DFA showed the short- and long-range fluctuations of heart rate were more strongly correlated in children with SDB compared to children without SDB. These findings confirm that the analysis

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of the PPG recorded using the Phone Oximeter™ could be the basis for a new screening tool for assessing PRV in non-clinical environment.

Keywords: sleep disordered breathing, pulse rate variability, mobile health, phone oximeter, photoplethysmogram, apnea/hypopnea

AQ1 (Some figures may appear in colour only in the online journal)

1. Introduction

Sleep disordered breathing (SDB) describes a family of disorders characterized by frequent episodes of partial or complete cessations of breathing during sleep (Baldwin and Quan 2002). These events often cause hypoxemia, systemic hypertension and decreased stroke volume (Somers *et al* 2008). They are generally accompanied by transition from deep sleep to light sleep or even complete arousal from sleep. Frequent sleep segmentation and disturbance in oxygenation affect activities of the cardiovascular system.

We have previously developed a mobile device which interfaces a commercial microcontroller-based pulse oximeter module with a smartphone (Karlen *et al* 2011). The Phone Oximeter™ (figure 1) has been further developed to perform all processing on the mobile device through the audio interface (Petersen *et al* 2013). The use of the smartphone as the pulse oximeter display and power source overcomes pertinent challenges of distributing the technology. The Phone Oximeter™ improves accessibility of pulse oximetry, enables the acquisition, monitoring and analysis of vital signs and provides intuitive display of information to health care providers (Petersen *et al* 2013). Usability studies of the Phone Oximeter™ prototype previously undertaken both in Canada and Uganda have shown overall usability scores of 82% and 78% respectively, indicating that a smartphone can be a functional oximeter interface (Hudson *et al* 2012).

In a previous study (Garde *et al* 2013), we showed that characterization of oxygen saturation recorded by the Phone Oximeter™ could identify children with SDB. However, we observed some instances of breathing cessation that occurred without oxygen desaturation. To improve identification of children with SDB, we have therefore chosen to evaluate the analysis of cardiac autonomic regulation in children, as the occurrence of breathing cessations are known to impact the autonomic regulation of heart rate (Khoo and Blasi 2013). The aim of this study was to assess cardiac autonomic modulation in children with SDB using photoplethysmography (PPG), recorded by the Phone Oximeter™. The findings of this study combined with characterization of oxygen saturation is used to propose a screening tool for monitoring children with SDB at home (Garde *et al* 2014).

1.1. Background

Obstructive sleep apnea syndrome (OSAS) is the most prevalent type of SDB in children and is characterized by periodic interruption of breathing (apnea/hypopnea) during sleep, generally caused by a collapse of the muscles of the upper airway (Malhotra and White 2002). The SDB severity is quantified by the number of apneas and hypopneas experienced per hour of sleep, referred to as the apnea/hypopnea index (AHI).

The autonomic nervous system (ANS) and circulating hormones play a significant role in regulating cardiovascular function. Regulation of heart rate is driven mainly by interaction between the sympathetic and parasympathetic branches of the ANS. To increase heart rate,

Figure 1. The Phone Oximeter™ interfacing a microcontroller-based pulse oximeter module with a smartphone.

the ANS increases sympathetic outflow to the sinoatrial (SA) node, and concurrently reduces parasympathetic tone. Depression of parasympathetic activity is necessary for the sympathetic nerves to increase heart rate because parasympathetic activity reduces the action of sympathetic nerve activity (Klabunde 2011). Since the regulation of heart rate is mainly controlled by the ANS, heart rate variability (HRV) has received significant attention as a promising non-invasive indicator of cardiac autonomic function. HRV is defined as the variation in the inter-beat intervals (RRIs) conventionally obtained from an electrocardiogram (ECG). RRIs time series are typically non-stationary and exhibit short and long-range fluctuations that occur in irregular and complex patterns, even during rest (Peng *et al* 1993, 1995, Ivanov 2003). Short-range fluctuations correspond to fast changes of heartbeat intervals associated with breathing and the regulation of blood pressure, whereas long-range fluctuations correspond to slow changes of heartbeat intervals and reflect the effort of the ANS to limit heart rate (Peng *et al* 1995).

Power spectral analysis of HRV has been extensively used to study the frequency distribution of heart rate. Measured in short segments of RRIs time series, the power in the frequency range of 0.15 to 0.4 Hz, referred to as the high frequency power (HF), is commonly utilized to quantify parasympathetic activity. The power of HRV in the frequency range of 0.04–0.15 Hz, referred to as the low frequency power (LF), can be related to both sympathetic and parasympathetic activity. The ratio of LF to HF (LF/HF ratio) is defined as an index that represents the sympathetic/parasympathetic balance; a higher LF/HF ratio implies a shift toward sympathetic activity (Ivanov 2003).

Power spectral analysis assumes that the studied signal is stationary, and may produce inaccurate results when applied to non-stationary signals. This makes power spectral analysis inappropriate for quantifying the long-range fluctuation of heart rate. To overcome this limitation, Peng *et al* introduced the Detrended Fluctuation Analysis (DFA) (Peng *et al* 1993). DFA determines the short- and long-range correlations in a time series, expressed as scaling exponents. Peng *et al* showed that it is possible to distinguish healthy subjects from those with severe heart failure by looking at the short and long-range correlations in heartbeat intervals (Peng *et al* 1995). Later, Penzel *et al* investigated the short- and long-range correlation of heart rate intervals measured by DFA in individuals with SDB in different sleep stages and found that DFA improved sleep apnea severity rating compared to spectral analysis (Penzel *et al* 2003).

Traditionally, HRV is measured from the RRIs of the ECG. However, it is possible to use pulse rate variability (PRV) extracted from the photoplethysmography signal (PPG) as an alternative measurement of HRV. In a study by Constant *et al*, PRV has been demonstrated not to reflect HRV precisely in standing position and in patients with low HRV (Constant *et al* 1999). More recent studies have shown that in stationary conditions PRV could be used as an estimate of HRV (Khandoker *et al* 2011, Dehkordi *et al* 2013). During non-stationary conditions, Gil *et al* (2010) reported that there was a positive bias, due to pulse time transit variability, in the estimation of PRV, especially in respiratory band. They demonstrated that these differences were sufficiently small to allow the use of PRV as an alternative measurement of HRV.

In individuals with SDB, intermittent sleep fragmentation and disturbance in normal respiration and oxygenation that accompany most apnea/hypopnea events cause changes in cardiac autonomic regulation (Khoo and Blasi 2013). These changes are reflected by reduced parasympathetic activity and enhanced sympathetic activity that persists during wakefulness (Khoo and Blasi 2013). Previous studies based on HRV analysis have demonstrated cardiac autonomic modulation due to SDB, and have shown that both the LF power and the LF/HF ratio are more pronounced in subjects with SDB, while the HF power is reduced (Narkiewicz *et al* 1998, Wang *et al* 2008). Cardiac sympathetic and parasympathetic modulation in response to apnea/hypopnea has been well studied in adults, but is less extensively studied in children.

In this study, we investigated the relative impact of SDB on sympathetic and parasympathetic activity in children through spectral analysis and DFA of PRV. We estimated PRV from the pulse-to-pulse intervals of the PPG signal. The PPG signals were recorded from 160 children using the Phone Oximeter^{TM} in the standard setting of overnight polysomnography (PSG).

2. Materials and methods

2.1. Participants

Following approval by the University of British Columbia Clinic Research Ethics Board (H11-01769) and informed parental consent, 160 children were recruited for this study. The children were suspected of having SDB and had been referred to the British Columbia Children's Hospital for overnight PSG. Children with a cardiac arrhythmia or abnormal hemoglobin were excluded from the study. The recordings of 14 subjects were removed from the dataset due to inadequate length of sleep (less than 3 h). The children were divided into two groups using the PSG outcomes and diagnostic report of the respiratory specialist: subjects with an AHI greater than 5 apnea/hour (SDB group) and children with an AHI less than 5 apnea/hour (non-SDB group) (table 1).

2.2. Data collection

Standard PSG recordings were performed with the Embla Sandman S4500 (Embla Systems, ON, Canada) and included overnight measurements of ECG, electroencephalography (EEG), oxygen saturation (SpO_2), PPG, chest and abdominal movement, nasal and oral airflow, left and right electrooculography (EOG), electromyography (EMG) and video capture. The PSG was later annotated by a sleep technician with sleep phases and events (apneas, hypopneas, and arousal).

Table 1. Demographics and AHI index of studied population expressed as mean ± standard deviation.

Dataset	SDB	non-SDB
Number (F, M)	56 (18, 38)	90 (41, 49)
Age (y)	8.8 ± 4.6	9.3 ± 4
AHI	19.7 ± 19.5[f]	1.4 ± 1.1
AHI in REM[ag]	34.8 ± 27.8[f]	4.4 ± 5.1
AHI in non-REM	15.8 ± 22.8[f]	0.8 ± 1.0
BMI[b] (kg m^{-2})	23.2 ± 8.3[e]	19.6 ± 6.6
Sleep efficiency (%)	75.1 ± 16.2	76.6 ± 15.3
TST[c] (min)	362.1 ± 82.6	368.0 ± 73.8
TBT[d] (min)	479.9 ± 40	481.4 ± 24.1
non-REM (%)	78.7 ± 9.3	81.7 ± 7.6
REM (%)	20.2 ± 8	18.2 ± 6.1
Awakenings	21.2 ± 10.6	18.6 ± 9.3
Respiratory arousals	13.6 ± 13.9[f]	01.0 ± 0.9

[a] Rapid Eye Movement;
[b] Body Mass Index;
[c] Total Sleep Time;
[d] Total Bed Time;
[e] $p < 0.001$;
[f] $p < 0.0001$ comparing SDB and non-SDB;
[g] p-value <0.001 comparing AHI in REM and non-REM sleep stages.

In addition to PSG, PPG, heart rate, and SpO_2 were recorded simultaneously with the Phone Oximeter™. The SpO_2 and PPG signals were sampled at 1 Hz and 62.5 Hz, respectively, with 32-bit resolution.

2.3. Pre-processing

After baseline removal and smoothing with a Savitzky–Golay FIR filter (order 3, frame size 11 samples), all PPG signals recorded using the Phone Oximeter™ were divided into one-minute segments with 30 s shift. These one-minute segments were used to assess autonomic cardiac modulation during the apnea/hypopnea events for each subject with SDB (intra-individual event analyses). In addition, the PPG signals were divided into five-minute segments with 30 s shift and used to assess autonomic cardiac modulation in subjects with and without SDB (inter-groups analyses).

Each segment was assigned a signal quality index between 0 and 100 based on a cross correlation method (Karlen *et al* 2012) and segments with low signal quality index (less than 50) were rejected from further analysis even if a very small part of segment was contaminated by artifact. In order to obtain the PPIs time series, a peak detection algorithm based on zero-crossing was used to locate the pulse peaks in the PPG signal, and the intervals between successive peaks were computed. PPIs shorter than 0.33 s and greater than 1.5 s were considered artifacts (Penzel *et al* 2003) and consequently deleted from the time series.

2.4. Sleep and apnea analysis

All segments were scored as wakefulness, Rapid Eye Movement (REM) or non-REM based on the labels in the PSG event log file. Segments with any sleep state transition containing multiple sleep state labels were removed from the data set.

One-minute segments with any period of SDB, such as obstructive or central sleep apnea were labelled as apnea/hypopnea (A/H). According to the AASM 2012 standard criteria (Berry *et al* 2012), obstructive apneas in children are defined as complete cessation of airflow (on airflow cannula) in the presence of respiratory effort lasting for more than 10 s. When respiratory effort partially or totally ceased, apneas were scored as mixed apnea or central apnea, respectively. Hypopneas were defined as a 30% airflow reduction for the duration of two breaths.

2.5. Parameter extraction

2.5.1. Time-domain parameters. Three time domain parameters were extracted from the PPIs time series, including the mean of the PPIs (meanPP), the standard deviation of the PPIs (SDPP) and the root mean square of difference of the successive PPIs (RMSSD).

2.5.2. Power spectral analysis. PPIs were resampled into the equivalent, uniformly spaced time series (so called PRV) at a sampling rate of 4 Hz using the Berger algorithm (Berger *et al* 1986). PRV was characterized in the spectral domain using power spectral density (PSD). To provide a better frequency resolution a parametric power spectral estimation was performed through an autoregressive modeling with 1024 points and an order of 16. The power in each of the following frequency bands was computed by determining the area under the PSD curve bounded by the band of interest: Very Low Frequency (VLF; 0.01–0.04 Hz), Low Frequency (LF; 0.04–0.15 Hz) and High Frequency (HF; 0.15–0.4 Hz). Normalized LF (nLF) and normalized HF (nHF) powers were determined by dividing LF and HF powers by the total spectral power of PRV between 0.04 and 0.4 Hz, respectively. The ratio of low-to-high frequency power (LF/HF ratio) was also computed.

2.5.3. Detrended fluctuation analysis (DFA). To quantify the short and long-range fluctuation of heart rate, we applied DFA to the PPIs time series. DFA detects the internal correlation of signal expressed by scaling properties. To calculate DFA, we followed a four-step procedure (Peng *et al* 1995):

Step 1: An integrated version of the original PPIs time series was calculated as

$$y(k) = \sum_{i=1}^{k} [\mathrm{PPI(i)} - \mathrm{PPI_{avg}}] \tag{1}$$

where PPI(i) was the *i*th PPIs, $\mathrm{PPI_{avg}}$ was the mean of PPIs and $k = 1,..., N$. N was the total number of pulses.

Step 2: The time series $y(k)$ was divided into equally spaced $N_n = \mathrm{int}(N/n)$ non-overlapping windows with length n (number of pulses in each window).

Step 3: For each window, the local trend $y_n(k)$ was separately calculated by a quadratic least-squares fit. Then the variance was determined for each window by

$$\sigma_n^2(v) = \frac{1}{n} \sum_{k=1}^{n} [\, y((v-1) * n + k) - y_n(k)]^2 \tag{2}$$

where $v = 1,...,N_n$.

Step 4: Finally, to obtain $F(n)$, the fluctuation function, the root-mean-square of all variances was calculated by

$$F(n) = \sqrt{\frac{1}{N_n}\sum_{v=1}^{N_n}\sigma_n^2(v)} \tag{3}$$

In order to determine how *F(n)* depends on the time scale n, the process was repeated for several time scales n. Typically, *F(n)* increases as a power law when n increases,

$$F(n) \sim n^{\alpha} \tag{4}$$

In a double logarithmic plot, the scaling exponent α shows the slope of a line that fits log *(F(n))* to log *(n)* (figure 2). An $\alpha = 0.5$ corresponds to an uncorrelated time series. $0 < \alpha < 0.5$ is indicative of anti-correlation time series, which means that short and large intervals are more likely to alternate. $0.5 < \alpha < 1$ represents correlation in the time series which means short intervals are more likely to be followed by short intervals and vice versa (Peng *et al* 1995).

In short-range correlations, α differs from 0.5 for small ns but will approach 0.5 for large ns. In long-range correlations α is greater than 0.5 and less than 1 for large ns.

To determine the short and long-range correlation in PPIs sequences, we defined α_S and α_L respectively, as the slopes of log *(F(n))* as a function of log *(n)* for the range $10 < n < 40$ and for the range $70 < n < 200$ (Penzel *et al* 2003).

2.6. Data analysis

The Lilliefors test showed that the extracted parameters were not normally distributed. The Wilcoxon Signed Rank test was therefore performed to evaluate the differences between the the segments with and without apnea/hypopnea events and the Wilcoxon Sum Rank test was used to assess the differenced between the parameters of the two groups with and without SDB. A probability of $p < 0.05$ was considered significant and no multiple-comparison correction method was used.

To distinguish children with and without SDB during the entire sleep, a model was fitted to the data set using the Least Absolute Shrinkage and Selection Operator (LASSO) method. λ was tuned by stratified 10-fold cross validation; significant features were selected based on the chosen λ. The LASSO model predicted the probability of having SDB for each subject. To classify subjects into SDB and non-SDB groups based on the predicted probabilities, instead of using a default threshold of 0.5, we calculated a risk threshold based on the maximum weighted classification score (Skaltsa *et al* 2010).

3. Results

In the following subsections, the estimation of different parameters during apnea/hypopnea events for the individual children with SDB (intra-individual event analyses) and also in groups with and without SDB (inter-groups analysis) have been presented.

3.1. Intra-individual event analysis

For the whole group, totalling 70 856 one minute segments, 32 574 were included in the analysis, with 38 282 excluded due to artifacts. Of a total of 5040 segments labelled as apnea/hypopnea, 3267 were included in the analysis, with 1377 excluded for artifacts and 326 excluded due to multiple sleep labels.

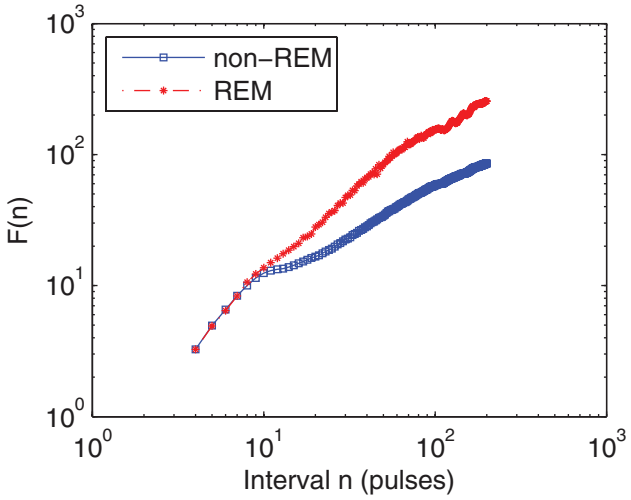


Figure 2. In double logarithmic plot, the fluctuation function of PPIs, *F(n)*, is plotted as a function of n (the number of pulses) for a child without SDB during non-REM (blue squares) and REM sleep (red stars). The slopes of the curves correspond to the fluctuation scaling exponent α.

Based on Wilcoxon Signed Rank test, spectral domain parameters differed significantly (p-value <0.0001) in apnea/hypopnea events.

For the duration of the entire sleep, the nLF increased in apnea/hypopnea events for 96% of the children with SDB. Similarly, the LF/HF ratio increased in apnea/hypopnea events for 96% of the children with SDB, while nHF decreased in 94% of children with SDB during apnea/hypopnea events (figure 3(a)). During non-REM sleep, for 95% of children with SDB, higher nLF, higher LF/HF ratio, and lower nHF were recognized in segments with apnea/hypopnea events compared to segments without (figure 3(b)). During REM sleep, for 73% of the children with SDB, the nLF and LF/HF ratio increased in apnea/hypopnea events. In addition, for 68% of the children with SDB, nHF decreased in the apnea/hypopnea events (figure 3(c)). The VLF increased during apnea/hypopnea events for almost 90% of the children with SDB during non-REM sleep and REM sleep (figure 3).

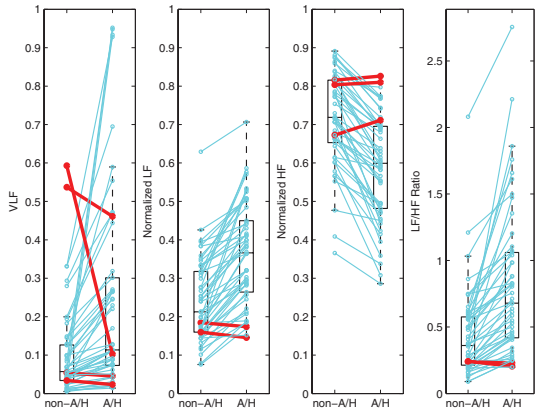
Time domain parameters differed in apnea/hypopnea events but the differences were not statistically significant.

3.2. Inter-groups analysis

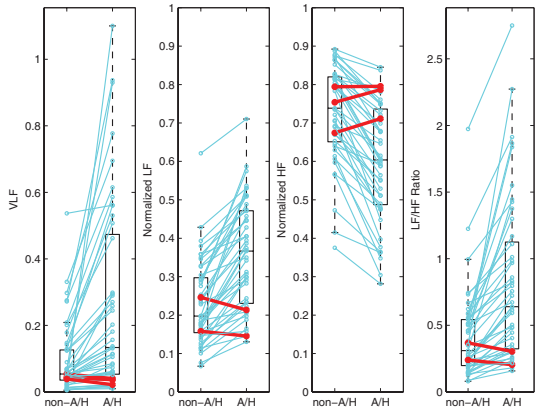
The meanPPIs were significantly shorter in children with SDB during whole sleep, non-REM and REM sleep. SDPP and RMSSD did not vary significantly between the two groups (tables 2–4).

The VLF was higher in children with SDB compared to the group without SDB. The differences were greater during non-REM sleep. Compared to children without SDB, in the SDB group, the nLF and LF/HF ratio were significantly higher during non-REM sleep, but did not differ significantly during REM sleep. The nHF was lower in children with SDB relative to children without. This difference was greater during non-REM sleep compared to REM sleep (figure 4, tables 2–4).

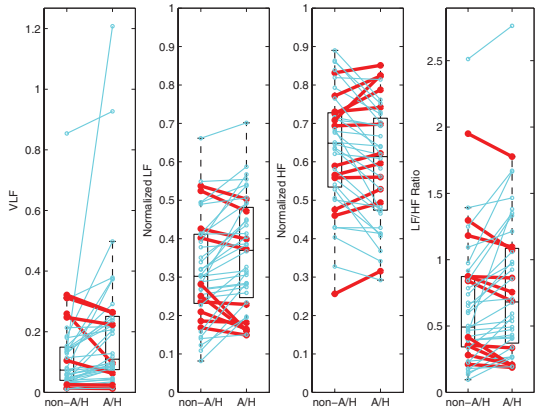
In a double logarithmic representation, the function *F(n)* in the range of $10 < n < 200$, was clearly distinct between the SDB group and the non-SDB group, during non-REM sleep



(a)



(b)



(c)

Figure 3. Comparison of spectral parameters in segments with and without apnea/hypopnea events for children with SDB (AHI > 5) during (a) the entire period of sleep, (b) non-REM sleep and (c) REM sleep. Blue (thin) and red (thick) lines show the mean increase and decrease of parameters respectively.

(figure 5). However, during REM sleep these two functions were not clearly demarcated. Greater α_S and α_L values were observed for children with SDB compared to children without. However, α_L varied much more significantly than α_S and the differences were greater during non-REM sleep (figure 6).

By applying the LASSO method to the data set to classify children with and without SDB during the entire sleep, a model with three significant features (meanPPIs, VLF, and α_L) was selected. Based on a calculated risk threshold of 0.36, an AUC of 78% was obtained for this model, providing accuracy, sensitivity and specificity of 71%, 76% and 68%, respectively.

4. Discussion

The results of this study showed that the cardiac sympathetic indices of PRV were higher at apnea/hypopnea events for more than 95% of children with SDB (AHI $>$ 5). These indices were also higher in children with SDB compared to children without. In addition, heart rate was higher and the short- and long-range fluctuations of heart rate were more strongly correlated in children with SDB. Also, we found that cardiac sympathetic indices were modulated by sleep stages.

Although many studies have been conducted in adults, few studies have investigated the effects of SDB on the autonomic cardiac regulation in children. In particular, few studies have examined autonomic function in children through the analysis of the PPG obtained from a pulse oximeter, and none have used a mobile device for this purpose. In the rest of this section, we compare our findings with the results of studies based on HRV. Gil *et al* showed that during non-stationary conditions there were some small differences between HRV and PRV, mainly in the respiratory band, which were related to the pulse transit time variability (Gil *et al* 2010). However, they concluded that these differences were sufficiently small to suggest the use of PRV as an alternative measurement of HRV.

4.1. Intra-individual event analysis

During non-REM sleep, the segments with apnea/hypopnea events were characterized by higher values of the nLF and LF/HF ratio and lower values of nHF for 95% of children with SDB. This may show that sympathetic modulation was predominant during apnea/hypopnea events while parasympathetic activity was diminished. During REM sleep, we found that for 73% of SDB children, the nLF and LF/HF ratios increased in apnea/hypopnea events and for 68% of children, the nHF power decreased in the apnea/hypopnea events. These results indicate that the predominance of sympathetic activity (increase in the nLF and LF/HF ratios) in apnea/hypopnea events is suppressed by cardiac sympathetic modulation during REM sleep.

The VLF was higher in apnea/hypopnea events for 90% of the children with SDB, during non-REM, consistent with an increase in the slow regulation of cardiac function (Khoo and Blasi 2013). However, longer signal segments ($>$1 min) are required to further validate these results.

Bahavaret *et al* employed HRV spectral analysis to assess autonomic cardiac regulation in children with SDB in overnight sleep studies (Baharav *et al* 1999). They also found that epochs containing obstructive sleep apneas had higher values of the nLF and LF/HF ratios and lower nHF than the epochs without the respiratory events.

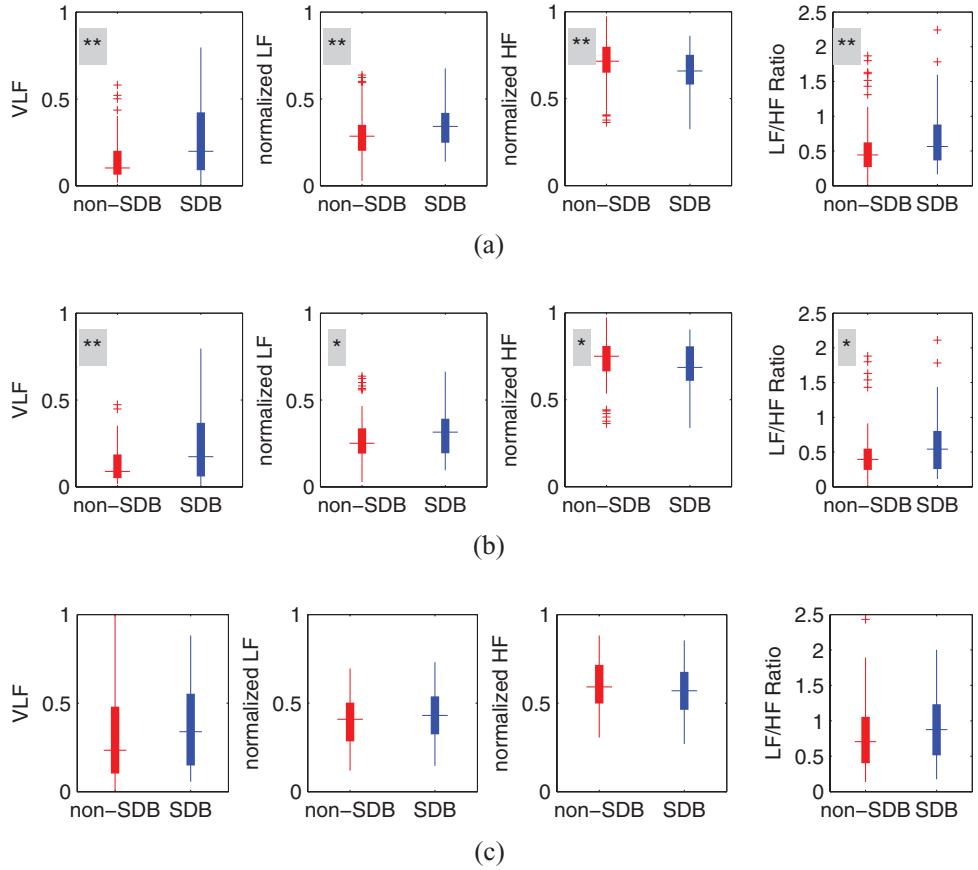


Figure 4. Frequency domain parameters in children with and without SDB during (a) the entire sleep period, (b) non-REM sleep and (c) REM sleep. Significant differences between the SDB and non-SDB groups are marked by one star (*) when p-value <0.05 and by two stars (**) when p-value <0.01. Quartile values are displayed as the bottom, middle and top horizontal line of the boxes. Whiskers are used to represent the most extreme values within 1.5 times the interquartile range from the median. Outliers (data with values beyond the ends of the whiskers) are displayed as (+).

4.2. Inter-groups analysis

During both REM and non-REM sleep, the PPIs appeared shorter in children with SDB (decreased meanPPIs). Since the meanPPIs did not significantly vary in apnea/hypopnea events, we would argue that heart rate was generally higher in children with SDB compared to those without, which may indicate higher sympathetic modulation in children with SDB. Khandoker *et al* who investigated PPIs during sleep apnea in adults also reported a significant higher heart rate (Khandoker *et al* 2011).

During non-REM sleep, we found that the nLF and LF/HF ratios were significantly higher and nHF was lower in the SDB group, relative to the non-SDB group. The same trend was observed in children with SDB during REM sleep, although these differences were not statistically significant. These findings showed an enhanced sympathetic activity and a diminished parasympathetic activity in children with SDB in response to sleep apnea. However, during REM sleep, this cardiac modulation was also provoked by the sleep state. Furthermore, we

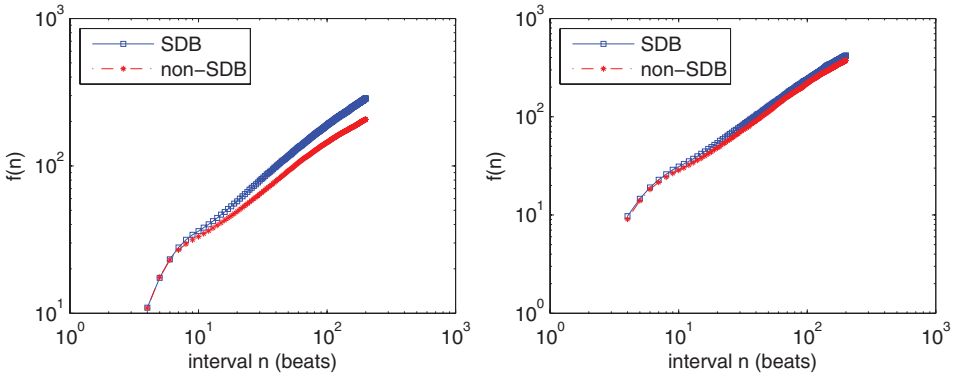


Figure 5. The fluctuation function *F(n)* for (a) non-REM sleep and (b) REM sleep for children with SDB children (blue squares) and non-SDB children (red stars).

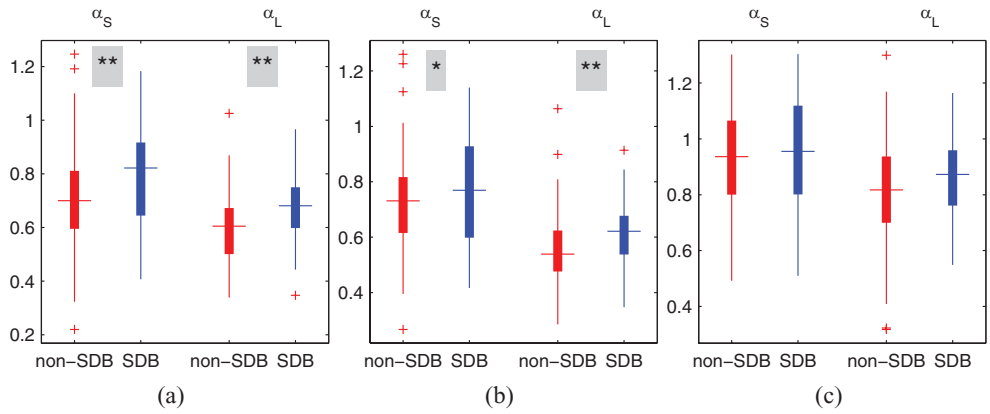


Figure 6. α_S and α_L in children with and without SDB during (a) entire sleep period, (b) non-REM sleep and (c) REM sleep. Significant differences between SDB and non-SDB group are represented by one star (*) when p-value <0.05 and by two stars (**) when p-value <0.01.

discovered that the decrease in the nHF in children with SDB was more significant than the increase in the nLF. This may indicate that children with SDB exhibit a stronger decrease of parasympathetic activity rather than an increase of sympathetic activity, as confirmed by Chouchou *et al* (2014).

Baharavet *et al* also showed that the nLF and LF/HF ratios were higher for children with SDB during non-REM and REM sleep (Baharav *et al* 1999). They reported statistically significant differences in nHF and LF/HF ratios during non-REM sleep between two groups, in agreement with our findings.

Our findings from DFA analysis suggest that the short- and long-range fluctuation of heart rate is more strongly correlated in children with SDB compared to children without SDB. We found that in children with SDB, both α_S and α_L were larger, relative to the children without SDB, during both non-REM and REM sleep stages. Since the short-range correlation is associated with the effects of breathing on heart rate, this large α_S value may indicate

Table 2. Descriptive results (median) of estimated parameters for children with and without SDB during the entire sleep period.

	Non-SDB	SDB	Mean differences	95% CI (Low, High)	p-value
meanPPIs	0.800	0.710	0.070	(0.012, 0.124)	0.005
SDPP	0.050	0.054	0.007	(−0.004, 0.017)	0.100
RMSSD	0.052	0.052	0.004	(−0.008, 0.014)	0.29
VLF	0.100	0.190	0.083	(0.024, 0.145)	0.0001
nLF	0.280	0.340	0.050	(0.005, 0.098)	0.001
nHF	0.710	0.650	0.050	(0.004, 0.098)	0.001
Ratio	0.443	0.560	0.130	(0.022, 0.258)	0.010
α_S	0.700	0.820	0.090	(0.015, 0.164)	0.010
α_L	0.600	0.680	0.078	(0.032, 0.122)	0.0005

Table 3. Descriptive results (median) of estimated parameters for children with and without SDB during non-REM sleep.

	Non-SDB	SDB	Mean differences	95% CI (Low, High)	p-value
meanPPIs	0.819	0.715	0.072	(0.011, 0.126)	0.005
SDPP	0.046	0.050	0.007	(−0.003, 0.017)	0.10
RMSSD	0.049	0.054	0.004	(−0.007, 0.015)	0.23
VLF	0.089	0.174	0.067	(0.012, 0.120)	0.005
nLF	0.251	0.314	0.041	(0.000, 0.091)	0.050
nHF	0.749	0.685	0.041	(0.000, 0.091)	0.050
Ratio	0.394	0.542	0.100	(0.000, 0.220)	0.040
α_S	0.688	0.777	0.077	(−0.007, 0.153)	0.030
α_L	0.539	0.621	0.065	(0.022, 0.108)	0.005

Table 4. Descriptive results (median) of estimated parameters for children with and without SDB during REM sleep.

	Non-SDB	SDB	Mean differences	95% CI (Low, High)	p-value
meanPPIs	0.761	0.697	0.070	(0.017, 0.120)	0.005
SDPP	0.049	0.059	0.004	(−0.005, 0.015)	0.21
RMSSD	0.047	0.044	0.002	(−0.008, 0.012)	0.35
VLF	0.233	0.338	0.048	(−0.044, 0.144)	0.14
nLF	0.408	0.430	0.026	(−0.035, 0.087)	0.2
nHF	0.591	0.569	0.026	(−0.035, 0.087)	0.2
Ratio	0.704	0.874	0.096	(−0.086, 0.301)	0.15
α_S	0.884	0.96	0.044	(−0.053, 0.134)	0.18
α_L	0.817	0.873	0.032	(−0.043, 0.105)	0.18

that the control of heart rate in the range of respiratory related time scales ($10 < n < 40$) is much tighter in children with SDB. Furthermore, as mentioned by Khoo and Blasi (2013), in subjects with SDB respiratory modulation is not limited to the high frequency band (0.15–0.4 Hz). In SDB, respiratory modulation of heart rate takes the form of a large cyclical variation that correlates with episodic apnea or hypopnea and mostly elevates the components of VLF band.

These results, showing greater values of α_L in children with SDB, are consistent with an elevated VLF band.

Penzel *et al* investigated the short and long range correlations of heart rate intervals measured by DFA in adults during different sleep stages (Penzel *et al* 2003). They found $\alpha_S = 1.00$ and $\alpha_L = 0.67$ for adults without SDB (age $= 33.0 \pm 6.4$ years) during the whole sleep. These values are larger than our values calculated for children without SDB (age $= 9.1 \pm 4.2$ years). This suggests that the fluctuation in the RRIs of adults without SDB is more strongly correlated than the fluctuation in PPIs of children without SDB. We analysed the different features of PRV in different sleep stages. We found that in non-REM sleep, the features of PRV varied significantly in apnea/hypopnea events. However, during REM sleep, the same features extracted from segments with apnea/hypopnea events were not distinguishable from segments without apnea/hypopnea events. Nevertheless, the results obtained from the PRV analysis applied to the whole sleep recording, showed that even without considering the stage of sleep, PRV features were significantly different in segments with apnea/hypopnea events. This means that even when the sleep stage information is not available, it is possible to distinguish apnea/hypopnea events through PRV.

To classify children with and without SDB based on only the PRV features across the entire sleep, we achieved an accuracy of 71% using a fitted model with the three selected features (meanPPIs, VLF, and α_L). This is comparable to the results of a study by Penzel *et al* (2003) which showed an accuracy of 72.9% classifying adults based on their apnea severity using eight spectral and DFA features of HRV.

In intra-individual event and inter-group analyses we characterized PRV using 1- and 5 min sliding windows respectively, to answer two different questions. In the intra-individual event analysis we compared the extracted temporal and spectral parameters between the segments with and without apnea/hypopnea events. We considered 1 min segments to ensure that the segments are small enough to contain only the apnea/hypopnea event(s) and/or the arousal(s) accompanying them. In the inter-individual analysis, to assess the cardiac modulation in SDB, we divided the children into two groups; those with and without SDB. According to a study by Penzel *et al* (2003), the DFA parameters extracted from segments with a duration of 5 min or more are more distinguishable between children with and without SDB in different sleep stages (figure 2). So, we estimated PPIs and extracted parameters for each group using a 5 min sliding window.

4.3. Limitations and future work

Several limitations of this study should be considered. Autonomic regulation of the cardiorespiratory system has multivariate dynamics based on the relationship of heart rate, respiratory rate, and blood pressure which are not completely captured in univariate analysis of PRV or HRV, submitting this study to the same limitations as the other studies in the literature.

We found that apnea/hypopnea events induced cardiac modulation; however, we did not investigate whether this modulation was influenced by arousal, hypoxia or the duration of apnea/hypopnea events.

In this study, we considered the AHI $>= 5$ as the criteria for SDB. However, there is no discrete definition of SDB based on AHI alone, but rather a continuum from normal to abnormal. We recognize that some studies consider an AHI $>= 2$ as mild SDB. Therefore, we will further investigate the characterization of PRV for monitoring children with SDB based on different AHI thresholds (AHI $>= 1$, AHI $>= 2$).

In this study, to characterize PRV in intra-individual event and inter-group analyses, we chose two sliding windows with different lengths, which may be considered as a study limitation.

4.4. Clinical relevance

The findings of this study confirm that SDB affects the regulation of cardiac function, suggesting that it would be possible to use the effects of SDB on cardiac modulation to detect apnea/hypopnoea events in children. Furthermore, we have previously shown that the characterization of overnight SpO_2 pattern measured by the Phone Oximeter^{TM} successfully identifies children with significant SDB (Garde *et al* 2013). Hence, combining the characterization of SpO_2 and PRV, both recorded by Phone Oximeter^{TM}, holds promise as a low-cost approach to automatically assess SDB at home (Garde *et al* 2014). This can greatly increase the accessibility to sleep apnea screening and improve the quality of life for the many children currently affected by SDB related disorders.

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