# Characterization of Cardiopulmonary Coupling in Pediatric Patients with Obstructive Sleep Apnea

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## Abstract

*This study aims to investigate the use of cardiopulmonary coupling (CPC), as biomarker for characterizing obstructive sleep apnea (OSA) severity in children. CPC analysis is based on the time-frequency coherence (TFC) between the respiratory effort signal and heart rate variability. We analyzed 255 children with no, mild, moderate, and severe OSA during wake, rapid eye movement (REM) sleep, and non-REM (NREM) sleep. Results showed that the TFC in the low-frequency (LF) band increased significantly with the severity of OSA in both NREM (p<0.001) and REM sleep (p<0.001). Conversely, the TFC in the HF band, the parameter estimating CPC, is significantly lower for increasing OSA severity categories during NREM (p=0.02) and REM (p=0.03). The findings suggest that TFC could be a useful biomarker for assessing OSA severity in children, and could provide additional information about underlying pathological mechanisms.*

## 1. Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repetitive episodes of upper airway obstruction during sleep. The gold standard for the diagnosis of OSA is overnight polysomnography (PSG), which measures various physiological signals, including electroencephalography, electrocardiography (ECG), respiration, and oxygen saturation (SpO2). However, the diagnosis of OSA is time-consuming, expensive, and requires specialized equipment and trained personnel. Hence, there is a need for alternative tools that are more convenient and readily accessible, aiming to alleviate the complexities associated with PSG.

Cardiopulmonary coupling (CPC) is a physiological phenomenon that reflects the interaction between the cardiac and respiratory regulation. By analyzing heart rate variability (HRV) and respiration signals, both routinely recorded during polysomnography (PSG), CPC can be assessed. The Respiratory Sinus Arrhythmia (RSA) is the main expression of CPC, which is the heart's acceleration and deceleration in response to inspiration and expiration, respectively. RSA enhances pulmonary gas exchange and facilitates cardiac efficiency by synchronizing perfusion and ventilation during the respiratory cycle. Studies suggest that CPC can serve as an effective ambulatory biomarker for sleep quality [1,2], and CPC based on time-frequency coherence (TFC) also shows potential for predicting extubation readiness in intensive care units [3].

Although some studies have explored the potential of CPC analysis for sleep apnea, the research in this area remains limited. Previous studies found decreased CPC in adults with OSA compared to healthy controls, suggesting that it may be a useful tool for the diagnosis and monitoring of this condition. They also found a preponderance of power in the low-frequency (LF) band in adults with OSA, which may be associated with abnormal behaviors during sleep-disordered breathing, such as periodic breathing, while high CPC values in the high-frequency (HF) band are associated with healthy respiratory sinus arrhythmia and deep sleep [1,4]. Other studies have shown that aging may lead to a reduced autonomic modulation during wake, S2, and REM sleep in older adults with OSA, when compared to younger individuals [5].

In this study, we aim to characterize CPC in children with OSA and explore its potential as a diagnostic tool for this condition in pediatric patients. We have the hypothesis that increasing OSA severity is also related with decreased CPC and the observed unbalanced Autonomic

Nervous System (ANS) regulation in adults. Stable sleep as estimated by CPC in the HF band would show reductions in pediatric patients with OSA, compared to patients who recovered from OSA.

## 2. Materials and Methods

### 2.1. Sleep Data

The Childhood Adenotonsillectomy Trial (CHAT) was a prospective randomized trial designed to evaluate the efficacy of various treatments for OSA [6]. All patients underwent a follow-up nocturnal PSG at a clinical laboratory to evaluate the current OSA status, seven months after treatment. Our study included 255 pediatric patients at follow-up, between the ages of 5-10 years. OSA severity was established using the apnea-hypopnea index (AHI) according to established guidelines [6], with severity categories ranging from no OSA (N=63) to mild (N=135), moderate (N=30), and severe OSA (N=27). We collected data from the PSG recordings, including the ECG, thoracic and abdominal respiratory signals, and sleep stage information, identified and labeled in 30-second epochs by trained sleep specialists.

### 2.2. Signal Preprocessing

First, the signal from the abdominal respiratory effort band, $r(t)$, is used to obtain the frequency signal, $F_r(t)$, which is derived using a peak-conditioned spectral averaging method [7]. After, the ECG signal is upsampled at 1000 Hz with cubic spline interpolation and the R-waves are detected by means of a wavelet-based method. In order to explain the cardiac regulation by the ANS, the HRV signal is estimated with the Time-Varying Integral Pulse Frequency Modulation model. Essentially, given a particular series of heatbeats after ectopic correction, the instantaneous HR can be expressed as $d_{HR}(t) = (1 + m(t))/T(t)$. The term $m(t)$ represents the modulating signal, which is assumed to contain the ANS modulation, and the instantaneous mean-HR, is obtained by low-pass filtering $d_{HR}(n)$ at 0.03 Hz. The evenly-sampled versions are obtained by resampling at 4Hz. For the interested reader, methods are extensively described in [3].

Since respiration affects HRV through changes in the respiratory frequency and the respiratory pattern, the analysis of HRV is guided by respiration. Therefore, the HF band is set to be at the respiratory frequency, $F_r(t)$, and time-varying: $\Omega_{HFc}(t) = [F_r(t) - 0.125, F_r(t) + 0.125]$ Hz. This is motivated since the average breathing rate in children is non-stationary, and usually above 24 breaths per minute (0.4Hz), which lies within the limits of the classic HF band, which was established for adults. The LF band is defined using the classic limits: $\Omega_{LF} = [0.04, 0.15]$ Hz.

## 2.3. Time-Frequency Coherence

The influence of respiration on HRV, i.e., CPC, can be captured using spectral coherence [8]:

$$\hat{\gamma}(t, f) = \frac{\left| \hat{S}_{r,m}(t, f) \right|}{\sqrt{\hat{S}_r(t, f)\hat{S}_m(t, f)}}, \tag{1}$$

where $\hat{\gamma}(t, f) \in [0, 1]$. $\hat{S}_r(t, f)$ and $\hat{S}_m(t, f)$ are the time-varying auto-power spectral densities calculated by means of the Cohen's Class Wigner Ville Distribution of respiration and HRV, $r(t)$ and $m(t)$, respectively, and $\hat{S}_{r,m}(t, f)$ is the cross-power spectral density. A time and frequency resolution of 11.25 s and 0.039 Hz is chosen [8], respectively. Figure 1 provides an illustrative example of the time-frequency spectral coherence.

A significant coherence level between HRV and respiration must be established by a threshold, namely $\gamma_{TH}(t, f; \alpha)$. This significant coherence threshold is established based on a surrogate data analysis, with $\alpha = 1\%$ risk that two signals are coupled when real coupling does not exist $\gamma_{TH}(t, f; 0.01) = \gamma_0$. To obtain $\gamma_0$, the spectral coherence, $\hat{\gamma}(t, f)$, of two 5-min length, white gaussian noise signals is calculated. This is repeated iteratively 1000 times, and the 99th percentile of $\hat{\gamma}(t, f)$ can be set as threshold of significant spectral coherence, $\gamma_0 = 0.8860$.
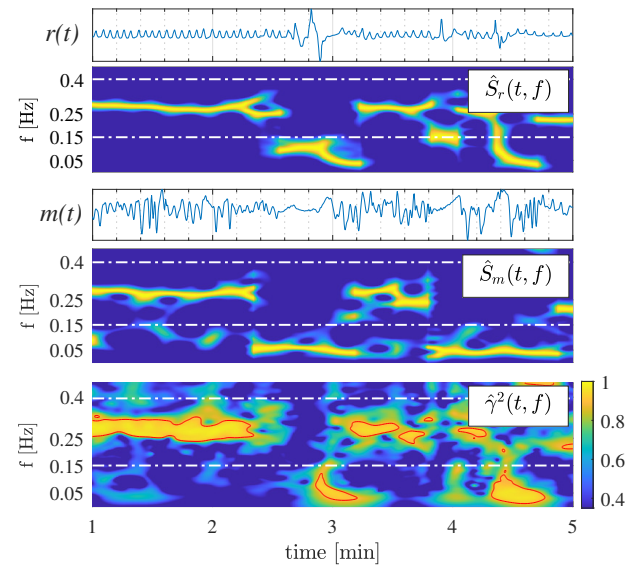


Figure 1: Time-Frequency Coherence. From respiratory signal, $r(t)$, and HRV signal, $m(t)$, TF spectra $S_r(t, f)$ and $S_m(t, f)$ are calculated, respectively. Quadratic spectral coherence $\gamma^2(t, f)$ is finally obtained from the cross-spectra between respiration and HRV. Significant spectral coherence, $\hat{\gamma}(t, f) > \gamma_0$, is outlined in red.

The CPC biomarker, based on the TFC between HRV and respiration in the HFc band [3], denoted as $\mathscr{C}_{\mathrm{HFc}}^{\mathcal{T}}$, is composed considering the average spectral coherence above $\gamma_0$, namely $\mathscr{C}_{\mathrm{HFc}}$, with the percentage of time in significant coherence in the epoch, $\mathscr{T}_{\mathrm{HFc}}$ (Fig. 1):

$$\mathscr{C}_{\mathrm{HFc}}^{\mathcal{T}} = \mathscr{C}_{\mathrm{HFc}} \cdot \mathscr{T}_{\mathrm{HFc}}. \tag{2}$$

For CPC, by definition, $\mathscr{C}_{\mathrm{HFc}}^{\mathcal{T}}$ should be calculated in the HFc band, but spectral coherence can be also calculated in different spectral bands like LF band, with the TFC-LF reading as $\mathscr{C}_{\mathrm{LF}}^{\mathcal{T}}$.

## 2.4. Statistical analysis

The CPC biomarkers are derived using 5-min epochs. We conduct a separate analysis of CPC results during the three sleep stages: wake (W), rapid-eye movement sleep (REM), and non-REM sleep (NREM). For an epoch to be considered in the analysis, it must have at least 90% of its time in the same sleep stage. For each patient, the average CPC in the epochs at the same sleep stage along the overnight recordings is calculated.

The TFC features considered do not fit either normality or homoscedasticity tests, therefore a Kruskal-Wallis (KW) test is conducted to compare differences in CPC biomarkers among the four severity groups (no OSA, mild OSA, moderate OSA, and severe OSA). A p-value $< 0.05$ for the KW test can be considered for statistical significance. Afterwards, a paired signed rank test was employed to compare the differences in TFC values of each patient between sleep stages. A p-value $< 0.01$ is considered for statistical significance, after correction for multiple comparisons.

## 3. Results and Discussion

Fig. 2 exhibits the boxplots of the TFC in the LF and HFc bands, comparing the values of the 4 groups of OSA severity for the three sleep stages. The CPC levels in each sleep stage, as measured by TFC in the HFc band, are significantly lower for increasing OSA severity categories during NREM (KW test, $p = 0.02$), and REM sleep (KW test, $p = 0.03$). On the contrary, the TFC in the LF band is significantly higher for increasing OSA severity categories, both during NREM (KW test, $p < 0.001$), and REM sleep (KW test, $p < 0.001$), which is consistent with results found in adults [1].

Tab. 1 shows the p-values of the signed rank test, comparing TFC values for the three sleep stages in the LF and HFc bands, of the different OSA severity levels. The statistical analysis shows that differences exist in CPC (TFC-HF) in all stages, except for the children with severe OSA, stating the fact that a separate analysis in sleep stages is

necessary for sleep apnea characterization. No significant differences are found in the LF band in severe OSA patients comparing TFC values in REM and NREM, whereas these differences are clear for no and mild OSA patients. Besides, as hypothesized, the CPC is also significantly lower during wake compared to NREM and REM in all OSA categories (Tab. 1b). According to previous research, processes such as sleep apnea and fibromyalgia, which lead to sleep fragmentation, have been shown to reduce the amount of CPC (TFC-HFc) [1]. In addition, higher TFC-LF values have been associated with a higher prevalence of hypertension and stroke in adults [9].

In general, the amount of apnea/hypopnea events are comparable between REM and NREM [10]: approximately 88% of 10-min epochs in REM sleep had less than 5 events per epoch, and 97% of the epochs in NREM sleep had less than 5 apnea/hypopnea events per epoch. The observed increased coupling in the LF band in severe OSA patients could be attributed to the higher prevalence of periodic breathing during REM sleep, as reported in [1], as well as to the pronounced cyclic variations in HRV in response to repeated apnea episodes. However, values of CPC in the HFc band where higher in REM sleep compared to NREM, or at least similar for severe OSA patients, which explains that the significant reduced CPC with increasing severity of OSA may not be due to effects related to apnea events, but rather due to other physiological factors like alterations in the sympathetic activity.

Note that it is necessary the use of a significant coherence threshold. Many existing works studying CPC based on spectral coherence, as biomarker on sleep quality, do not rely on the fact that two white-noise signals will have a baseline level of coherence $\gamma_0$, where zero coherence should be reported by definition. Our results show that this methodology might provide additional phenotypic information to better classify between sleep stages, since wake and REM sleep are sometimes indistinguishable [1].

This study has a limitation in that respiratory signals other than the nasal pressure signal were used. Previous studies have also used alternative respiratory signals [1, 4], such as ECG-derived respiration (EDR). In fact, Varon et al. reported that errors in CPC were significantly greater during apnea events than during normal activity when using EDR signals as surrogate [11]. Owing to chest movements captured by EDR, it may not be related to actual respiration during apnea events, causing an overestimation of CPC. We demonstrated the usefulness of CPC using recordings of respiratory effort bands, but future works should consider using the nasal pressure cannula signal, which would lead to a potential reduction in CPC values in the presence of obstructive respiratory events.
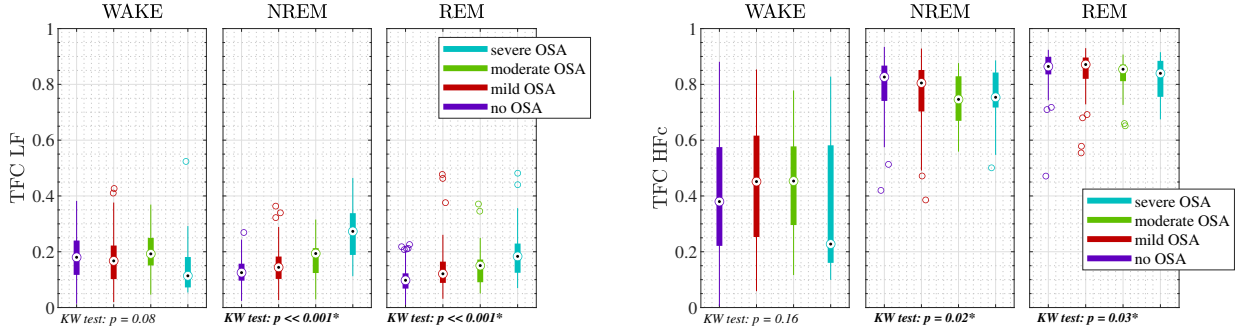
Figure 2: Boxplots of the TFC in the LF band (left), and in the HFc band (right), comparing the values of the 4 groups of OSA severity (no, mild, moderate and severe OSA), for the three sleep stages (Wake, NREM and REM). Statistical significant difference between TFC values of the OSA severity groups is obtained using the Kruskal Wallis (KW) test, for each sleep stage.

Table 1: P-values obtained from the paired signed rank test, comparing the TFC values of each patient between the three sleep stages. The analysis is done in the LF (a), and HFc bands (b), for the different OSA severity levels. Statistical significance is considered for p-values <0.01, to correct for multiple comparisons.

| a) **TFC (LF)** | W-NREM | W-REM | NREM-REM |
|---|---|---|---|
| No OSA | ≪0.01 | ≪0.01 | ≪0.01 |
| Mild OSA | 0.03 | ≪0.01 | ≪0.01 |
| Moderate OSA | 0.54 | 0.09 | 0.03 |
| Severe OSA | *0.004* | 0.05 | 0.02 |

| b) **TFC (HFc)** | W-NREM | W-REM | NREM-REM |
|---|---|---|---|
| No OSA | ≪0.01 | ≪0.01 | ≪0.01 |
| Mild OSA | ≪0.01 | ≪0.01 | ≪0.01 |
| Moderate OSA | ≪0.01 | ≪0.01 | ≪0.01 |
| Severe OSA | ≪0.01 | ≪0.01 | 0.04 |

## 4. Conclusion

Overall, we can conclude that the TFC in the LF band could be a useful biomarker for assessing the severity of OSA, while CPC as measured by TFC in the HF band could provide additional information about the pathological mechanisms underlying OSA. However, further studies with larger sample sizes are needed to confirm these findings and to investigate the use of respiratory signals in conjunction with HRV analysis.

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