Title: HHT based Cardiopulmonary Coupling Analysis for Sleep Apnea Detection

Article Type: Original Article

Keywords: OSAHS; Hilbert-Huang Transform; Cardiopulmonary Coupling; Sleep Spectrum; ECG; Coupling.

Abstract: Study Objectives: To validate the feasibility of the Hilbert-Huang transform (HHT) based cardiopulmonary coupling (CPC) technique in respiratory events detection and estimating 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 Physionet Sleep Apnea Database. Sleep spectrograms generated by both original and the improved CPC method were compared on the structure distribution and time-frequency resolution. The performance of respiratory events detection by using 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 seconds and 0.001 Hz) compared with the original CPC (8.5 minutes 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 server, 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.
Dear Editor,

This is the revision of our manuscript “HHT based Cardiopulmonary Coupling Analysis for Sleep Apnea Detection” (#SLEEP-D-11-00323).

In this revised manuscript, both the Reviewer’s and the Editor’s comments are carefully examined and accepted to make the paper perfect.

The main points of the reversion have been described in the repose letter to reviewers. In addition, a clean version of the revised paper, and a separate marked-up version to specifically indicate the changes that have been made in response to the reviewers’ comments were also submitted.

As commented by the Reviewer, the work presented in our manuscript is “a new very interesting technique, this method has actually many methodological advantages”, we will keep on the studies to reveal more of the physiologic relationships between sleep diseases and cardiopulmonary coupling.

We would appreciate your considerations to publish this paper in Sleep Medicine. If you need any more materials, please let us know.

Sincerely yours
Jue Zhang
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RESPONSE TO REVIEWER #1

1) Why did you choose (on which arguments) the Hibert-Huang transform: there are many other methods/tools such as Wavelet Transform with a choice of the « mother » wavelet to be based on the « real » morphology of the analyzed signal.

We appreciate your comments.

(1) We chose HHT (EMD) because it is a fully data driven, adaptive method; i.e., it does not use any pre-determined basic functions. Moreover, as EMD is based on the local characteristics of the data, it is highly suitable for decomposing time-series produced by nonlinear and non-stationary processes such as those examined in the current study. The wavelet transform, on the other hand, is not an adaptive method because the basic function is pre-determined. As a result, the decomposition is affected greatly by the choice of basic wavelet.

(2) For the wavelet analysis, the resolution of a time-frequency representation is constrained by Heisenberg's uncertainty principle. The HHT method, however, can derive instantaneous amplitude, phase, and frequency for a signal with no a priori knowledge.

We have added the comparison between wavelet and HHT to the discussion section (page 13, line 8).

2) Is a sampling rate of signal acquisition of 100 Hz (QRS) adequate to use the proposed CPC method?

Thank you for the good comment. Yes. As quantification of CPC is based on the R-R time series and EDR signal. Higher sampling rate will definitely improve the quality of ECG, but we do not think there will be significant influence to the analysis result of cardiopulmonary coupling. Since there are studies reported that there were no statistically significant differences in HRV spectrum for both baroreflex sensitivity and frequency bands ranging from VLF to HF using 100 Hz sampling rate instead of the original 300 or 500 Hz.


We have added the importance of sampling rate to discussion section (page 16, line 10) and cited these two above references.

On the other hand, this database has been used in many studies for similar studies, thus we think this will be sufficient to be used in the study.


3) The Physionet Database served as a reference is perfectly suited to this type of study. Then, it seems that, during the initial challenge organized around the screening of OSAS, one participant proposed a somewhat similar method based on wavelet transform of the RR series. What the authors analyzed the cardiopulmonary coupling rather than on the RR and is there a significant increase in screening accuracy? The reference could be added.

Thank you for your valuable comment. We have studied and added this reference. The method reported in that paper, which was primarily based on detection of cardiac
interbeat (R-R) interval dynamics, is of limited use in subjects with reduced heart-rate variability. Certain disease conditions (e.g., congestive heart failure or autonomic neuropathy) and drugs (e.g., parasympatholytics) are associated with a marked reduction in variability. Heart-rate variability also varies considerably between individuals and is affected by age and physical conditioning.

In contrast, the cardiopulmonary coupling analysis provides information not only on R-R characteristics but also on the EDR, which is independent of R-R variability. EDR is more related to the heart and transthoracic impedance varies as the lungs fill and empty. Although screening accuracy may not increase in all cases, the cardiopulmonary coupling measure may be more accurate in specific cases. For example, even if R-R variability is low, quantification of R-wave amplitude modulation in the EDR signal driven by respiration can be detected and the degree of coupling between heart-rate variability and breathing can be quantified.

4) A set of validation appears essential to check the ability of this new screening method. A direct comparison with the « authentic » old but validated method already widely used in CPC should be made in this study: the results for sensitivity and specificity shown here should be comparable for the reader as well as the W values of the ROC curves (and its confidence interval).

Thank you for your comment and we understand your concern. Usually, respiratory events happen quickly (i.e., within seconds or a few minutes). The time resolution of the previous CPC method, which was 8.5 minutes, may thus be a disadvantage because it will blur rapid alterations in state. In order to directly compare the previous method with our HHT-CPC method, a 1 minute linear interpolation must be applied between the consecutive measurements of the previous CPC method. The comparison is showed in Table 1. As you can see, in addition to improved accuracy, sensitivity, specificity and predictive values, the proposed HHT-CPC is more relievable than the interpolated results.
Table 1. Comparison of original CPC method and HHT-CPC.

<table>
<thead>
<tr>
<th></th>
<th>Fourier based CPC</th>
<th>HHT-CPC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy</strong></td>
<td>75.4%</td>
<td>79.1%</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>66.8%</td>
<td>73.1%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>72.9%</td>
<td>71.2%</td>
</tr>
<tr>
<td><strong>Positive predictive value</strong></td>
<td>79.4%</td>
<td>80.8%</td>
</tr>
<tr>
<td><strong>Negative predictive value</strong></td>
<td>58.4%</td>
<td>63.2%</td>
</tr>
</tbody>
</table>

We have added the comparison of original CPC and HHT-CPC also this table to the discussion section (page 15, line 13).

5) **The positive and negative predictive values** should also be reported. The latter are probably not very high. Authors should be able to bring into the discussion section some elements of explanation of false positives and false negatives found in this study (other causes of sleep fragmentation, snoring subjects with episodes of upper airway resistance ...)

The positive and negative predictive values have been presented in Table 1 above. 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 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.
We have added the explanation of false positives and false negatives to the discussion section (page 14, line 5).

6) The authors use essentially the LF spectral band to detect respiratory events: some longer or shorter events were certainly out of this frequency band. How the authors could improve their algorithm to these events there?

The low-frequency component of sleep spectrum increased significantly during respiratory events, as well as high-frequency and very low-frequency component will represent different patterns from normal breathing states. Therefore, we can design an optimal criterion for respiratory events identification by combining weighted information of LF, HF and VLF, such like using the ratio of HF to LF and weighted with effects of VLF. This optimal approach has been added to discussion section (page 14, line 11).

7) Finally the authors are positive on the temporal correlation between the presence of CAP and the frequency changes/switch encountered during the night in the subjects understudied. This request has to be more clearly demonstrated.

Thank you for your comment. We have added references to better demonstrate the correlation between CAP/non-CAP and the frequency switch (page 10, line 8). Briefly, we have described this relationship as

In the sleep 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.

The correlation between the CAP/non-CAP and the low/high frequency band of HRV has been demonstrated in many studies.


Therefore the cardiopulmonary coupling should also follow the CPA/non-CAP scoring (see the mathematization of cardiopulmonary coupling in appendix section), and this has been proved in study (4).

RESPONSE TO REVIEWER #1

1) The paper studies the feasibility of the Hilbert-Huang transform based cardiopulmonary coupling technique in sleep apnea event detection to estimate the severity of sleep disordered breathing in patients. The paper introduces a new very interesting technique which proved to show fine details in the cardiopulmonary coupling in patients with sleep apnea. Whether this new technique is a valid improvement over the existing CPC techniques needs to be validated in a clinical study which provides additional severity criteria. The best criteria would be morbidity and mortality in patients to check. How do you plan to reach this goal?

We appreciate the reviewer time spent discussing our results and we thank for the useful comments. The goals of the current study were to describe and validate this new technique. By utilizing the Physionet database, we demonstrated that the HHT-CPC technique is more accurate than the original CPC method. Therefore, the next step is to further validate the clinical importance of the HHT-CPC and the info that it provides by using it to analyze another database that contains info on subject morbidity/mortality.

2) Data are 69 single lead ECG signals from Physionet sleep apnea database. This is useful since the data had been used in other studies. Please give reference to the other studies using these data. A paper describing this dataset should be cited too.

Thank you for your suggestion. We have added the requested references to the manuscript (page 6, line 9).


(2) Thomas RJ, Mietus JE, Peng CK, Gilmartin G, Daly RW, Goldberger AL, Gottlieb DJ.


3) The data from the Physionet sleep apnea database are also limited because they do not provide any additional severity information. For that additional sleep lab recorded data would be advantageous. Do you have such data as a second data set, say for validation of your new approach?

We do not have access to such a database at this time. As such, we have described the lack of severity information within the extant database as a limitation of our study (page 16, line 5). However, the reviewer #1 comments that the data we used only from Physionet is already perfectly suited to our study.

We are grateful for your good suggestion. In order to test the proposed technique with more clinical data, we have tried our best to collect data from the hospital during last 20 days.

Unfortunately, doctors there seldom use the ECG signals, thus the quality of ECG signals is not good for analyzing. Only 15 data are available, but most of them are collected from patients with mild OSAHS.

Although the HHT-CPC results of these 15 clinical data are as good as the previous results reported in the paper, the amount of data is too small.

Actually, we have published an abstract of this work and gave a presentation on "the Third International Conference on Hilbert-Huang Transform: Theory and Applications"
There are numerous people were attracted. Some clinical researchers think the new method is interesting and they look forward to more details. That’s why we hope to publish our study on sleep medicine. We think scientists who focus on sleep medicine and sleep research will be interested in our work which might supply a new thought and a new analysis approach to them.

As you mentioned the Physionet sleep apnea database has been used in many other studies as a validation dataset.

Besides that we found some papers published on journals about clinic and public health using data only from database such like Physionet for validation. For example: Technology and Health Care, Journal of Electrocardiology, Journal of Medical Systems and so on.

((1)Nemati S et al., T-wave alternans patterns during sleep in healthy, cardiac disease, and sleep apnea patients, J Electrocardiol, 44(2):126-30(2011);

We are very pleased to have a further study on the HHT-CPC technique, but we need help on dataset from researchers who are also interested in the HHT-CPC method.

4) **A comparison of the new technique with arousal scoring would be very interesting. For this full polysomnography data would be required. Can you check your method against arousal scoring?**

Thank you for the good suggestion and we agree that the HHT-CPC method would be extremely useful for arousal scoring and the oxygen desaturation index. Unfortunately, we do not have an additional database right now. Since we do not have access to a database with this information, additional analyses on arousal are beyond the scope of the current study.
The new method as described in the Appendix appears to be sound and sold. Since you are looking into more details, I am curious about the influence of sampling rate on your results. ECG for the sleep apnea database was sampled with 100 Hz. Today recommendation require 200 Hz minimal and 500 Hz optimal sampling rate for polysomnography. How do your evaluations change with this?

As quantification of CPC is based on the R-R time series and EDR signal. Higher sampling rate will definitely improve the quality of ECG, but we do not think there will be significant influence to the analysis result of cardiopulmonary coupling. Since there are studies reported that there were no statistically significant differences in HRV spectrum for both baroreflex sensitivity and frequency bands ranging from VLF to HF using 100 Hz sampling rate instead of the original 300 or 500 Hz.


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On the other hand, this database has been used in many studies for similar studies, thus we think this will be sufficient to be used in the study.


HHT based Cardiopulmonary Coupling Analysis for Sleep Apnea Detection

Dongdong Liu¹, Xiaochen Yang¹, Jing Ma²,³, Yanhui Liu⁴, Chung-Kang Peng³,⁴, Jue Zhang¹,³,*, Jing Fang¹,³

1. College of Engineering, Peking University, Beijing, China
2. Department of Pulmonary Medicine, Peking University First Hospital, Beijing, China
3. Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, China
4. Margret & H.A. Rey Institute for Nonlinear Dynamics in Physiology and Medicine, Division of Interdisciplinary Medicine and Biotechnology, Beth Israel Deaconess Medical Center / Harvard Medical School, Boston, MA, USA

Co-corresponding author: Jue Zhang

Tele: +86-010-6275-5036

Email: zhangjue@pku.edu.cn

Fax: +86-010-6275-3562
ABSTRACT

**Study Objectives:** To validate the feasibility of the Hilbert-Huang transform (HHT) based cardiopulmonary coupling (CPC) technique in respiratory events detection and estimating 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 Physionet Sleep Apnea Database. Sleep spectrograms generated by both original and the improved CPC method were compared on the structure distribution and time-frequency resolution. The performance of respiratory events detection by using 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 seconds and 0.001 Hz) compared with the original CPC (8.5 minutes 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 server, 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.
Keywords: OSAHS, Hilbert-Huang Transform, Cardiopulmonary Coupling, Sleep Spectrum, ECG, Coupling
1. Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is the most common type of sleep-disordered breathing (SDB), with a reported prevalence of 2 percent in middle-aged women and 4 percent among middle-aged men in US [1]. Sleep patterns are disrupted in patients with OSAHS, such as increased fast wave sleep (stages 1 & 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. Especially, the sleep stage 3 shows a decrease and is generally replaced by the stage 2 across the lifespan, thus reducing the value of traditional PSG scoring in the accurate evaluation of sleep quality [4]. Moreover, it was 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 the OSAHS comprehensively.

In fact, many previous literatures have reported that autonomic nervous system (ANS) dynamics 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 HRV (rather flat HRV trace), i.e. those affected by drug treatments or individuals who has 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 the altered sympathetic and parasympathetic activities during sleep [16].

The original CPC algorithm is based on Fourier analysis and, therefore, is limited by stationary assumption to 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 a 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, and 69 were selected to satisfy the following criteria: at least 6 hours of ECG recording after artifact removed, at least 80% ECG data with quality to perform HHT-CPC analysis. The subjects of these recordings are adult men and women aged from 27 to 63 years old with different levels of OSAHS. All apneas in these recordings are either obstructive or mixed and each recording includes 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) are 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 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 Normal, 5-15 Mild, 15-30 Moderate, and above 30 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 decreases 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 8s and 0.001Hz, respectively. The technical details were described in the Appendix section.

2.4. Low frequency coupling (LFC)

As reported in original CPC technique, high frequency coupling (HFC) was associated with physiologic respiratory sinus arrhythmia (stable sleep state) and low frequency coupling (LFC) 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 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 switches spontaneously depended on different sleep states, while in patients with SDB, relatively abrupt transitions usually tend to occur due to respiratory events, and was 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 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) is 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 Phyionet 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 minutes, 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 of cardiopulmonary coupling in appendix section) and this has been proven din study [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 0.004Hz and 8.5 minutes, while 0.001Hz and 8 seconds for that of HHT-CPC.
3.3 Detection of Respiratory Events by pLFC

For the SDB detection minute-by-minute, there 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 the apnea/hypopnea and normal breathing.

3.4 TVDF as a indicator to differentiate the different severity 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, AHIs≤5; 2) mild sleep apnea, 5<AHI≤15; 3) moderate sleep apnea, 15<AHI≤30; 4) Severe sleep apnea, AHI>30. From the corresponding DF time series during a roughly 60-minute period, it was also observed clearly 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 3 subjects had mild OSAHS in the current database, therefore we put them together with the moderate group to form a mild & moderate group.

Fig.4 suggested that there were statistically significant difference in TVDF generated by HHT-CPC sleep spectrum among the normal group, the combined mild and moderate 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 was -0.71 (p=6.1*10^{-12}), which was illustrated in Fig.5.

4. Discussion

This study had four key findings. (1) 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 can be used to detect respiratory events minute-by-minute with good agreement to PSG based manual scoring. (4) TVDF revealed 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 many 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 fragments period from full night sleep in patients with OSAHS [32]. Besides, 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 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 those 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, 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 too.

The HHT, a model-free timescale-adaptive detrending approach was developed for analyzing data from nonstationary and nonlinear systems. Compare to Fourier based technique, the basis 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 HHT technique, the proposed method measured the strength of cardiopulmonary coupling between heart rate and respiration, thus improving significantly both time and frequency resolution in HHT-CPC sleep spectrum by 8s and 0.001Hz (Fig.1). Therefore, it can exhibit a more refined micro-architecture of full night sleep, especially the rapid alternations in CAP and NCAP states over time, which was represented by the index TVDF.

Meanwhile, by using pLFC, it allowed the identification of respiratory events
minute-by-minute (or even shorter epochs) without any interpolation. The results suggested the accuracy of pLFC based CAP detection (Fig. 2; AUC = 0.79) compared favorably with what was considered as the excellent interscorer reliability (>0.80) in the Sleep Heart Health Study resulting from an extensive training [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 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 like using the ration of HF/LF and 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 correlates 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 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 statistic differences 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 \(^{-11}\)). Therefore, it 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. Besides, it also might be a potential marker of ANS activity for investigating some pathophysiological issues of sleep apnea, such as the inconsistent sleepiness or the 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 minutes, thus, in order to compare with the proposed method, a 1-minute linear interpolation must be applied between the consecutive measurements of the old CPC method. The result presented in Table 3 demonstrated that the proposed HHT-CPC could provide an improved accuracy, sensitivity, 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 solely based on a single-lead ECG, application in the presence of cardiac arrhythmias is not feasible, such as atrial fibrillation, ventricular ectopy or ventricular trigeminy.

The study database does not contain recordings with episodes of pure central apnea, capability to identify apnea phenotypes of SDB was not tested. On the other hand, the data from the Physionet sleep apnea database may also be 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 higher sampling rate will improve the quality of ECG and may lead to a better R peak and QRS complex detection. However there will be slight influence to the cardiopulmonary coupling analysis, since there are studies reported that there were no statistically significant differences in HRV spectrum for both baroreflex sensitivity and frequency bands ranging from VLF to HF using 100 Hz sampling rate instead of the original 300 or 500 Hz [36, 37].

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

As a matter of fact, any fragmenting stimulus will alter the spontaneous coupling shift pattern in 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 Hilbert-Huang Transform, we presented an improved spectrographic method for estimating the cardiopulmonary coupling during sleep. Comparing 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.

Acknowledgments

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Reference


17. Thomas RJ, Mietus JE, Peng CK, Gilmartin G, Daly RW, Goldberger AL, Gottlieb DJ.


26. Langley P, Bowers EJ, Murray A. Principal component analysis as a tool for analyzing


electrocardiogram-based technique. Sleep 2010; 33:643-46.

36. Ziemssen T, Gasch J, Ruediger H. Influence of ECG sampling frequency on spectral analysis of
2008; 22(2):159-68.

37. Bianchi AM, Mainardi L, Petrucci E, Signorini MG, Mainardi M, and Cerutti S. Time-Variant
Power Spectrum Analysis for the Detection of Transient Episodes in HRV Signal. IEEE
transactions on biomedical engineering. 1993; 40 (2).
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 $E(t)$ . The mathematical treatment of 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 are carried out as following: These two signals are 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 $R_i$ and $E_i$ are the $i$th IMF and $r_n$ is the residue ($i=1,2,3,...,n$). The Hilbert Transform of an IMF for these two time series is denoted as

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

and

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

where $P$ indicates the Cauchy principal value. Then

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

and

$Z_{E,i}(t) = E_i(t) + iY_{E,i}(t)$ (4)
are defined as the analytic signals. The instantaneous amplitudes can be subsequently expressed as \( a_{R,i}(t) = \sqrt{(X_i^2(t) + Y_R^2(t))} \) and \( a_{E,i}(t) = \sqrt{(X_i^2(t) + Y_E^2(t))} \). Similar

\[
\theta_{R,i}(t) = \arctan\left(\frac{Y_R^i(t)}{R_i(t)}\right) \quad \text{and} \quad \theta_{E,i}(t) = \arctan\left(\frac{Y_E^i(t)}{E_i(t)}\right)
\]

are the instantaneous phases.

Furthermore, the instantaneous frequency can be computed as

\[
\omega_{R,i} = \frac{d\theta_{R,i}(t)}{dt} \quad \text{and} \quad \omega_{E,i} = \frac{d\theta_{E,i}(t)}{dt}.
\]

In fact, based on the above obtained amplitude and phase, we can 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 seconds) was chosen as the window size.

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

Find out two windows (one from RR, the other from EDR) with the most similar frequency, for frequency \( f_J \), calculate the cross-spectrum as follow:

\[
\Gamma_J(R, E) = R_m^\wedge(t) E_n^\wedge(t) = A_m(t)B_n(t)e^{i(\phi_m(t) - \phi_n(t))},
\]

where the * indicates the complex conjugate, \( m \) and \( n \) indicates the \( m \)th and \( n \)th window. The coherence measures the consistency of the phase difference between two time series, is calculated by the following equation:

\[
\Lambda_J = \frac{<\Gamma_J(R, E)>^2}{<R_J^2><E_J^2>},
\]

where \( \Lambda_J \) denotes the coherence, and the < > represents averaging multiple measurements at
a given frequency, as the coherence is a statistical result.

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

\[
CPC(f_j) = \langle \Gamma_j(R, E) \rangle >^2 \Lambda_j
\]  

(7)
HHT based Cardiopulmonary Coupling Analysis for Sleep Apnea Detection

Dongdong Liu¹, Xiaochen Yang¹, Jing Ma²,³, Yanhui Liu⁴, Chung-Kang Peng³,⁴, Jue Zhang¹,³*, Jing Fang¹,³

1. College of Engineering, Peking University, Beijing, China
2. Department of Pulmonary Medicine, Peking University First Hospital, Beijing, China
3. Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, China
4. Margret & H.A. Rey Institute for Nonlinear Dynamics in Physiology and Medicine, Division of Interdisciplinary Medicine and Biotechnology, Beth Israel Deaconess Medical Center / Harvard Medical School, Boston, MA, USA

Co-corresponding author: Jue Zhang

Tele: +86-010-6275-5036

Email: zhangjue@pku.edu.cn

Fax: +86-010-6275-3562
ABSTRACT

**Study Objectives:** To validate the feasibility of the Hilbert-Huang transform (HHT) based cardiopulmonary coupling (CPC) technique in respiratory events detection and estimating 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 Physionet Sleep Apnea Database. Sleep spectrograms generated by both original and the improved CPC method were compared on the structure distribution and time-frequency resolution. The performance of respiratory events detection by using 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 seconds and 0.001 Hz) compared with the original CPC (8.5 minutes 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.
Keywords: OSAHS, Hilbert-Huang Transform, Cardiopulmonary Coupling, Sleep Spectrum, ECG, Coupling
1. Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is the most common type of sleep-disordered breathing (SDB), with a reported prevalence of 2 percent in middle-aged women and 4 percent among middle-aged men in US [1]. Sleep patterns are disrupted in patients with OSAHS, such as increased fast wave sleep (stages 1 & 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. Especially, the sleep stage 3 shows a decrease and is generally replaced by the stage 2 across the lifespan, thus reducing the value of traditional PSG scoring in the accurate evaluation of sleep quality [4]. Moreover, it was 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 the OSAHS comprehensively.

In fact, many previous literatures have reported that autonomic nervous system (ANS) dynamics 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 HRV (rather flat HRV trace), i.e. those affected by drug treatments or individuals who has 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 the altered sympathetic and parasympathetic activities during sleep [16].

The original CPC algorithm is based on Fourier analysis and, therefore, is limited by stationary assumption to 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 a 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, and 69 were selected to satisfy the following criteria: at least 6 hours of ECG recording after artifact removed, at least 80% ECG data with quality to perform HHT-CPC analysis. The subjects of these recordings are adult men and women aged from 27 to 63 years old with different levels of OSAHS. All apneas in these recordings are either obstructive or mixed and each recording includes 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) are 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 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 Normal, 5-15 Mild, 15-30 Moderate, and above 30 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 decreases 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 8s and 0.001Hz, respectively. The technical details were described in the Appendix section.

2.4. Low frequency coupling (LFC)

As reported in original CPC technique, high frequency coupling (HFC) was associated with physiologic respiratory sinus arrhythmia (stable sleep state) and low frequency coupling (LFC) 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 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 switches spontaneously depended on different sleep states, while in patients with SDB, relatively abrupt transitions usually tend to occur due to respiratory events, and was 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 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) is 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 Phyionet 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 minutes, 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 section) [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 0.004Hz and 8.5 minutes, while 0.001Hz and 8 seconds for that of HHT-CPC.
3.3 Detection of Respiratory Events by pLFC

For the SDB detection minute-by-minute, there 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 the apnea/hypopnea and normal breathing.

3.4 TVDF as an indicator to differentiate the different severity 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≤5; 2) mild sleep apnea, 5<AHI≤15; 3) moderate sleep apnea, 15<AHI≤30; 4) Severe sleep apnea, AHI>30. From the corresponding DF time series during a roughly 60-minute period, it was also observed clearly 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 3 subjects had mild OSAHS in the current database, therefore we put them together with the moderate group to form a mild & moderate group.

Fig.4 suggested that there were statistically significant difference in TVDF generated by HHT-CPC sleep spectrum among the normal group, the combined mild and moderate 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 was -0.71 ($p=6.1\times10^{-12}$), which was illustrated in Fig.5.

4. Discussion

This study had four key findings. (1) 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 can be used to detect respiratory events minute-by-minute with good agreement to PSG based manual scoring. (4) TVDF revealed 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 many 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 fragments period from full night sleep in patients with OSAHS [32]. Besides, 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 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 those 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, 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 too.

The HHT, a model-free timescale-adaptive detrending approach was developed for analyzing data from nonstationary and nonlinear systems. Compare to Fourier based technique, the basis 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 HHT technique, the proposed method measured the strength of cardiopulmonary coupling between heart rate and respiration, thus improving significantly both time and frequency resolution in HHT-CPC sleep spectrum by 8s and 0.001Hz (Fig. 1). Therefore, it can exhibit a more refined micro-architecture of full night sleep, especially the rapid alternations in CAP and NCAP states over time, which was represented by the index TVDF.

Meanwhile, by using pLFC, it allowed the identification of respiratory events
minute-by-minute (or even shorter epochs) without any interpolation. The results suggested the accuracy of pLFC based CAP detection (Fig. 2; AUC = 0.79) compared favorably with what was considered as the excellent interscorer reliability (>0.80) in the Sleep Heart Health Study resulting from an extensive training [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 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 like using the ration of HF/LF and 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 correlates 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 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 statistic differences 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}). Therefore, it 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. Besides, it also might be a potential marker of ANS activity for investigating some pathophysiological issues of sleep apnea, such as the inconsistent sleepiness or the 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 minutes, thus, in order to compare with the proposed method, a 1-minute linear interpolation must be applied between the consecutive measurements of the old CPC method. The result presented in Table 3 demonstrated that the proposed HHT-CPC could provide an improved accuracy, sensitivity, 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 estimate cardiopulmonary coupling solely based on a single-lead ECG, application in the presence of cardiac arrhythmias is not feasible, such as atrial fibrillation, ventricular ectopy or ventricular trigeminy.

The study database does not contain recording with episodes of pure central apnea, 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 higher sampling rate will improve the quality of ECG and may leads to a better R peak and QRS complex detection. However there will be slight influence to the cardiopulmonary coupling analysis, since there are studies reported that there were no statistically significant differences in HRV spectrum for both baroreflex sensitivity and frequency bands ranging from VLF to HF using 100 Hz sampling rate instead of the original 300 or 500 Hz [36, 37].

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

As a matter of fact, any fragmenting stimulus will alter the spontaneous coupling shift pattern in 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 Hilbert-Huang Transform, we presented an improved spectrographic method for estimating the cardiopulmonary coupling during sleep. Comparing 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.

Acknowledgments

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Reference


17. Thomas RJ, Mietus JE, Peng CK, Gilmartin G, Daly RW, Goldberger AL, Gottlieb DJ.


26. Langley P, Bowers EJ, Murray A. Principal component analysis as a tool for analyzing


electrocardiogram-based technique. Sleep 2010; 33:643-46.


APPENDIX

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 \( E(t) \). The mathematical treatment of 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 are carried out as following: These two signals are decomposed by EMD into a series of IMF and a residual component respectively, expressed as

\[
R(t) = \sum_{i=1}^{n} R_i + r_n \quad \text{and} \quad E(t) = \sum_{i=1}^{n} E_i + r_n ,
\]

where \( R_i \) and \( E_i \) are the \( i \)th IMF and \( r_n \) is the residue (\( i=1,2,3,...,n \)). The Hilbert Transform of an IMF for these two time series is denoted as

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

and

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

where \( P \) indicates the Cauchy principal value. Then

\[
Z_{R,i}(t) = R_i(t) + iY_{R,i}(t)
\]

and

\[
Z_{E,i}(t) = E_i(t) + iY_{E,i}(t)
\]
are defined as the analytic signals. The instantaneous amplitudes can be subsequently expressed as

\[ a_{R,i}(t) = |X_i^2(t) + Y_i^2(t)|^{1/2} \quad \text{and} \quad a_{E,i}(t) = |X_i^2(t) + Y_i^2(t)|^{1/2}. \]

Similar

\[ \theta_{R,i}(t) = \arctan\left(\frac{Y_i(t)}{R_i(t)}\right) \quad \text{and} \quad \theta_{E,i}(t) = \arctan\left(\frac{Y_i(t)}{E_i(t)}\right) \]

are the instantaneous phases.

Furthermore, the instantaneous frequency can be computed as

\[ \omega_{R,i} = \frac{d\theta_{R,i}(t)}{dt} \quad \text{and} \quad \omega_{E,i} = \frac{d\theta_{E,i}(t)}{dt}. \]

In fact, based on the above obtained amplitude and phase, we can 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 seconds) was chosen as the window size.

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

Find out two windows (one from RR, the other from EDR) with the most similar frequency, for frequency \( f_j \), calculate the cross-spectrum as follow:

\[ \Gamma_j(R, E) = \hat{R}_m(t) \hat{E}_n(t) = A_m(t)B_n(t)e^{i[j\phi_{R,i}(t) - \phi_{E,i}(t)]}, \]  

where the * indicates the complex conjugate, \( m \) and \( n \) indicates the \( m \)th and \( n \)th window. The coherence measures the consistency of the phase difference between two time series, is calculated by the following equation:

\[ \Lambda_j = \frac{\langle \Gamma_j(R, E) \rangle^2}{\langle \hat{R}_j^2 \rangle \langle \hat{E}_j^2 \rangle}, \]

where \( \Lambda_j \) 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 combines both cross-spectral power and coherence is defined as:

\[ CPC(f_j) = \langle \Gamma_j(R,E) \rangle^2 \Lambda_j \]  

(7)
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 hours 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.

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 approximate 8 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 4 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 were distributed in 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 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 a roughly 60 minutes periods, respectively.

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)

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 0-93.5. A strong negative correlation was observed, the Spearman's correlation coefficient is -0.71 and p=6.1*10^{-12}.
### Table 1

The severity distribution of subjects in groups.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Number of subject</th>
<th>Mean AHI/(h)</th>
<th>AHI range/(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>23</td>
<td>0.51</td>
<td>AHI≤5</td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>12.77</td>
<td>5&lt;AHI≤15</td>
</tr>
<tr>
<td>Moderate</td>
<td>12</td>
<td>19.99</td>
<td>15&lt;AHI≤30</td>
</tr>
<tr>
<td>Severe</td>
<td>31</td>
<td>54.92</td>
<td>AHI&gt;30</td>
</tr>
</tbody>
</table>

### Table 2

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

<table>
<thead>
<tr>
<th>Severity</th>
<th>Number of subject</th>
<th>wTVDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>23</td>
<td>0.70±0.12</td>
</tr>
<tr>
<td>Mild &amp; Moderate</td>
<td>3 &amp; 12</td>
<td>0.52±0.17</td>
</tr>
<tr>
<td>Severe</td>
<td>31</td>
<td>0.37±0.17</td>
</tr>
</tbody>
</table>

SD, standard deviation.
Table 3

Comparison of Fourier based CPC and HHT-CPC.

<table>
<thead>
<tr>
<th></th>
<th>Fourier based CPC</th>
<th>HHT-CPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>75.4%</td>
<td>79.1%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>66.8%</td>
<td>73.1%</td>
</tr>
<tr>
<td>Specificity</td>
<td>72.9%</td>
<td>71.2%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>79.4%</td>
<td>80.8%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>58.4%</td>
<td>63.2%</td>
</tr>
</tbody>
</table>
Figure 4

Box plots showing TVDF (Total Vascular Density Fraction) for different severity grades: Normal, Mild & Moderate, and Severe. The plots indicate statistically significant differences with p-values of less than 0.001, marked by four asterisks.
Figure 5

The scatter plot shows a negative correlation between AHI and TVDF, with a correlation coefficient of $r = -0.71$, and a significance level of $p < 0.001$. The data points are distributed along a straight line, indicating a strong linear relationship.