Electrocardiogram-based sleep analysis for sleep apnea screening and diagnosis

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Abstract
Purpose Despite the increasing number of research studies of cardiopulmonary coupling (CPC) analysis, an electrocardiogram-based technique, the use of CPC in underserved population remains underexplored. This study aimed to first evaluate the reliability of CPC analysis for the detection of obstructive sleep apnea (OSA) by comparing with polysomnography (PSG)-derived sleep outcomes.

Methods Two hundred five PSG data (149 males, age 46.8 ± 12.8 years) were used for the evaluation of CPC regarding the detection of OSA. Automated CPC analyses were based on ECG signals only. Respiratory event index (REI) derived from CPC and apnea–hypopnea index (AHI) derived from PSG were compared for agreement tests.

Results CPC-REI positively correlated with PSG-AHI (r = 0.851, p < 0.001). After adjusting for age and gender, CPC-REI and PSG-AHI were still significantly correlated (r = 0.840, p < 0.001). The overall results of sensitivity and specificity of CPC-REI were good.

Conclusion Compared with the gold standard PSG, CPC approach yielded acceptable results among OSA patients. ECG recording can be used for the screening or diagnosis of OSA in the general population.

Keywords Autonomic nervous system · Obstructive sleep apnea · Cardiopulmonary coupling · Electrocardiogram · Polysomnography · Portable monitoring

Introduction
Obstructive sleep apnea (OSA) is a major form of sleep-disordered breathing (SDB) with an estimated prevalence ranging from 9 to 38% among the general population [1]. OSA causes or contributes to hypoxemia, hypercapnia, nocturia, sleep fragmentation, morning headaches, and excessive daytime sleepiness. It also increases the risks of cardiovascular disease, neurocognitive dysfunction, mood or psychiatric disorders, metabolic syndrome or diabetes, gastroesophageal reflux disease, impaired work performance, degraded quality of life, all-cause mortality, or even sudden death. Screening to identify unrecognized OSA followed by appropriate treatment may improve sleep quality and normalize the respiration and oxygen saturation levels to prevent adverse health outcomes.

Although attended in-lab polysomnography (PSG) is the current gold standard diagnostic test for SDB, the high cost, requirement of multiple sensors during an overnight stay in the laboratory, and hours of manual scoring make it difficult to expand services. On the other hand, there is uncertainty about the accuracy or clinical utility of all potential screening tools. There is increasing demand for simple, readily obtained, and cost-effective screening approaches for OSA diagnosis, particularly in China, where OSA and its comorbid are significantly underdiagnosed [2], and the large population overwhelms its limited medical resources.
In recent years, several new techniques have been proposed for OSA screening or diagnosis [3, 4]. Although most of them are portable, they require several sensors for accuracy, or scarify accuracy for easy use. Home screening tools based on a few or single signals include devices using respiratory flow and/or respiratory effort, peripheral arterial tonometry (PAT) or WatchPAT [5–7], pulse transit time (PTT) [8], photoplethysmography (PPG) [9], and actigraphy [10]. Another approach is to detect SDB by altered heart rate dynamics. Since the autonomic nervous system (ANS) dynamics vary according to sleep depth and states [11, 12], ECG-based approaches can be used for sleep studies. However, traditional heart rate variability (HRV) has many limitations [13–19] and does not distinguish the power spectra due to signal non-stationarity or cyclic variation patterns resulting from repeated sleep apneas [20]. In addition, some HRV measures (e.g., rMSSD, pNN50, HF) can be exaggerated due to scanning error (uneven beat detection, missed or misclassified beats) or from irregular HR patterns (erratic rhythm) that are not reflective of better parasympathetic nervous system functioning. Although commonly reported and potentially meaningful, HRV measures need to be interpreted with caution [13]. Many years ago, a cyclic variation of heart rate (CVHR) [21, 22] was proposed as a marker of SDB because apnea/hypopnea episodes result in repeated autonomic arousals associated with cyclic changes in heart rate. More recently, a novel approach, known as cardiopulmonary coupling (CPC), incorporates the respiration coupling concept into HRV analysis [20]; thus, it is able to enhance the potential diagnostic utility by “filtering” out power spectra due to non-respiratory-induced heart rate changes [13].

As the CPC technique was first developed [20] and evaluated by cyclic alternating pattern identified from electroencephalography (EEG), it is often utilized as sleep stability assessment and has been introduced in a series of publications describing potential clinical applications. The agreement in the detection of stable/unstable sleep of CPC sleep states was previously proven by comparing with EEG-based measures [20]. In addition, CPC may also be used for sleep apnea detection and classification, since SDB is associated with predictable characteristics from the ANS dynamics. By now, there are little published studies showing the sensitivity and specificity of CPC in the use of OSA detection. In this study, we aimed to evaluate the reliability of CPC analysis and assess the agreement of the respiratory event index derived from CPC (CPC-REI) and apnea–hypopnea index derived from conventional PSG (PSG-AHI) in the general population to fill the gaps.

Methods

The datasets included in this study were collected previously from clinical studies with separate protocols approved by different Institutional Review Boards (IRB) accordingly, and all experiments were performed in accordance with relevant guidelines and regulations. All the data we used in this secondary analysis study were de-identified. Therefore, additional IRB approval can be waived.

Database for PSG vs CPC comparison

The accuracy of the cardiopulmonary coupling measure was evaluated on data from two sleep centers, Guang’anan Hospital of China Academy of Chinese Medical Sciences and Nanjing First Hospital. All included data were from outpatients referred for evaluation of suspected OSA. One hundred twenty polysomnograms from each hospital were randomly acquired backward from September 2014, by using random number sequence (A001–A120 and B001–B120). The data analyzed in this study were selected using the following criteria: (1) subjects with age over 18 years, (2) standard overnight diagnostic PSG study with sleep time no less than 4 h, and (3) continuous ECG signal can be extracted from the PSG recording for no less than 4 h. Data were excluded for (1) patients with use of ventricular pacing, atrial fibrillation, severe arrhythmia, or severe comorbidities, such as symptomatic coronary heart disease, congestive heart failure, uncontrolled pulmonary disease, wearing pacemaker, or pregnancy and (2) those who are currently under interventions including oxygen therapy or positive airway pressure.

Polysomnography protocols and scoring

All subjects from the two sleep centers underwent attended overnight PSG in the sleep laboratories. Sleep studies were performed using the Compumedics E-Series and Compumedics Siesta (Compumedics Ltd., Abbotsford, Australia), SW-SM2000C (Curative Medical Technology Inc., China), or Respironics Alice 5 Diagnostic Sleep System (Philips Respironics, USA). PSG montages were placed according to the American Academy of Sleep Medicine (AASM) recommendations [23], at least including six EEG channels, two electromyogram channels, a vibration snore sensor, nasal pressure airflow, oronasal thermocouple, submental electromyography, one ECG channel, dual thoracoabdominal respiratory inductance plethysmography belts, finger pulse oximetry, bilateral anterior tibialis electromyography, and body position.

All PSG studies were independently and manually scored by three registered polysomnographic technologists (RPSGT) following the AASM recommendations (AASM Manual for the Scoring of Sleep and Associated Events, version 2.3) [23]. Every PSG recording was scored by two RPSGTs. To reduce the inter-scorer difference, once disagreement occurred between the two RPSGTs, the third RPSGT will involve, and the scoring agreed by two RPSGTs was used as the final result. All the RPSGTs were blinded to any results from...
CPC analyses. After manual PSG scoring and CPC automated analyses were completed, the results were collected by an independent statistician for agreement analysis.

An apneic event was defined when all of the following criteria are met [9, 23]: (a) there is a drop in the peak signal excursion by ≥90% of pre-event baseline using an oronasal thermal sensor; (b) the duration of the ≥90% drop in sensor signal lasts at least the minimum duration as specified by obstructive, mixed, or central apnea duration criteria; and (c) the event meets respiratory effort criteria for obstructive, central, or mixed apnea. Hypopnea is scored if all of the following criteria are met: (a) the peak signal excursions drop by ≥30% of pre-event baseline using nasal pressure or an alternative hypopnea sensor; (b) the duration of the ≥30% drop in signal excursion is ≥10 s; and (c) there is a ≥3% oxygen desaturation from pre-event baseline or the event is associated with an arousal.

PSG-derived apnea–hypopnea index (PSG-AHI) was defined as the total number of apnea and hypopnea events per hour of sleep, and OSA diagnosis is based on the International Classification of Sleep Disorders, Third Edition (ICSD-3) [24]. Mild, moderate, and severe OSA were defined using PSG-AHI cut-off points of 5, 15, and 30, respectively [25].

Cardiopulmonary coupling analysis

The cardiopulmonary coupling analysis technique is based on two features of a continuous ECG signal: heart rate variability and the respiratory modulation of QRS waveform on a beat-to-beat basis. These signals have two basic patterns: a high-frequency component due to physiological sinus arrhythmia that reflects intra-breath fluctuations and a low-frequency component that reflected cyclic variation across multiple breaths. The cross-power and coherence between these two signals can be calculated as a way of quantification of cardiac and respiratory interactions. By analyzing the coupling between heart rate variability (HRV) and ECG-derived respiration (EDR), the CPC algorithm can generate an ECG-derived sleep spectrogram. Physiological sleep states derived from CPC analysis include stable sleep (indicated by high-frequency coupling, or HFC, 0.1–0.4 Hz), unstable or fragmented sleep (indicated by low-frequency coupling, or LFC, 0.01–0.1 Hz), and REM/wakeful states (indicated by very-low-frequency coupling, or VLFC, 0.001–0.01 Hz). Elevated-low frequency coupling (e-LFC), a subset of LFC, reflects predominant obstructive upper airway and sustained strong chemoreflex effects on sleep respiration [26]. When sleep apnea occurs, heart rate typically shows cyclic increases and decreases associated with apneic phase and resumption of breathing. Therefore, respiratory events during sleep can be detected and quantified. CPC-derived respiratory event index (CPC-REI) is defined as the total number of respiratory events per hour of sleep. It is an automated measure detecting the changes in heart rate that occur during apneas, called a cyclic variation of heart rate (CVHR), which consists of bradycardia during apnea followed by abrupt tachycardia near the end of the apnea [27]. CPC-REI was defined as the total number of respiratory events per hour of sleep.

Statistical analyses

Statistical analyses were performed using SPSS version 19.0 (IBM SPSS Statistics, NY, USA), and receiver operating characteristic (ROC) analysis was done using R (R 3.4.0 for Windows). Descriptive statistics were reported as mean ± standard deviation (SD) for normal distributed data or median (interquartile range (IQR)) for skewed data, and number (percentage) for categorical data. Correlations between continuous variables were tested by Pearson correlation. Partial correlation and linear regression models were used to adjust covariates. Comparisons of categorical variables were made using the chi-squared or Fisher’s exact test. Comparisons of continuous variables were assessed by t test or non-parametric test (Mann–Whitney U). Agreement analysis included calculations of sensitivity, specificity, positive and negative likelihood ratios (LR+, LR–), negative predictive value, positive predictive value, accuracy, and Kappa test by SPSS using the PSG-AHI as the referenced standard. Analyses were performed based on the diagnosis by comparing the final OSA severity categorization (normal, mild, moderate, severe) of CPC-REI and PSG-AHI. The Bland–Altman plot and ROC curves were generated to show the agreement between CPC-REI and PSG-AHI. All statistical tests were 2-tailed and a p value <0.05 was considered statistically significant.

Results

Subject characteristics

A total of 205 overnight attended polysomnograms were included in the study. Demographic characters of the included subjects from the test database were shown in Table 1. As for OSA severity indicated by PSG-AHI, there were 49 (23.9%) normal subjects, 29 (14.1%) mild, 33 (16.1%) moderate, and 94 (45.9%) severe OSA among all.

Correlations between PSG-based and CPC-based measures

As shown in Fig. 1a, significant correlations were found between CPC-REI and PSG-AHI (r = 0.851, p < 0.001). After adjusting for age, gender, and TST, CPC-REI and PSG-AHI were still significantly correlated (r = 0.838, p < 0.001). Although the Bland–Altman plots (Fig. 1b) showed that most estimates were within two standard deviations of the mean,
CPC-REI seemed to be overestimating normal and mild individuals.

### Diagnostic accuracy of the CPC measures

Compared with PSG-AHI, the performance of automated CPC analysis regarding the diagnostic accuracy of CPC-REI was evaluated by sensitivity, specificity, positive and negative predictive values, agreement, positive and negative likelihood ratios, and kappa value (as shown in Table 2). By ROC analysis (Fig. 2), the three curves were shown with the AHI cut-off points set at 5, 15, and 30 events/h, and the area under the curve (AUC) is 0.900, 0.939, and 0.935, respectively. According to ROC analysis, the cut-off points of CPC-REI to distinguish none, mild, moderate, and severe sleep apnea were found to be 4.5, 14.2, and 19.2 events/h, respectively. Accordingly, the sensitivities are 88.5%, 81.1%, and 86.2% and specificities are 81.6%, 88.5%, and 84.7%, respectively. Since CPC-REI and PSG-AHI were significantly correlated, and most of the current alternative approaches still take the same cut-off points as PSG-AHI (5, 15, and 30 events/h), we also analyzed the diagnostic accuracy of CPC-REI using the same cut-off points (Table 2). For mild+ (AHI ≥ 5), moderate+ (AHI ≥ 15), and severe (AHI ≥ 30) sleep apnea, CPC presented a sensitivity of 93.8%, 92.7%, and 89.5% and a specificity of 67.8%, 72.2%, and 79.8%, respectively.

### Correlations of OSA severity and PSG- or CPC-derived parameters

The parameters derived from PSG and CPC were included in correlation analyses (Table 3). Weak correlations were found between PSG-AHI and N1, N2, and REM sleep, while no correlations were found between PSG-AHI and N3 sleep or sleep efficiency (Fig. 3). In contrast, significantly strong correlations were found between PSG-AHI and all CPC-derived parameters (e.g., CPC-REI, HFC, LFC, VLFC). PSG-AHI is negatively correlated with HFC ($r = -0.641$, $p < 0.001$; Fig. 3) and VLFC ($r = -0.412$, $p < 0.001$) and positively correlated with LFC ($r = 0.759$, $p < 0.001$; Fig. 3) with an adjustment for age, gender, and total sleep time (TST).

### Discussion

This study included 205 subjects with PSG-based sleep studies. The performance of CPC-REI was compared with PSG-AHI. In moderate and severe OSA patients, CPC-based
diagnostic accuracy was 83.0%, suggesting that the screening results from CPC were consistent with the currently recommended criteria for portable monitoring device to rule-in OSA (AHI ≥ 15 events/h) in clinical settings [3]. In a recently published study with smaller sample size, Hilmisson et al. [28] performed a similar evaluation on the accuracy of CPC and they reported that CPC identified patients with moderate to severe sleep apnea with a sensitivity of 100%, specificity of 81%, agreement of 93%, and kappa of 0.85 compared with manual scoring of AHI.

Our results in the Chinese population are in line with existing evidence from Caucasians to support the reliability of CPC as a screening tool for sleep apnea. For sleep apnea detection, a recent study combined CPC and CVHR in the ambulatory screening for sleep apnea and found a high degree of agreement between the CPC+CVHR algorithms against both the manually rescored AHI (sensitivity 89%, specificity 79%, agreement 85%) and the computerized-scored AHI (sensitivity 93%, specificity 79%, agreement 87%) to identify patients with moderate and severe sleep apnea (AHI > 15) [21]. For sleep quality in sleep apneic patients, Harrington et al. [29] compared PSG- versus CPC-based sleep measures, reported that CPC can be used to study sleep quality in patients with OSA, and distinguish successful and unsuccessful continuous positive airway pressure (CPAP) response. All these pieces of evidence yield comparable or more reliable results to other screening tools.

Beyond the screening of SDB, since the early publication on CPC technique [20], single-channel ECG has been used in many sleep-related studies, including sleep stability and quality in a broad range of conditions (e.g., insomnia [30–32], depression [33–36], fibromyalgia [37], and heritability of abnormalities [38]), subtypes of SDB [39], assessment for

### Table 2 Diagnostic accuracy of CPC-REI compared with PSG-AHI

<table>
<thead>
<tr>
<th>Group-based PSG-AHI</th>
<th>AUC</th>
<th>95% CI</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
<th>LR+</th>
<th>LR−</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI &lt; 5 vs AHI ≥ 5</td>
<td>0.900</td>
<td>0.858–0.943</td>
<td>93.8</td>
<td>67.8</td>
<td>87.8</td>
<td>81.6</td>
<td>86.3</td>
<td>2.91</td>
<td>0.09</td>
<td>0.649</td>
</tr>
<tr>
<td>AHI &lt; 15 vs AHI ≥ 15</td>
<td>0.939</td>
<td>0.909–0.969</td>
<td>92.7</td>
<td>72.2</td>
<td>78.9</td>
<td>89.7</td>
<td>83.0</td>
<td>3.33</td>
<td>0.10</td>
<td>0.663</td>
</tr>
<tr>
<td>AHI &lt; 30 vs AHI ≥ 30</td>
<td>0.935</td>
<td>0.904–0.966</td>
<td>89.5</td>
<td>79.8</td>
<td>72.3</td>
<td>92.8</td>
<td>83.4</td>
<td>4.44</td>
<td>0.13</td>
<td>0.735</td>
</tr>
</tbody>
</table>

AHI, apnea–hypopnea index; AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; LR, likelihood ratio; +, positive; −, negative
treatment options [40, 41], pre- and post-treatment evaluation [42–45].

EEG-based recording allows multiple approaches to analyze the dynamic changes of brain activities during sleep [46–51]. Our results indicate that ECG also provides possibilities to study sleep differently; an ECG-based monitor can be used to screen OSA in the general population. The main advantages of using ECG monitor as an OSA screening tool include the following: (1) It reduces the number of electrodes attached to patients, and it is significantly easier for the patients, as there are only 3 electrodes that need to be attached to a patient for a one-lead ECG; (2) The algorithm is completely automated, no time-consuming manual scoring is needed, which also avoids inter-scorer discrepancies; and (3) The

<table>
<thead>
<tr>
<th></th>
<th>PSG-AHI</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSG-AHI</td>
<td>Unadjusted</td>
<td>1</td>
<td>0.222* (0.001)</td>
<td>−0.257* (&lt;0.001)</td>
<td>0.074 (0.291)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1</td>
<td>0.196* (0.005)</td>
<td>−0.235* (0.001)</td>
<td>0.104 (0.139)</td>
</tr>
<tr>
<td>CPC-REI</td>
<td>Unadjusted</td>
<td>0.851* (&lt;0.001)</td>
<td>0.142* (0.042)</td>
<td>−0.195* (0.005)</td>
<td>0.129 (0.065)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>0.838* (&lt;0.001)</td>
<td>0.103 (0.143)</td>
<td>−0.167* (0.017)</td>
<td>0.167* (0.018)</td>
</tr>
<tr>
<td>HFC</td>
<td>Unadjusted</td>
<td>−0.667* (&lt;0.001)</td>
<td>−0.192* (0.006)</td>
<td>0.265* (&lt;0.001)</td>
<td>−0.062 (0.381)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>−0.642* (&lt;0.001)</td>
<td>−0.135 (0.056)</td>
<td>0.236* (0.001)</td>
<td>−0.106 (0.133)</td>
</tr>
<tr>
<td>LFC</td>
<td>Unadjusted</td>
<td>0.777* (&lt;0.001)</td>
<td>0.214* (0.002)</td>
<td>−0.253* (&lt;0.001)</td>
<td>0.075 (0.287)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>0.759* (&lt;0.001)</td>
<td>0.147* (0.037)</td>
<td>−0.218* (0.002)</td>
<td>0.1328 (0.060)</td>
</tr>
<tr>
<td>VLFC</td>
<td>Unadjusted</td>
<td>−0.454* (&lt;0.001)</td>
<td>−0.120 (0.088)</td>
<td>0.043 (0.544)</td>
<td>−0.042 (0.550)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>−0.410* (&lt;0.001)</td>
<td>−0.065 (0.355)</td>
<td>−0.002 (0.975)</td>
<td>−0.079 (0.264)</td>
</tr>
</tbody>
</table>

*PSG-AHI, apnea-hypopnea index derived from polysomnogram; CPC-REI, respiratory event index derived from cardiopulmonary coupling analysis; HFC, high-frequency coupling; LFC, low-frequency coupling; VLFC, very-low-frequency coupling

Data reported in this table are results from correlation analyses, presented as $r (p)$, where $r$ is the Pearson correlation coefficient. Adjusted partial correlations were analyzed by controlling for age, gender, and total sleep time. *Statistical significance when $p < 0.05$

Fig. 3 Scatter plots to show correlations between AHI and sleep parameters derived from PSG and CPC
CPC technique can also provide valuable measures (e.g., HFC, LFC) that are related to sleep structure and quality. PSG scoring rules require that the change of breathing has to meet the criteria (e.g., length and amplitude) to be marked as a respiratory event. By CPC techniques, when the power on the e-LFC bands was detected, a respiratory event was automatically marked. Some events with breathing disturbance that barely meet the “at least 10-second” rule may be sensitively detected by CPC, leading to a possible overestimation by CPC-REI. In addition, we also noticed the lack of correlation between CPC-HFC and N3 sleep, which may be because effective sleep is restorative and spans both conventional SWS and periods of stage N2 [52]. Respiratory effort-related arousal (RERA) may induce LFC/e-LFC and can cause a discrepancy in such analyses. Further investigations on the correlation between RERA and CPC outcomes are encouraged.

Evidence from systematic reviews shows that sensitivities decreased and specificities increased for detecting moderate or greater OSA (AHI ≥ 15) or severe OSA (AHI ≥ 30). The ranges of sensitivity and specificity reported across studies for type IV monitors were wide [9, 53]. To meet the demand of home sleep testings, other alternative approaches are currently available with a recording of different physiological signals. Actigraphy may assist to distinguish wake and sleep during the night; thus, the combination of actigraphy and respiratory recording may allow a more accurate AHI or REI. The use of oximetry enables proper risk stratification and can improve the diagnostic accuracy and provide complementary values in clinical interventions [9].

A preferred approach for sleep evaluation is that the measures can objectively illustrate how abnormalities impact sleep quality or sleep stability. For example, sleep apnea is known to worsen deep sleep and sleep continuity. However, our results showed that PSG-AHI and slow wave sleep (i.e., N3 stage) are not correlated. This result is in agreement with the criticism that conventional sleep stages often cannot reflect disease severity [56–59]. In contrast, significant correlations have been found between PSG-AHI and HFC, LFC, and VLFC derived from CPC, suggesting that a higher AHI negatively impact stable sleep or deep sleep and positively increase unstable sleep, which is in line with the existing findings from the clinical practice. Implying that CPC measures, which focus on physiologic aspects of sleep instead of EEG morphology, can bring valuable insight into a quantitative description of sleep quality.

SDB was linked to a higher prevalence of metabolic syndrome [60] and abnormal blood pressure patterns [2] in the general population. Therefore, large-scale screening of high-risk population to identify subjects with SDB for appropriate management is warranted [2, 60]. Previous studies have found ECG-based approach to be cost-efficient and may provide clinical insight into abnormal sleep, because it can be used in various populations, illustrate sleep states (stable or unstable sleep), and provide reliable estimation of SDB [61]. Our findings suggest that CPC offers opportunity for OSA screening or diagnosis to be simple, cost-effective, and less resource-intensive and can also be potentially for monitoring the efficacy of intervention.

While we found a significant association between CPC-REI and PSG-AHI, we were unable to evaluate the compliance of ECG monitoring at home settings. However, previous studies using ECG at home may support that CPC techniques can be used for home monitoring. The predicting value in OSA screening is worth further studies. Second, in our analyses, only CPC-REI measures with PSG outcomes were compared. Future comparison studies are encouraged to include different portable approaches for the use of home testing. A combination of CPC with other signal-based measures may further improve the accuracy of home diagnosis, and such studies are encouraged given the increasing needs for SDB screening. For example, there are many situations when knowing the oxygenation profile matters, including for severity, which the ECG technique is blind to, including deep REM desaturation and hypoventilation. When ECG recording is combined with actigraphy, the accuracy of sleep period estimates may be improved. Third, the exclusion of subjects with comorbidities (e.g., symptomatic coronary heart disease, congestive heart failure, uncontrolled pulmonary disease) may limit the generalizability of this approach to the general population. CPC techniques are not applicable for patients with cardiac arrhythmia, especially atrial fibrillation and continuous bigeminy, and for patients using some medications like beta blockers. Future studies are encouraged to investigate whether this technique is also applicable across patients with these types of common comorbidities or conditions. In addition, severely fragmented sleep from other causes may cause an apnea-like signature on the CPC spectrum. Proper context (e.g., snoring, sleepiness) should be considered for clinical differential diagnosis.

**Conclusion**

The performance of CPC techniques with an automated estimation of REI was shown with reliable diagnostic values that are consistent with standard PSG measures. CPC-REI has significant correlation and good agreement with PSG-AHI, and the sensitivity, specificity, and positive and negative predictive values indicated good accuracy on the detection of respiratory events from ECG recordings. The use of ECG signals allows the possibilities for simple, less resource-intensive and cost-effective methods for OSA screening or treatment follow-ups.
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Compliance with ethical standards

Conflict of interest Chung-Kang Peng is a co-patent holder for the ECG-based analytic technique for phenotyping sleep and sleep apnea, known as cardiac pulmonary coupling (CPC) analysis. He also receives royalties from a license issued by Beth Israel Deaconess Medical Center to MyCardio, LLC. The other authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Ethical approval and informed consent The datasets included in this study were collected previously from clinical studies with separate Institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Therefore, additional IRB approval was waived.

Abbreviations AASM, American Academy of Sleep Medicine; AHI, apnea–hypopnea index; AUC, area under the curve; CPC, cardiopulmonary coupling; eLFC, elevated low-frequency coupling; ECG, electrocardiogram; EEG, electroencephalography; FDA, Food and Drug Administration; HFC, high-frequency coupling; HRV, heart-rate variability; IRB, Institutional Review Board; LFC, low-frequency coupling; LR, likelihood ratio; NPV, negative predictive value; OCST, out of center sleep testing; OSA, obstructive sleep apnea; PPV, positive predictive value; PSG, polysomnography; REI, respiratory event index; ROC, receiver operating characteristic; RPSGT, registered polysomnographic technologists; SD, standard deviation; SDB, sleep-disordered breathing; TIB, time in bed; TST, total sleep time; VLFC, very-low-frequency coupling

References


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Comment

With the caveats of limitations, cardiopulmonary coupling patterns may be a useful approach to screen for apnea in high risk populations. However, the addition of oximetry to the assessment would be complementary - thus those with mildly hypoxic disease will be detected, while those with severe hypoxia can be risk stratified.

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MA, USA