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Original Article

HHT based cardiopulmonary coupling analysis for sleep apnea detection

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ABSTRACT

Study objectives: To validate the feasibility of the Hilbert–Huang transform (HHT) based cardiopulmonary coupling (CPC) technique in respiratory events detection and estimation of the severity of apnea/hypopnea.
Methods: The HHT-CPC sleep spectrogram technique was applied to a total of 69 single-lead ECG signals downloaded from the Physionet Sleep Apnea Database. Sleep spectrograms generated by both the original and the improved CPC method were compared on the structure distribution and time–frequency resolution. The performance of respiratory events detection by using the power of low frequency coupling (pLFC) in the new method was estimated by receiver operating characteristic analysis. Furthermore, correlation between HHT-CPC index (temporal Variability of Dominant Frequency, TVDF) and conventional OSAHS scoring was computed.
Results: The HHT-CPC spectrum provides much finer temporal resolution and frequency resolution (8 s and 0.001 Hz) compared with the original CPC (8.5 min and 0.004 Hz). The area under the ROC curve of pLFC was 0.79 in distinguishing respiratory events from normal breathing. Significant differences were found in TVDF among groups with different severities of OSAHS (normal, mild, moderate, and severe, $p < 0.001$). TVDF has a strong negative correlation with the apnea/hypopnea index (AHI, correlation coefficient −0.71).
Conclusions: The HHT-CPC spectrum could exhibit more detailed temporal-frequency information about cardiopulmonary coupling during sleep. As two spectrographic markers, pLFC and TVDF can be used to identify respiratory events and represent the disruption extent of sleep architecture in patients with sleep apnea/hypopnea, respectively. The proposed technique might serve as a complementary approach to enhance diagnostic efforts.

1. Introduction

Obstructive sleep apnea–hypopnea syndrome (OSAHS) is the most common type of sleep-disordered breathing (SDB), with a reported prevalence of 2% in middle-aged women and 4% among middle-aged men in the US [1]. Sleep patterns are disrupted in patients with OSAHS, such as increased fast wave sleep (stages 1 and 2), decreased slow wave sleep (stages 3) [2], sleep fragmentation, and more respiratory-related microarousal [3]. Polysomnography (PSG) is the gold standard in the diagnosis of OSAHS in clinical practice. However, PSG is expensive and encumbering. Sleep stage 3, especially, shows a decrease and is generally replaced by stage 2 across the human lifespan, thus reducing the value of traditional PSG scoring in the accurate evaluation of sleep quality [4]. Moreover, it has been reported that excessive daytime sleepiness, one of the important clinical symptoms of OSAHS, is not universally present in all patients and is related to sleep quality, arousals, the apnea hypopnea index (AHI), and hypoxemia [5]. So, more optimal and convenient evaluating methods or parameters are needed to study OSAHS comprehensively.

In fact, much of the previous literature has reported that the autonomic nervous system (ANS) dynamic relates closely to sleep depth and type and could be revealed by respiration and heart rate variability (HRV) [6,7]. Furthermore, the alterations of the ANS in patients with SDB are predictable from the characteristics of these variables, such as the periodic cycling of respiration and heart rate variability [8,9]. Subsequently, a number of methods have been proposed to detect SDB based on the analysis of cardiac inter-beat (R–R) interval dynamics from surface ECG signals [10–14]. However, these methods are limited when used for subjects with low

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HRV (rather, flat HRV trace), i.e., those affected by drug treatments or individuals who have chronically low HRV.

Recently, Thomas et al. introduced a single-lead electrocardiograph (ECG) based cardiopulmonary coupling (CPC) technique to characterize different sleep stages, as well as to identify sleep apnea events. Independent of R–R interval, the complementary information, ECG-derived respiration (EDR) was also extracted from the surface ECG as a surrogate respiration signal. By simultaneously incorporating these two signals, a sleep spectrogram was generated to represent the cardiopulmonary coupling dynamic behaviors during sleep [15]. In comparison with conventional PSG technique, the CPC technique is convenient and more related to the fundamental physiologic mechanisms of altered sympathetic and parasympathetic activities during sleep [16].

The original CPC algorithm is based on Fourier analysis and, therefore, is limited by the stationary assumption of ECG signals that often cannot be satisfied. In addition, using Fourier transform, high frequency resolution and high temporal resolution cannot simultaneously be obtained, inevitably leading to the blurred details of alterations in states in the spectrographic results. As a result, this method is suited to provide a general insight of sleep quality by giving a percentage of recording time detected as SDB rather than a precise SDB detection [17]. In preliminary observations we have found that Hilbert–Huang transform (HHT) [18], an adaptive analysis method for nonlinear and nonstationary time series, can be used to overcome the aforementioned limitation and extend the utility of the original CPC method. By employing HHT-based techniques, the product of the cross-spectral power and coherence of R–R and EDR information was computed to generate a new measure of cardiopulmonary coupling dynamics during sleep. This HHT based CPC (HHT-CPC) technique was supposed to be able to detect SDB minute by minute.

The purpose of the present study is (1) to evaluate this improved spectrographic measure of cardiopulmonary coupling obtained from HHT-CPC technique, (2) to investigate the accuracy of SDB detecting in each minute by using HHT-CPC, and (3) to assess the correlation of an HHT-CPC derived index that gives the overall severity of sleep apnea and a conventional apnea–hypopnea index (AHI).

2. Method

2.1. Database

Data for the present study were available on the open-access Physionet Sleep Apnea Database (http://www.physionet.org/physiobank/database/apnea-ecg/) [19–22]. The data set consists of 70 ECG recordings with a sampling rate of 100 Hz, of which 69 were selected to satisfy the following criteria: at least 6 h of ECG recording after artifacts were removed and at least 80% ECG data with quality to perform HHT-CPC analysis. The subjects of these recordings were adult men and women aged from 27 to 63 years old with different levels of OSAHS. All apneas in these recordings were either obstructive or mixed and each recording included a minute-by-minute apnea annotation indicating the presence or absence of apnea during that minute, made by human experts according to simultaneously recorded respiration signals and related signals. Additional information including (for all recordings) age, gender, height, weight, AI (apnea index), HI (hypopnea index), and AHI (apnea–hypopnea index) were also included.

2.2. Respiratory event scoring

An apnea was defined as the absence of airflow for more than 10 s in the presence of continued respiratory effort. In the study data set, minutes containing hypopneas are also marked as minutes containing apnea. A hypopnea was defined as a reduction in the amplitude of respiratory effort to between 10% and 50% of the baseline level during sleep for a duration of at least 10 s and accompanied with oxygen desaturation of at least 4%. The overall severity of sleep apnea including sleep disruptions and desaturations was described by the apnea–hypopnea index (AHI). AHI values are typically categorized as follows: 0–5 are normal, 5–15 are mild, 15–30 are moderate, and above 30 are severe.

2.3. HHT based cardiopulmonary coupling analysis

In this study, similar with the original CPC technique, we also utilized R–R interval series and its associated surrogate respiration signals (EDR signal) to evaluate the degree of cardiopulmonary coupling with the product of the weighted coherence and cross-spectral power of these two signals. According to the strategy mentioned in previous reports, after extracting a time series of normal-to-normal sinus (N–N) intervals [23] and the associated EDR signals from ECG signals [24–26], outliers due to false negative R-wave detections were removed using a moving average filter with a window of 41 data points. Central points in the window would be rejected while lying outside 20% of the average. These two filtered signals were then evenly resampled at 2 Hz using cubic spline interpolation.

For the improved cardiopulmonary coupling analysis approach proposed in our work, HHT analysis rather than Fourier analysis was employed to analyze N–N signals and EDR signals. By using Empirical Mode Decomposition (EMD) the N–N interval time series and associated EDR signals are first decomposed into a set of intrinsic mode functions (IMFs), respectively [18]. In general, the first IMF mode always contains the highest frequency components and the oscillatory frequencies decrease with increasing IMF mode index. Furthermore, for each IMF mode it can effectively represent the instantaneous frequency, phase, and amplitude at a given time by applying HHT due to its narrow-band feature. Then, the HHT spectrums of N–N interval and EDR signals were employed to estimate the cross-spectral power and coherence of these signals, and we finally obtained the HHT-CPC based sleep spectrum, in which the temporal and frequency resolution chosen were 8 s and 0.001 Hz, respectively. The technical details were described in the Appendix.

2.4. Low frequency coupling (LFC)

As reported in the original CPC technique, high frequency coupling (HFC) was associated with physiologic respiratory sinus arrhythmia (stable sleep state) and low frequency coupling (LFC) was related to periodic respiration during SDB (unstable sleep state). Meanwhile, the elevated LFC was used as an indicator to explore the total percentage that respiratory events occupied during sleep [17].

In the present work, based on the HHT-CPC spectrum with higher temporal resolution, the quantitative power of LFC (pLFC) could be used to identify the sleep apnea events minute by minute. For a specific moment, the pLFC was estimated by the sum of CPC power occupied in the LFC component at that moment.

2.5. Temporal Variability of Dominant Frequency (TVDF)

Basically, in HHT-CPC sleep spectrograms it was observed that, for normal subjects, cardiopulmonary coupling at low and high frequency bands switched spontaneously dependent on different sleep states, while in patients with SDB relatively abrupt transitions usually tended to occur due to respiratory events, and were represented as a sustained predomination coupling at low frequency band.

In order to reflect the OSAHS-induced disturbance on the properties of the states fluctuation, in this work, we extracted the dominant frequency (DF) at a given time from the HHT-CPC spectrogram to construct a DF time series, which is associated with the transition of coupling states along with time. Consequently, by calculating the zero-crossing rate of the DF time series, a novel index, temporal Variability of Dominant Frequency (TVDF), was then introduced to evaluate the severity of OSAHS.

2.6. Statistical methods

In order to verify the significant difference in pLFC based on HHT-CPC spectrum between stable sleep conditions and respiratory events the two sample *t*-test was used. Furthermore, we investigated the classification performances of the pLFC by the receiver operating characteristic analysis [27], which offered an optimal pLFC threshold to discriminate SDB events from normal breathing conditions. The sensitivity is the percentage of respiratory events correctly identified using the above criteria, and the specificity is the percentage of normal breathing state correctly identified. The performance of the investigated method could be illustrated by the plot of sensitivity vs. 1-specificity (receiver operating characteristic curve), and quantified by the parameter area under the curve (AUC).

To verify the significant differences in TVDF among groups with different OSAHS severities, one-way analysis of variance (ANOVA) was employed after the variance homogeneity and distributional normality were confirmed by the Bartlett test and Kolmogorov–Smirnov test, and then the Student–Newman–Keuls test, a typical post hoc procedure, was subsequently utilized.

Finally, Spearman's correlation coefficients were employed to evaluate the relationship between TVDF and AHI.

3. Results

3.1. Subject characteristics

The 69 subjects from the Physionet clinical database included 13 females and 56 males, aged from 27 to 63 years old (mean age 40.4 years old; SD 10.7), with the amount of sleep totaling 33,842 min, among which 13,061 (38.6%) were scored as containing episodes of apnea/hypopnea. The mean BMI was 28.1 (SD 6.5; range 19.2–45.3). The mean AHI was 28.9 (SD 27.4; range 0–93.5).

3.2. Comparison of sleep spectrums between CPC and HHT-CPC

In the spectrums, the power of cardiopulmonary coupling is simultaneously incorporating both R–R and EDR information. These signals tend to present two basic patterns: a low-frequency component which is associated with cyclic variation across multiple breaths and a high-frequency component which is associated with normal breath-to-breath fluctuations due to physiologic respiratory sinus arrhythmia [17]. For a typical patient with OSAHS, both the original CPC and the HHT-CPC results were shown in Fig. 1. The correlation between the EEG-based bi-stable (CAP and non-CAP) paradigm [28] and the low/high frequency component of HRV has been demonstrated in many studies [29–31]. The cardiopulmonary coupling will also follow the paradigm (see the mathematization in Appendix) [15]. In the figure, both of these two CPC sleep spectrums exhibited a similar coupling switch pattern between high/low frequency ranges following CAP/non-CAP scoring.

It was also observed that, compared to the original CPC, the HHT based sleep spectrograms characterize the distribution of cardiopulmonary coupling during sleep with much higher frequency and temporal resolution. In fact, the frequency and temporal resolution of original CPC are 0.004 Hz and 8.5 min, while 0.001 Hz and 8 s for that of HHT-CPC.

3.3. Detection of respiratory events by pLFC

The SDB detection minute-by-minute showed a significant difference in pLFC between stable sleep conditions and respiratory events ($p < 0.001$), shown in Fig. 2(a). Meanwhile, Fig. 2(b) demonstrated the ROC analysis result of pLFC, exploring the optimal threshold for classification as 0.07 normalized units. With the threshold, the accuracy of apnea/hypopnea detection was estimated by the area under the ROC curve as 0.79, indicating that the HHT-CPC measure serves as a good discriminator between apnea/hypopnea and normal breathing.

3.4. TVDF as an indictor to differentiate the severities of OSAHS

The HHT-CPC derived sleep spectrums across normal and typical different severities of OSAHS were presented in Fig. 3(a). The results demonstrated from top to bottom: (1) healthy subject, AHI $\leqslant$ 5; (2) mild sleep apnea, 5 < AHI $\leqslant$ 15; (3) moderate sleep apnea, 15 < AHI $\leqslant$ 30; (4) severe sleep apnea, AHI > 30. From the corresponding DF time series during a roughly 60-min period it was also clearly observed that TVDF decreased with increasing severity of OSAHS, shown in Fig. 3(b).

Normal subjects and groups with different severities of OSAHS were summarized in Table 1. Since only three subjects had mild OSAHS in the current database, we put them together with the moderate group to form a mild & moderate group.

Fig. 4 suggested that there were statistically significant differences in TVDF generated by HHT-CPC sleep spectrums among the normal group, the combined mild & moderate group, and the severe group (one-way ANOVA with SNK test, $p < 0.001$). The TVDF value in each group was represented as mean ± SD in Table 2.

Furthermore, the TVDF showed a strong negative correlation with AHI, where correlation coefficients were −0.71 ($p = 6.1 \times 10^{-12}$), which is illustrated in Fig. 5.

4. Discussion

This study had four key findings: (1) A application of the proposed spectrographic measure of cardiopulmonary coupling based on HHT analysis revealed the similar bimodal-type pattern to the original CPC method, which related to CAP/non-CAP alternation. (2) The improved sleep spectrogram had a capacity to provide more detailed temporal-frequency information about cardiopulmonary coupling during sleep. (3) As an indicator of SDB, the pLFC based on the HHT-CPC spectral profile could be used to detect respiratory events minute-by-minute with good agreement to PSG based manual scoring. (4) TVDF revealed a strong correlation with conventional apnea–hypopnea index in discriminating the severity of OSAHS.

4.1. Hilbert–Huang transform in cardiopulmonary coupling assessment

The basic idea of the original cardiopulmonary coupling (CPC) analysis was to form a spectrographic exhibition of cardiopulmonary coupling dynamics with Fourier-based technique by using R-R interval series and EDR signal.

It has been observed in much of the previous literatures that the spontaneous shifts between high and low frequency coupling in sleep spectrum generated by CPC method show a strong relationship with CAP/non-CAP scoring, reflecting fundamentally distinct physiologic states [15,17]. Furthermore, the distribution of the bimodal stability states has been used to detect abnormal fragment

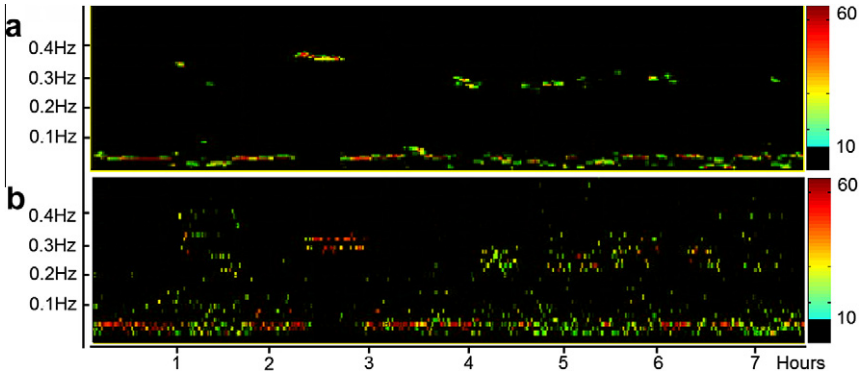

Fig. 1. Comparison of sleep spectrums derived from the original CPC and the HHT-CPC analysis in a 54-year-old man with obstructive sleep-disordered breathing across 8 h of sleep. (a) Original CPC sleep spectrogram. (b) HHT-CPC sleep spectrogram. In each sleep spectrogram, the degree of cardiopulmonary coupling is indicated by the intensity of the color that changes from black (low) to red (high) proportionally.

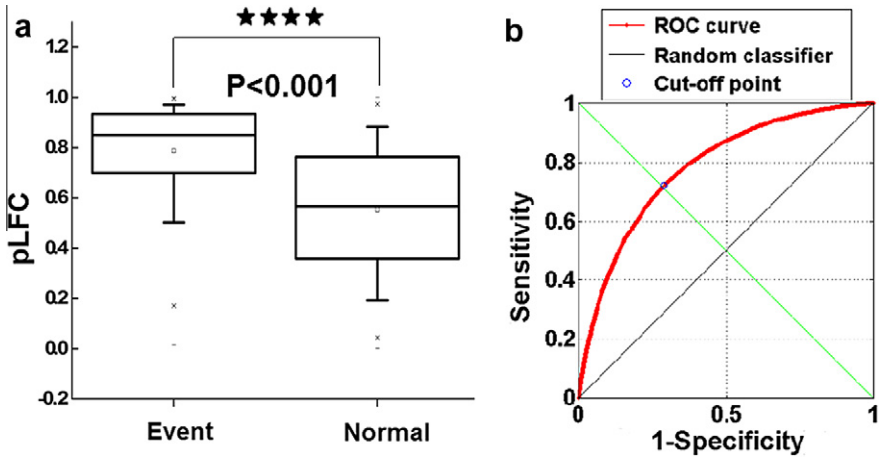

Fig. 2. Detection of respiratory events using pLFC based on HHT-CPC sleep spectrums. (a) Comparison of pLFC during apnea/hypopnea events or normal breathing periods ($p < 0.001$). (b) ROC curve of pLFC (red) and a random classifier (black) in the classification of normal breathing and SDB. The y axis is the sensitivity, representing the percentage of events detected; and the x axis is the 1-specificity. The area under the curve is 0.79. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

periods from full night sleep in patients with OSAHS [32]. In addition, most recently, the duration and mean frequency of the low frequency component in CPC sleep spectrum have also been used to assess sleep physiology in severe pediatric SDB [33].

However, for nonlinear and nonstationary time series such as R–R and EDR signals, Fourier based analysis technique, which needs to meet the requirements of stationarity and linearity, has salient limitations, such as the fact that forcing a linear superposition of non-stationary data or trigonometric functions with the predefined and uniform sine/cosine basis would induce many additional harmonic components. With this preset uniform basis, Fourier analysis may give misleading spectral results and make little physical sense in many biomedical related cases. Although the data can be assumed to be piecewise stationary and analyzing along a sliding window of finite length, the time–frequency resolution is strongly limited by the choice of a window length [18]. In addition, in other technologies such as wavelet approach, which resembles an adjustable window Fourier spectral analysis, its basic functions are also pre-determined. Besides that, the resolution of a time–frequency representation is constrained by Heisenberg's uncertainty principle as well.

The HHT, a model-free timescale-adaptive detrending approach, was developed for analyzing data from nonstationary and nonlinear systems. Compare to a Fourier based technique, the basic functions of HHT were derived adaptively from the signal itself as a collection of IMFs with physical sense. As an oscillatory mode IMF is locally symmetrical and has only a single frequency at any given time (mono-component). With the Hilbert transform the instantaneous frequency can be calculated meaningfully.

Based on the HHT technique, the proposed method measured the strength of cardiopulmonary coupling between heart rate and respiration, thus significantly improving both time and frequency resolution in HHT-CPC sleep spectrum by 8 s and 0.001 Hz (Fig. 1). Therefore, it can exhibit a more refined microarchitecture of full night sleep, especially the rapid alternations in CAP and NCAP states over time, which were represented by the index TVDF.

Meanwhile, by using pLFC, it allowed for the identification of respiratory events minute-by-minute (or even shorter epochs) without any interpolation. The results suggested that the accuracy of pLFC based CAP detection (Fig. 2; AUC = 0.79) compared favorably with what was considered the excellent interscorer reliability (>0.80), resulting from extensive training, in the sleep heart health study [34].

Since the HHT-CPC algorithm is not based on the change in respiratory flow, but instead on the oscillation in heart rate caused by respiration, it is expected that some false predictions will occur. For example, to classify a flow reduction as hypopnea (manual), 30% or greater flow reduction is typically required. However, a flow reduction of less than 30% may also cause robust heart rate

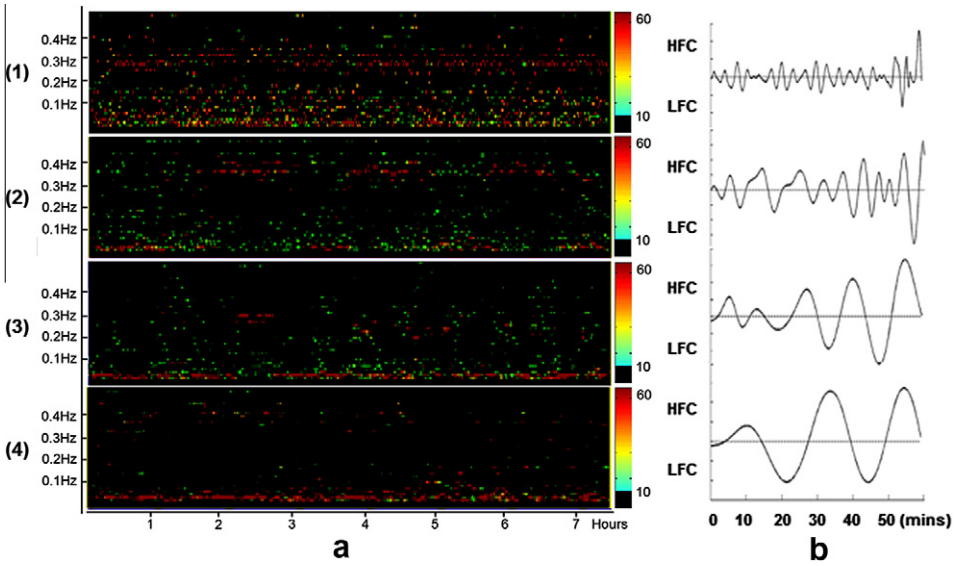

Fig. 3. Sleep spectrums of HHT-CPC and their corresponding DF time series. (a) Typical ECG-derived sleep spectrograms in normal individuals and in patients with apnea of various severities. All the recordings contain approximately eight consecutive hours of full night sleep. The magnitude of the coupling at each frequency is indicated by color from black (low) to red (high). The four panels showed from top to bottom: (1) HHT-CPC result of a 44-year old healthy woman, with AHI 0.13. Note that the spectrographic display of cardiopulmonary coupling shows a healthy pattern dominated by high-frequency cardiopulmonary coupling. (2) HHT-CPC result of a 39-year old man with mild apnea (AHI = 10), nearly 60% of the coherent cross power was distributed in the high-frequency coupling regime. (3) HHT-CPC result of a 54-year old man with moderate sleep apnea (AHI = 39.1). Note the visually apparent decrease of high-frequency coupling compared to the first two results. (4) HHT-CPC result of a 51-year old man with severe sleep apnea (AHI = 69.6). Note only a few amounts of high-frequency coupling. (b) Illustration of the corresponding DF time series of (a) during roughly 60 min periods, respectively.

Table 1
The severity distribution of subjects in groups.

Severity	Number of subject	Mean AHI (/h)	AHI range (/h)
Normal	23	0.51	AHI $\leqslant$ 5
Mild	3	12.77	5 < AHI $\leqslant$ 15
Moderate	12	19.99	15 < AHI $\leqslant$ 30
Severe	31	54.92	AHI > 30

acceleration and deceleration and, therefore, directly influence the presentation of the HHT-CPC sleep spectrum.

On the other hand, in the current study, the quantified LFC was used as the only criterion of SDB. However, some longer or shorter events may occur during sleep and are out of the LF frequency band. Thus, we need to further optimize the criterion of SDB identification by combing the information of high frequency coupling and very low frequency coupling, such as by using the ration of HF/LF weighted by VLF.

4.2. Temporal Variability of Dominant Frequency in sleep spectrum of HHT-CPC

In the HHT-CPC sleep spectrogram a predomination of low frequency coupling correlated with CAP, while a dominant high frequency coupling correlate with non-CAP. Consistent with previous studies [15,17,32,35], it was found that a spontaneous bimodal "switching" behavior between low and high frequency cardiopulmonary coupling regimes suggested a healthy sleep structure, while respiratory abnormality (apnea/hypopnea) induced a prolonged stay in a low frequency coupling state (Fig. 3). Thus, it was reasonable to imagine that the rate of switch between these two states might relate to the severity that combines apneas and hypopneas.

The novel index TVDF, which reflected the activities of sympathetic/parasympathetic alternating, was then proposed to serve as a potential marker to differentiate the severity of SDB. It further demonstrated a significant statistical difference among the normal group and the groups with different severity (Fig. 4; normal and mild & moderate: $p < 0.001$; mild & moderate and server: $p < 0.001$). Furthermore, significant negative correlation was also observed between HHT-CPC based TVDF and AHI (Fig. 5; $r = -0.71$, $p < 10^{-11}$).

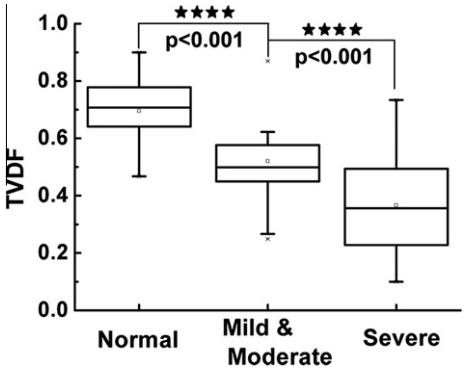

Fig. 4. Box-plotting of the normalized TVDF in OSAHS population with different severities. The TVDF shows statistical significant difference between each two groups (normal and mild & moderate, $p < 0.001$; mild & moderate and severe, $p < 0.001$).

Therefore, it is suggested that the TVDF derived from HHT-CPC could reveal the degree of the fluctuation of the internal environment during sleep apnea, which was associated with the severity of OSAHS and might be valuable for treatment assessment. It also might be a potential marker of ANS activity for investigating certain pathophysiological issues of sleep apnea, such as the inconsistent sleepiness or subsequent hypertension.

4.3. Comparison of original CPC and HHT-CPC

A direct comparison between the original CPC method and HHT-CPC was also made in this study. As we mentioned, the temporal resolution of the Fourier based CPC method is 8.5 min; thus, in order to compare with the proposed method, a 1-min linear interpolation must be applied between the consecutive measurements of

Table 2
Distribution of patients in different severity groups and their corresponding TVDF (mean ± SD).

Severity	Number of subject	wTVDF
Normal	23	0.70 ± 0.12
Mild & moderate	3 and 12	0.52 ± 0.17
Severe	31	0.37 ± 0.17

SD, standard deviation.

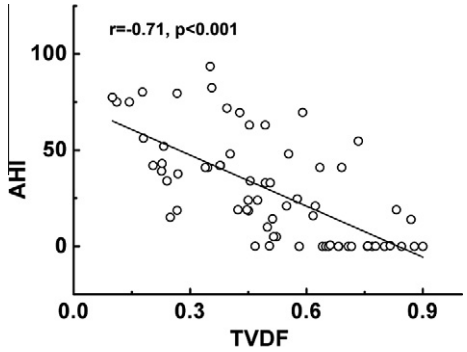

Fig. 5. Correlation between TVDF and AHI. The *x*-axis stood for the normalized TVDF values, and the *y*-axis represented the corresponding AHI values in 69 subjects ranged from 0 to 93.5. A strong negative correlation was observed, the Spearman's correlation coefficient is −0.71 and $p = 6.1 \times 10^{-12}$.

the old CPC method. The results presented in Table 3, demonstrated that the proposed HHT-CPC could provide an improved accuracy, sensitivity, and specificity, positive and negative predictive values in SDB identification. Furthermore, the most important improvement was the proposed method provided more relievable cardiopulmonary coupling estimation in this case rather than the interpolated results.

4.4. Limitations

Since this technique estimates cardiopulmonary coupling based solely on a single-lead ECG, application in the presence of cardiac arrhythmias, such as atrial fibrillation, ventricular ectopy, or ventricular trigeminy is not feasible.

The study database does not contain recordings with episodes of pure central apnea and capability to identify apnea phenotypes of SDB was not tested. On the other hand, the data from the Physionet Sleep Apnea Database are also limited because they do not provide any additional severity information, such as arousal scoring and the oxygen desaturation index. For that, additional sleep lab recorded data would be advantageous for the further study of the proposed new method.

The sampling rate of the current dataset is 100 Hz, so a higher sampling rate would improve the quality of ECG and might lead to a better R peak and QRS complex detection. However, there would be slight influence on the cardiopulmonary coupling analysis, since there are studies which have reported that there were no statistically significant differences in HRV spectrum for either baroreflex sensitivity or frequency bands ranging from VLF to HF using a 100 Hz sampling rate instead of the original 300 or 500 Hz [36,37].

In this study, although the pLFC, contributing mainly using low frequency coupling components, showed a good agreement with manual scoring in the setting of SDB, HFC components associated with non-CAP were not considered since HFC might still occur in obstructive hypoventilation and, in this instance, it might not necessarily correlate with normal physiology [15].

Table 3
Comparison of Fourier based CPC and HHT-CPC.

	Fourier based CPC (%)	HHT-CPC (%)
Accuracy	75.4	79.1
Sensitivity	66.8	73.1
Specificity	72.9	71.2
Positive predictive value	79.4	80.8
Negative predictive value	58.4	63.2

As a matter of fact, any fragmenting stimulus will alter the spontaneous coupling shift pattern in the sleep spectrum, resulting in an increased pLFC and then decreasing the value of TVDF. Therefore, clinical context and clinical manifestation should be considered in advance.

In summary, on the basis of the Hilbert–Huang transform, we presented an improved spectrographic method for estimating cardiopulmonary coupling during sleep. Compared with the original Fourier based CPC technique it provides much finer temporal resolution and frequency resolution and has a capacity of SBD detection minute by minute using pLFC. Additionally, the newly introduced index TVDF demonstrates a strong negative correlation with AHI, suggesting that it could be valuable for potential applications in severity differentiation and might be useful for treatment assessment of OASHS. We believe the proposed HHT-CPC technique could be helpful for further understanding of sleep physiology and pathology.

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.2011.10.030.

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Appendix A

HHT. based cardiopulmonary coupling assessment and generation of sleep spectrograms

The proposed method was based on a single-lead electrocardiogram (ECG) signal and employed Hilbert–Huang transform to analyze two physiologic time series derived from the signal: (1) the variability of the cardiac interbeat (RR) and (2) the surrogate respiration signal EDR, the fluctuations in QRS amplitude caused by respiration. These data are numerically resampled at 2 Hz for comparison (in order to make the detection of coupling frequencies up to 1 Hz due to the Nyquist frequency), and denoted as a function of time $R(t)$ for RR and $E(t)$ for EDR time series.

The mathematical treatment of the original CPC technique was considered. The degree of the cardiopulmonary coupling was quantified by the product of the coherence and cross-spectral power of these two time series as the cardiopulmonary coupling index. Computational procedures were carried out as following: These two signals were decomposed by EMD into a series of IMF and a residual component respectively, expressed as $R(t) = \sum_{i=1}^{n} R_i + r_n$ and $E(t) = \sum_{i=1}^{n} E_i + r_n$, where R_i, E_i were the ith IMF and r_n was the residue ($i = 1,2,3,\ldots,n$). The Hilbert transform of an IMF for these two time series was denoted as

$$Y_{R,i}(t) = \frac{1}{\pi} P \int_{-\infty}^{\infty} \frac{R_i(\tau)}{t-\tau} d\tau, \quad (1)$$

and

$$Y_{E,i}(t) = \frac{1}{\pi} P \int_{-\infty}^{\infty} \frac{E_i(\tau)}{t-\tau} d\tau \quad (2)$$

where P indicates the Cauchy principal value. Then

$$Z_{R,i}(t) = R_i(t) + iY_{R,i}(t) \quad (3)$$

and

$$Z_{E,i}(t) = E_i(t) + iY_{E,i}(t) \quad (4)$$

were defined as the analytic signals. The instantaneous amplitudes could be subsequently expressed as $a_{R,i}(t) = [X_i^2(t) + Y_{R,i}^2(t)]^{1/2}$ and $a_{E,i}(t) = [X_i^2(t) + Y_{E,i}^2(t)]^{1/2}$. Similarly $\theta_{R,i}(t) = \arctan\left(\frac{Y_{R,i}(t)}{R_i(t)}\right)$ and $\theta_{E,i}(t) = \arctan\left(\frac{Y_{E,i}(t)}{E_i(t)}\right)$ were the instantaneous phases. Furthermore, the instantaneous frequency could be computed as $\omega_{R,i} = \frac{d\theta_{R,i}(t)}{d(t)}$ and $\omega_{E,i} = \frac{d\theta_{E,i}(t)}{d(t)}$.

In fact, based on the above obtained amplitude and phase, we could calculate the cross-spectrum and coherence between RR and EDR time series point by point.

However, the coherence is a statistical property, thus a sliding window was used to achieve a reliable compute. In our measurements of the coherence 16 data points (8 s) was chosen as the window size.

In each observation window, we first calculate the frequency by averaging the instantaneous frequency.

We found out two windows (one from RR, the other from EDR) with the most similar frequency, for frequency f_j, calculating the cross-spectrum as follows:

$$\Gamma_j(R,E) = a_{R,m}(t)a_{E,n}(t)e^{i[\theta_{R,m}(t)-\theta_{E,n}(t)]}, \quad (5)$$

where m and n indicates the mth and nth window. The coherence measures for the consistency of the phase difference between two time series, were calculated using the following equation:

$$\Lambda_j = \frac{<\Gamma_j(R,E)>^2}{<[a_{R,m}(t)e^{i\theta_{R,m}(t)}]^2><[a_{E,n}(t)e^{i\theta_{E,n}(t)}]^2>}, \quad (6)$$

where Λ_j denotes the coherence, and the $\langle\ \rangle$ represents averaging multiple measurements at a given frequency, as the coherence is a statistical result.

The quantitative degree of cardiopulmonary coupling combining both cross-spectral power and coherence was defined as:

$$\mathrm{CPC}(f_j) = \langle\Gamma_j(R,E)\rangle^2\Lambda_j \quad (7)$$

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