



Original Article

ECG-derived cardiopulmonary analysis of pediatric sleep-disordered breathing

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ABSTRACT

Background: The diagnosis of sleep-disordered breathing (SDB) and evaluation of sleep quality in the pediatric population is dependent on resource intensive attended polysomnography. An ECG-derived cardiopulmonary coupling sleep spectrogram (CPC) analysis previously described in adults can provide information about the severity of SDB and coupled interactions of sleep modulated autonomic drive and respiration. We hypothesized that CPC algorithm-derived metrics will correlate with nasal pressure-based apnea-hypopnea scoring in pediatric population.

Methods: A total of 63 subjects (mean 6.2 years; range 2–12 years) were analyzed by both CPC and conventional nasal flow and desaturation scoring obtained during cardiorespiratory recordings. The characteristics of CPC indices and correlation with conventional SDB scoring were computed.

Results: High-frequency coupling (HFC), the CPC marker of stable sleep state, is reduced in proportion to SDB. The HFC durations are negatively correlated with the nasal flow-derived respiratory disturbance index (RDI), a CPC-derived RDI (CPC-RDI), and the 3% oxygen desaturation index (correlation coefficient -0.60 , -0.78 and -0.54 , respectively). CPC-RDI has a strong positive correlation with the conventional nasal-flow RDI (correlation coefficient 0.70). In this group with a mean nasal-flow RDI $36.1/h$, the percentage of correct CPC diagnosis was 85.7% in total, 40% in the non-severe group (10 subjects, RDI $<20/h$) and 94.3% in the severe group (53 subjects, RDI $>20/h$).

Conclusions: ECG-derived sleep spectrogram metrics are correlated with nasal flow-derived respiratory abnormality in pediatric SDB. In suitable clinical contexts, this method may have screening utility and possibly allow tracking of treatment effects, specifically in the children with severe SDB.

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1. Introduction

Pediatric sleep-disordered breathing (SDB) has been associated with attention and behavioral disorders, learning difficulty, and executive dysfunction. It is reported that 1–3% of children have clinically significant SDB, and there is a 3–12% habitual snoring prevalence in the general pediatric population [1–3]. The diagnosis of pediatric SDB typically depends on attended polysomnography (PSG), making it difficult to rapidly expand services both in developed and developing countries. Even after diagnosis, objectively tracking effects of treatment face similar challenges. Simplified, cheaper and less resource-intensive methods for diagnosis and tracking of pediatric SDB could be clinically useful.

ECG-derived cardiopulmonary coupling (CPC) analysis is a technique developed in adults that shows usefulness to evaluate sleep

quality and phenotype SDB [4,5]. Autonomic nervous system dynamics as measured by heart rate variability and respiration, have characteristic patterns that vary according to sleep depth and type [6,7]. Low frequency periodic cycling of heart rate [8–12] is a typical feature of SDB, sometimes called “cyclic variation in heart rate.” A number of methods that primarily use R–R (inter-beat) interval information to detect SDB from the surface ECG have been proposed [13–20]. One limitation of this approach is that individuals with very low heart rate variability may not show clear R–R variability. Independent of R–R variability, a surrogate respiration signal referred to as ECG-derived respiration (EDR) can be extracted from the ECG [21,22]. The EDR technique is based on the observation that the positions of the ECG electrodes on the chest surface move relative to the heart, and transthoracic impedance varies as the lungs fill and empty. In essence, the R-wave amplitude varies as tidal volume changes. A detailed description of this technique, as well the source code for the algorithm, is available online (<http://www.physionet.org/physiotools/edr/>).

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The CPC technique combines R–R and EDR information to generate “coupling” metrics – high, low and very low frequency coupling. NREM sleep shows predominantly a bimodal characteristic, minimally correlated with conventional NREM sleep stages but reasonably well correlated with visually determined cyclic alternating pattern (CAP)/non-CAP in adults [4].

Healthy subjects show a predominance of high-frequency coupling, while those with untreated SDB show a predominance of low frequency coupling. We hypothesized that CPC algorithm-derived metrics will correlate with nasal pressure-based apnea–hypopnea scoring.

The purpose of the present study is, therefore, (1) to evaluate the spectrographic characteristics of cardiopulmonary coupling in pediatric SDB and (2) to assess correlations of a CPC-derived respiratory disturbance index (CPC-RDI) and conventional respiratory flow recording in pediatrics.

2. Methods

2.1. Database

Clinically-indicated (ordered for suspected sleep apnea) pediatric sleep studies were used. From 246 attended sleep cardiorespiratory recordings collected in 2007 by the Sleep Disorders Center, Meitan General Hospital, Beijing, China, 63 were selected. All subjects were outpatients with a primary complaint of daytime sleepiness or behavioral problems, snoring or mouth-open breathing during sleep. The subjects analyzed here were selected to satisfy all of the following criteria: 2–12 years old, at least 6 h of artifact-free respiration recording, at least 80% of the ECG data of quality to perform CPC analysis, a completed pediatric life quality questionnaire OSA-18 [23]. Most subjects (about 60%) were excluded because of uncompleted questionnaire and bad airflow signal quality, as the children tended to remove the nasal pressure cannula during the full-night examination.

2.2. Cardiorespiratory polysomnography

A single night recording was performed using the Hypno PTT system (Tyco Healthcare, USA), which includes nasal pressure recording (by nasal cannula), oronasal thermistor, ECG, finger pulse

oximetry, pulse transit time, and body position. The nasal cannula used was an oxygen absorbing tube (size 12, manufactured by Yue Liang Ltd., Suzhou, Jiangsu province, China). Another lead of ECG for cardiopulmonary coupling analysis was simultaneously recorded by a Holter device (DynaDx Corporation, USA). The Pediatric Life Quality questionnaire OSA-18 [23] was completed by the subject’s caregiver before he/she began the sleep study (Table 1). The sleep period was estimated from behavioral measures of sleep.

2.3. Respiratory event scoring

Apneas and hypopneas were scored using a nasal pressure cannula and a thermistor. Respiratory events were required to be at least two respiratory cycles in duration. An apnea was defined as an absence of airflow in the nasal cannula and a simultaneous reduction in the oral thermistor signal to <10% of baseline (when nasal flow was lost, the thermistor signal was used). An hypopnea was defined as any evident (typically >30%) reduction in amplitude of the nasal pressure signal, or flow limited breaths, abruptly terminating with a return to a rebounded or sinusoidal flow profile or a large recovery breath. Hypopneas were scored with and without desaturation (Fig. 1). The apnea–hypopnea index regardless of desaturation per hour of sleep was called the respiratory disturbance index (RDI). A 3% oxygen desaturation index was computed by the Hypno PTT software. To diagnose a subject with SDB, a nasal flow RDI \geq 5/h of estimated sleep is required.

2.4. Pulse transit time arousal index

The Hypno PTT software computed an arousal index based on the pulse transit time (PTT). PTT is the time taken for the arterial pressure wave to travel from the aortic valve to the periphery [24]. It is measured by calculating time from the ECG R-wave to the pulse wave recorded at the finger via the plethysmographic signal obtained by the oximeter. The PTT is affected by many factors including blood pressure. When an arousal occurs during sleep, sympathetic tone is transiently elevated, the blood pressure arises, and PTT is shortened. The PTT-arousal index is generated by computing the minima of the PTT per hour (set by the Hypno PTT software).

2.5. Cardiopulmonary coupling analysis

Details of the method have been published [4]. To estimate the degree of cardiopulmonary coupling between heart rate and respiration, we employed Fourier-based techniques to analyze the R–R interval series and its associated EDR signal. Two key factors need to be considered in evaluating the strength of the coupling between these two signals. (1) If, at a given frequency, both signals have relatively large oscillation amplitudes, then it is likely that these two signals are coupled with each other. This effect can be measured by computing the cross-spectral power, i.e., the product of the powers of the two individual signals at a given frequency. (2) If the oscillations of these two signals are synchronized with each other (i.e., they maintain a constant phase relationship), this effect can be measured by computing the coherence of these signals. We used the product of the coherence and the cross-spectral power to weigh these two effects in order to quantify the degree of the cardiopulmonary coupling.

Using a single-lead ECG, an automated beat detection algorithm [25,26] was used to detect beats and classify them as either normal or ectopic, based on their morphology and timing. In addition, amplitude variations in the QRS complex due to shifts in the cardiac electrical axis relative to the electrodes during respiration and changes in thoracic impedance were determined. These fluctuations in the mean cardiac electrical axis correlate with phasic changes in the respiratory cycle. From these amplitude variations, a surrogate

Table 1

OSA-18 questionnaire. The questionnaire includes 18 items grouped in five domains, where items are scored in an ordinal 7-point classification (1 – none of the time, 2 – hardly any of the time, 3 – a little of the time, 4 – some of the time, 5 – a good bit of the time, 6 – most of the time, 7 – all of the time). The total OSA-18 score may be between 18 and 126. Parents rate symptom frequency during the previous 4 weeks.

1. Sleep disturbance	Loud snoring Breath holding spells or pauses in breathing at night Choking or gasping sounds while asleep Restless sleep or frequent awakenings from sleep
2. Physical symptoms	Mouth breathing because of nasal obstruction Frequent colds or upper respiratory infections Nasal discharge or runny nose Difficulty swallowing foods
3. Emotional distress	Mood swings or temper tantrums Aggressive or hyperactive behavior Discipline problems
4. Daytime function	Excessive daytime drowsiness or sleepiness Poor attention span or concentration Difficulty getting out of bed in the morning
5. Caregiver concerns	Worrying about child’s general health because of above problems Concern that child is not getting enough air at night Inability to perform daily activities because of above problems Frustration because of above problems

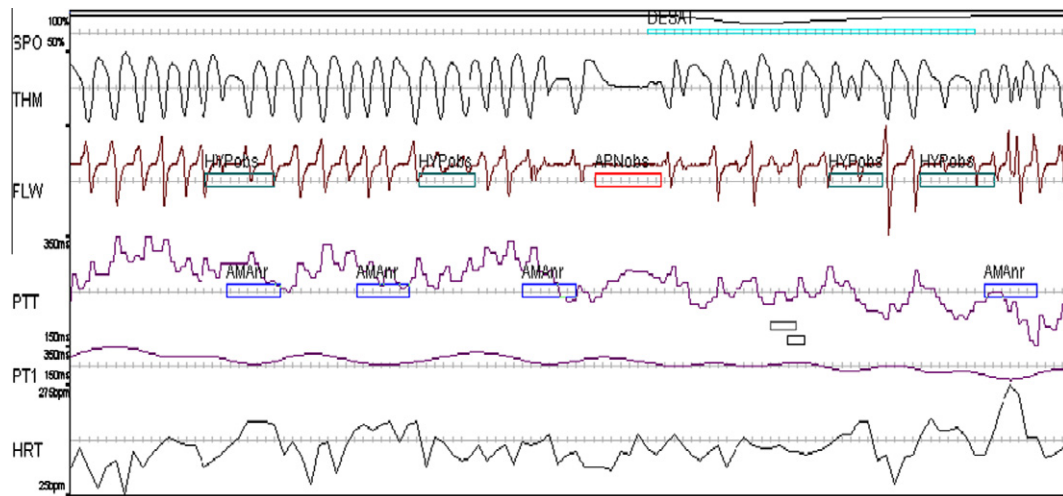


Fig. 1. Cardiorespiratory recording. A two-min Hypno-PTT snapshot showing respiratory events, PTT arousals, and a desaturation event. The x-axis is the time axis during recording. THM: thoracic movement, FLW: nasal pressure-based flow, PTT: pulse transit time, PT1: PTT signal filtered by low pass filter, HRT: heart rate.

EDR was obtained as previously described [21,22]. A time series of normal-to-normal sinus (N–N) intervals and the time series of the EDR associated with these N–N intervals was then extracted from the R–R interval time series. The resulting N–N interval series and its associated EDR signal were then resampled at 2 Hz, using cubic spline interpolation. The cross-spectral power and coherence of these two signals were calculated over a 1024-sample (8.5-min) window using the fast Fourier transform. For each 1024 window, the product of the coherence and cross-spectral power was used to calculate the ratio of the sum of the two maximal coherent cross-power peaks in the low-frequency band (0.01–0.1 Hz) to the sum of the two maximal peaks in the high-frequency band (0.1–0.4 Hz). The cardiopulmonary coupling spectrum is generated based on this ratio. A preponderance of power in the low-frequency band is associated with periodic respiration during SDB [10], while excess power in the high-frequency band is associated with physiologic respiratory sinus arrhythmia due to increased vagal tone that appears in deep sleep [27]. Wake and unfragmented REM sleep shows coupling in the very low frequency (0.001–0.01 Hz) range. Fragmented REM sleep shows low frequency (0.01–0.1 Hz) coupling [4].

A CPC analysis derived RDI (CPC-RDI) was generated, using the duration and mean frequency of the low frequency coupling (LFC) periods, and expressed as number/h by multiplying two quantities: (1) the average portion of time (minutes per hour) that a subject's sleep was spent in the low frequency coupling state and (2) the average frequency (cycles per min) of low frequency coupling.

2.6. Statistical methods

Summary statistics were tabulated as means and standard deviation. Spearman's correlation coefficients were computed for nasal pressure, PTT, OSA-18 score and CPC derived metrics. A receiver operating characteristic (ROC) curve was generated to show the relationship between CPC-RDI and the nasal-flow RDI. Bland and Altman graph was generated to compare the difference between nasal-flow RDI and CPC-RDI.

3. Results

3.1. Subject clinical characteristics

The 63 subjects included 22 females and 41 males. The mean age was 6.22 years old (SD 2.50; range 2–12 years). The mean OSA-18 score was 50.2 (SD 15.7; range 13–92).

3.2. CPC and cardiorespiratory measures

The conventional respiration scoring summary was a mean RDI of 36.11 ± 22.3 /h of sleep. The 3% oxygen desaturation index was 4.7 ± 8.9 /h of sleep, the lowest saturation was $90.4 \pm 7.1\%$, and the mean saturation for the whole night was $98.4 \pm 1.2\%$. The CPC generated RDI was 31.2 ± 18.25 /h. The percentage of sleep detected as high-frequency coupling (HFC), low frequency coupling (LFC), and very low frequency coupling (VLFC) was $52.6 \pm 17.6\%$, $25.3 \pm 14.6\%$, and $20.8 \pm 7.1\%$, respectively, with 1% classified as indeterminate. The PTT-arousal index was $59.1 \pm 18.7\%$.

Examples of ECG-derived sleep spectrograms across a range of severities of sleep apnea are shown in Figs. 2–4.

3.3. Correlation and agreement between CPC and cardiorespiratory metrics

High-frequency coupling (a marker of stable sleep) duration of the 63 subjects was negatively correlated with the nasal-flow RDI and the desaturation index as shown in Table 2. The CPC-RDI was positively correlated with the conventional nasal-flow RDI (correlation coefficient 0.70). Conventional nasal-flow RDI, desaturation index, and the CPC metrics did not show statistically significant correlations with the Hypno-PTT auto-detected PTT-arousal index or the OSA-18 questionnaire score. Since only one subject had normal respiration in the current database, the subjects were separated into two groups to assess agreement between methods, a nasal flow RDI >20 /h (severe) or nasal flow RDI ≤ 20 /h (non-severe). Based on a calculation of the ROC (Fig. A1), the CPC-RDI boundary to separate severity and non-severity was found to be 15/h. The percentage of correct CPC diagnosis was 85.7% in total, 40% in the non-severe group (10 subjects) and 94.3% in the severe group (53 subjects). As expected, the Bland and Altman plot show relatively big inter-method differences (Fig. 5). The reason is explained in Section 4.

4. Discussion

The key findings of this study are that (1) CPC analysis may provide useful surrogates of conventional respiratory polysomnographic indices in severe pediatric patients (specifically, reduced high and increased low frequency coupling were the spectrographic hallmarks of pediatric sleep apnea), (2) different metrics may be sampling complementary elements of sleep physiology,

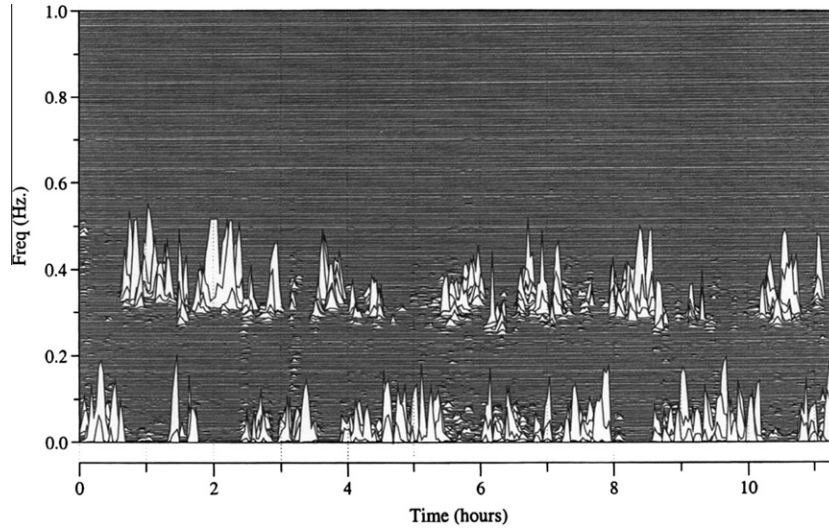


Fig. 2. Minimal to mild sleep apnea. CPC analysis in a 3-year old boy, with nasal-flow RDI of 8.2/h of sleep. Note that nearly 70% of the recording is spent in high-frequency coupling (upper “mountain range”), occurring in discrete periods across the night. There are spontaneous switches between high and low frequency coupling periods, a pattern identical to that seen in healthy adults [4].

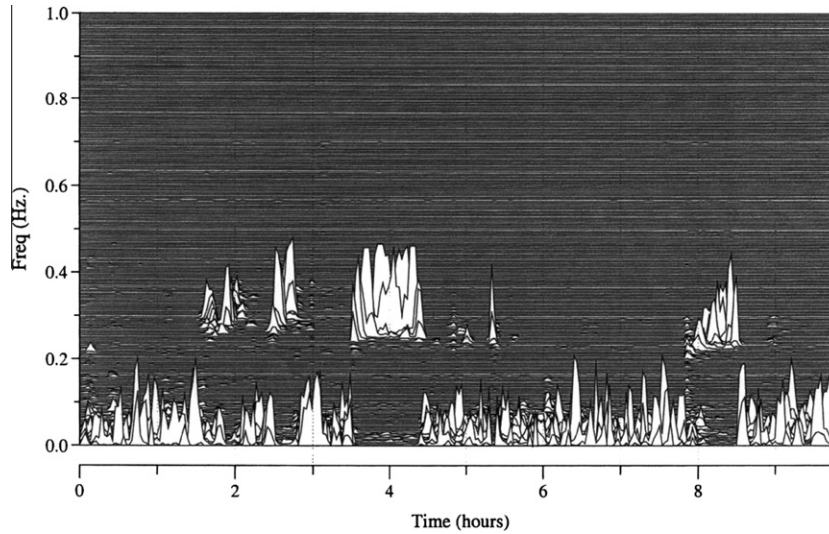


Fig. 3. Severe sleep apnea. CPC analysis in a 2-year old male, with a nasal-flow RDI of 57.1/h of sleep. Note the visually apparent reduction of high-frequency coupling (HFC) compared to the example shown in Fig. 2.

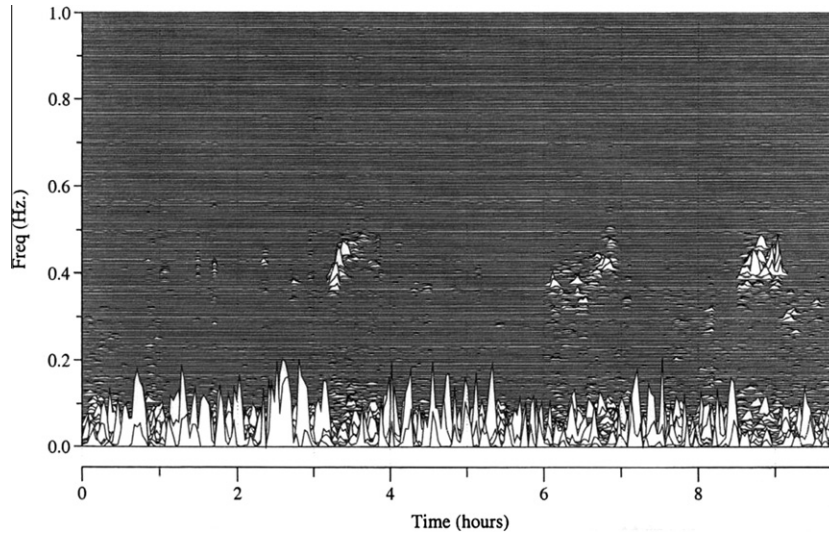


Fig. 4. Very severe sleep apnea. CPC analysis in a 7-year old male, with nasal-flow RDI 126.1/h. Note minimal amounts of high-frequency coupling (HFC).

Table 2

Correlations between ECG-derived CPC measures and conventional cardiorespiratory indices. All indices were calculated in unit times per hour. The asterisk indicates that the correlation is significant at the 0.01 level. The CPC-RDI shows strong positive correlations with the manually scored nasal flow-RDI, and desaturation index, and a strong negative correlation with HFC, marker of stable sleep. There were no correlations found between the PTT-arousal index and other indexes, or with the OSA-18 questionnaire score.

	LFC	HFC	CPC-RDI	Nasal-flow RDI	ODI	PTT-arousal index	OSA-18
LFC	1	−0.90*	0.92*	0.61*	0.58*	0.15	−0.13
HFC	−0.91*	1	−0.89*	−0.60*	−0.54*	−0.14	0.05
CPC-RDI	0.92*	−0.89*	1	0.70*	0.70*	0.19	−0.03
Nasal-flow RDI	0.61*	−0.60*	0.70*	1	0.67*	0.05	0.19
ODI	0.58*	−0.54*	0.70*	0.67*	1	0.09	0.11
PTT-arousal index	0.15	−0.14	0.19	0.05	0.09	1	0.00
OSA-18	−0.13	0.05	−0.03	0.19	0.11	0.00	1

CPC: cardiopulmonary coupling, RDI: respiratory disturbance index, LFC: low-frequency coupling, HFC: high-frequency coupling, ODI: 3% oxygen desaturation index, PTT: pulse transit time, OSA-18: obstructive sleep apnea questionnaire.

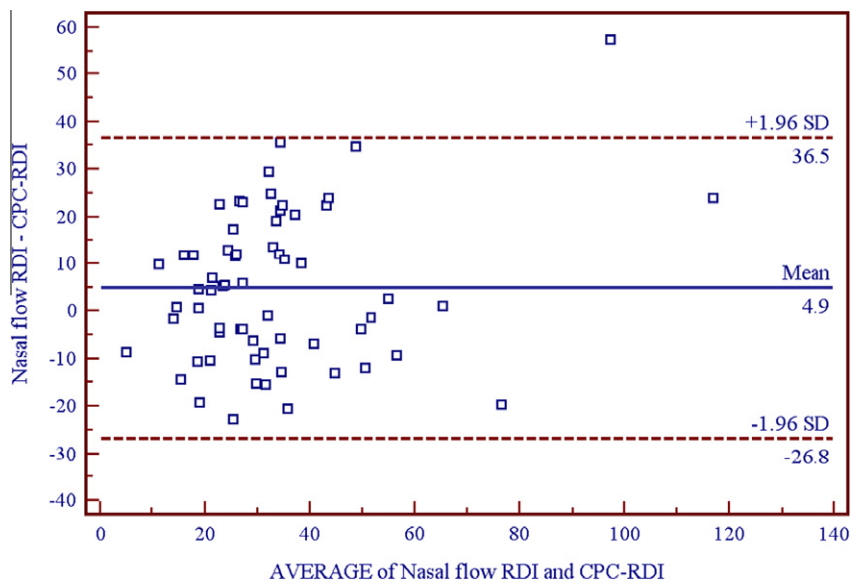


Fig. 5. Bland and Altman plot. It is expected that CPC-RDI and nasal-flow RDI will show inter-method differences. For example, to score a flow reduction as hypopnea (part of nasal-flow RDI), typically 30% or greater flow reduction is required. However, a flow reduction of less than 30% may also cause robust heart rate acceleration and deceleration, which will influence the CPC-RDI directly.

(3) no metric correlated with clinical symptoms as assessed by the questionnaire OSA-18.

Sleep fragmenting stimuli induce an increase in low frequency oscillations of multiple physiological traces during sleep [28,29]. These oscillations are seen in the form of cyclic variation in heart rate, tidal volume fluctuations, blood pressure surges, and phasic EEG complexes called cyclic alternating pattern [28–30]. Such dominance of low frequency oscillations is seen most readily in SDB syndromes in adults and children [10], but also in heart failure [12], insomnia [31], in response to auditory stimuli during sleep, and fibromyalgia [32].

In SDB patients, respiratory abnormality drives the majority of these low frequency oscillations, resulting in significant correlations (correlation coefficient 0.7) of nasal flow based RDI and the CPC-derived RDI. Thus, in the suitable clinical context, such as when there is a high clinical probability of sleep apnea (e.g., snoring + poor school performance) the CPC-RDI may be a useful surrogate of a conventional RDI. It might be helpful for screening subjects at risk for severe sleep apnea since it has a high sensitivity for this subgroup and its implementation is very simple compared to conventional PSG-based measures. While the utility of the CPC-RDI alone in the final diagnosis of SDB is likely limited, adding oximetry could improve detection characteristics. Once the diagnosis is established, the ease of obtaining the ECG increases

attractiveness as a method to track effects of treatment, such as tonsillectomy or weight loss. Figs. 2–4 show the graphical representation of the ECG-spectrogram, which can also generate useful metrics such as the proportion of the sleep period in high-frequency coupling – this may be expected to increase as disease is overcome and healthy sleep patterns dominate.

It is expected that CPC-RDI and nasal-flow RDI will show inter-method differences. Since the CPC algorithm is not based on respiratory flow change but on the respiration related oscillation in heart rate, it is expected that differences will occur. For example, to score a flow reduction as hypopnea (part of nasal-flow RDI), typically 30% or greater flow reduction is required. But a flow reduction of less than 30% may also cause robust heart rate acceleration and deceleration, which will influence the CPC-RDI directly. CPC cannot directly replace flow measurements, but may have a role in screening and tracking, as ECG recordings are convenient.

Different types of measurements may reflect complementary aspects of sleep physiology and pathology. For example, in our data set with abnormal respiration, the PTT-arousal index did not correlate with CPC or nasal pressure-based RDI estimates. Nevertheless, such measurements may have utility in tracking therapy and clinical status over time. The lack of correlation between any of the polysomnographic measures with questionnaire-based symptoms

may reflect the limitations of questionnaires, multiple etiologies of similar clinical symptoms, complex host–environment interactions, accuracy of scoring methods, and difficulty in determining the most important disease effects.

There are important limitations of the ECG-based CPC approach. Sleep onset is not accurately detected; adding actigraphy could help overcome this limitation. Periods of high-frequency coupling may still show obstructive hypoventilation, a common disease pattern in children. Any fragmenting stimulus will decrease high-frequency coupling and increase the computed CPC-RDI; thus, the method is not disease specific. The algorithm will not work in the presence of cardiac arrhythmias such as very frequent ventricular ectopy or bigeminy or continuous atrial fibrillation; however, these are not common problems in children. The current database is a group with severe sleep apnea, so the results cannot be readily extrapolated to those with milder disease.

In summary, we describe potential utility of an ECG-derived method to assess sleep physiology in severe pediatric SDB. The technique may have potential advantages in screening for severe SDB, tracking treatment effects, and could enhance diagnostic efforts when used along with other commonly acquired signals during diagnostic polysomnography.

Conflict of Interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi: [10.1016/j.sleep.2010.09.011](https://doi.org/10.1016/j.sleep.2010.09.011).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:[10.1016/j.sleep.2010.09.011](https://doi.org/10.1016/j.sleep.2010.09.011).

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