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METHODS • ORIGINAL ARTICLE

Validation of a portable monitoring device for the diagnosis of obstructive sleep apnea: electrocardiogram-based cardiopulmonary coupling

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Abstract

Purpose We aimed to evaluate the validity of the cardiopulmonary coupling (CPC) device, a limited-channel portable monitoring device for obstructive sleep apnea (OSA) screening in one single-center cohort, in particular in those with some cardiovascular diseases since the cardiopulmonary coupling might be different from those without.

Methods Consecutive patients referred to the sleep medical center for assessment of possible OSA were enrolled in this study. Patients were examined with standard polysomnography (PSG) and CPC evaluation simultaneously. The results of the two examinations were compared in all subjects and in those with or without cardiovascular abnormalities.

Results A total of 179 subjects suspected with OSA were finally analyzed. According to OSA severity degree based on AHI, the area under ROC curve for the CPC device in the whole cohort patients was 0.79 (mild), 0.79 (moderate), and 0.86 (severe OSA), respectively (all $p < 0.001$). For patients with cardiovascular disease with different OSA severity, the area under the ROC curve was 0.86 (mild), 0.73 (moderate), and 0.83 (severe OSA), respectively (all $p < 0.0001$), and 0.74 (mild), 0.85 (moderate), and 0.91 (severe OSA), respectively in patients without cardiovascular disease (all $p < 0.0001$).

Conclusions The overall performance of CPC technique was acceptable to assess OSA in subjects with clinical suspicion of OSA, and thus it might act as a fast tool to screen OSA patients. However, the sensitivity of CPC technology for patients with cardiovascular disease was relatively insufficient. Therefore, CPC technology should be carefully interpreted in OSA screening in those with cardiovascular disease.

Keywords Cardiopulmonary coupling analysis · Validation · Obstructive sleep apnea · Cardiovascular disease

Introduction

The prevalence of obstructive sleep apnea (OSA) is approximately 24% for men and 9% for women in the general population [1]. As a public health problem, it is likely to increase dramatically given the ongoing obesity epidemic. In view of the close relationship of OSA with cardiovascular disease [2, 3], cerebrovascular events [4], metabolic disorder [5], and motor vehicle accidents [6], it is of particular concern. In addition, patients with untreated OSA have a higher risk of all-cause mortality rates independent of other risk factors and use more healthcare resources for downstream treatment than subjects without OSA [7, 8]. Timely and accurate diagnosis is paramount for the prevention and management of OSA; however, about 82% of men and 93% of women with moderate to severe sleep apnea syndrome remain undiagnosed and untreated [9]. One of the underlying reasons is that the confirmation of OSA depends on polysomnography (PSG), the gold standard of OSA diagnosis [10]. Overnight in-laboratory PSG monitoring is technically complex, labor and time intensive, and expensive, which leads to long waiting lists for patients

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The work was performed in Beijing Anzhen Hospital, Capital Medical University.

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and limited availability in many areas. In contrast, portable monitoring device can save labor resources, reduce cost, be deployed quickly, and be recorded in a natural sleep environment. For these reasons, many laboratories have incorporated portable monitoring device in order to facilitate the diagnosis of OSA.

Recently, the electrocardiogram (ECG)–based cardiopulmonary coupling (CPC) technique has been introduced as a new ambulatory methodology for the evaluation of OSA and sleep quality [11–13]. It involves extracting and mathematically combining heart rate variability and ECG-derived respiration (EDR) signal, and calculating the coupling degree of these two signals to assess sleep stability and the presence of sleep-disordered breathing [14]. However, acceptance of this emerging new technology has been impeded by the lack of adequate evidence about its diagnostic accuracy. Magnusdottir et al. [15] compared a simultaneous CPC recording and PSG in 47 adults (body mass index [BMI], 33.9 ± 9.2 kg/m^2). For an AHI greater than 15 events/h, the sensitivity, specificity, and agreement of CPC were 89%, 79%, and 85%, respectively. But this study was limited by the small sample size and relatively obese patients. We therefore conducted the current study to validate the CPC technique with more subjects and to evaluate its performance in less obese Asian patients. Moreover, heart rate variability decreases in cardiovascular disease which may impact its performance [16]. Therefore, another purpose was to assess the accuracy and effectiveness of CPC for OSA screening in patients with cardiovascular abnormalities.

Methods

Participants

Consecutive samples of patients referred to the sleep medical center for evaluation of OSA were recruited in this study. The inclusion criteria were ≥ 18 years and consented to have simultaneous recordings of PSG and CPC. The exclusion criteria included central sleep apnea, obesity hypoventilation syndrome, periodic limb movement disorder, restless legs syndrome, narcolepsy, insomnia, or rapid eye movement behavior disorder; a history of chronic obstructive pulmonary disease, arrhythmia or heart failure; and shift work. OSA patients receiving continuous positive airway pressure (CPAP), surgical, or oxygen therapy were also excluded. BMI was calculated as body weight divided by the square of the participant's height. Obesity was defined as a BMI ≥ 25 kg/m^2. Hypertension was defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg or patients having antihypertensive medication. Valvular heart disease was diagnosed by transthoracic echocardiography (VIVID E9, GE, USA) or based on the patient's history. Coronary artery disease and old myocardial infarction were also based on the patient's medical history.

This study was approved by the local institutional review board of Beijing Anzhen Hospital (Capital Medical University, Beijing, China) and was registered in the Chinese Clinical Trial Register (ChiCTR-ROC-17011027). All subjects were required to provide informed consent.

Measurements

PSG

A full-night laboratory-based PSG (Grael, Compumedics, Australia) was conducted according to the recommendations of the American Academy of Sleep Medicine (AASM) [17]. PSG montage comprised frontal, central, and occipital electroencephalogram (EEG), bilateral electro-oculogram (EOG), chin muscle electromyogram (EMG), electrocardiogram (ECG), nasal airflow using a pressure transducer, oral airflow by a thermistor, thoracic-abdominal effort, snoring, body position, bilateral leg movements, and oxygen saturation by a finger-pulse oximeter. Two experienced sleep technicians who were blinded to the results of CPC manually scored the PSG data with dedicated software profusionpsg4 according to the AASM 2012 scoring criteria [18]. Apnea was scored when there was ≥ 90% drop in airflow from pre-event baseline for ≥ 10 s on the oronasal thermal sensor or an alternative apnea sensor. Obstructive apnea was defined as an apnea event with continued respiratory effort. Hypopnea was defined as ≥ 30% drop in airflow from pre-event baseline for ≥ 10 s in association with either ≥ 3% arterial oxygen desaturation or an arousal. AHI was calculated as total numbers of apnea and hypopnea present in the PSG per hour of sleep. The severity of OSA can be categorized as mild, moderate, or severe based on AHI(5~15, mild; 15~30, moderate; ≥ 30, severe) [19].

CPC analysis

CPC (Nanjing Fengsheng Yongkang Software Technology Co., Ltd., Nanjing, China) evaluation was undertaken during the PSG recording. The CPC is obtained solely from a continuous single-lead ECG signal using the Fourier transform to analyze heart rate variability and EDR signal. The connected software can calculate the cross-power and coherence between two signals to assess sleep stability and the presence of sleep-disordered breathing [14]. Details of the original algorithm were described as reported [14, 20]. Specific classification of cardiopulmonary coupling degree was as follows: high-frequency coupling (HFC, frequency range of 0.1 to 0.4 Hz), low-frequency coupling (LFC, frequency range of 0.01 to 0.1 Hz), elevated low-frequency coupling (e-LFC, a subset of LFC), and very-low-frequency coupling (VLFC, frequency range of 0.001 to 0.01 Hz). Thomas et al.

demonstrated that e-LFC coincided with periods of apnea/hypopnea [20] and they speculated AHI could be calculated by e-LFC in a CPC analysis.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range) and categorical variables were described as frequencies (percentage), as appropriate. To evaluate the validity of CPC technique for OSA screening, the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratios, and negative likelihood ratios were calculated at PSG-AHI cutoff values of 5, 15, and 30 events/h. The receiver operating characteristic (ROC) curves were also constructed for the same PSG-AHI cutoff values as stated above. To evaluate the agreement between the AHI obtained from PSG and CPC, the intraclass correlation (ICC) and Bland-Altman agreement plots were performed. Subgroup analyses were done to evaluate the impact of cardiovascular conditions on the diagnostic accuracy of CPC technique. Data was analyzed using IBM SPSS statistics (version 19, Chicago, IL). A p value < 0.05 was considered statistically significant.

Results

Of 231 participants referred to the sleep medical center, 179 subjects completed the protocol and their records were considered valid. Detailed flow chart of the study design is shown in Fig. 1.

Subject characteristics

Most of the patients were males ($n = 152$, 84.9%), the mean age was 44.9 years (range 21–72 years), the mean BMI was 28.0 kg/m^2, and the percentage of obesity was 45.8% (82/179). According to PSG, the prevalence of mild, moderate, and severe OSA was 91.6% ($n = 164$), 64.8% ($n = 117$), and 50.3% ($n = 90$), respectively. By questionnaire assessment, the median Epworth Sleepiness Scale (ESS) score was 12.0. The detailed basic demographics, clinical characteristics, sleep monitoring data are summarized in Table 1. In our cohort, 105 (58.7%) patients had more than one of the following cardiovascular disease: hypertension ($n = 97$), coronary artery disease ($n = 41$), valvular heart disease ($n = 14$), and old myocardial infarction ($n = 2$). The prevalence of mild, moderate, and severe OSA in those patients was 96.2% ($n = 101$), 72.4% ($n = 76$), and 53.3% ($n = 56$), respectively.

Sleep study results and diagnostic accuracy of CPC

The median AHI analyzed by CPC was lower than that of PSG, 30.1 (interquartile range of 11.4 to 49.9) versus 15.9 (interquartile range of 3.9 to 34.3). The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and best cutoff value of CPC at different AHI-PSG cutoff values are presented in Table 2**.** We found that the diagnostic sensitivity increased substantially with AHI-PSG while specificity was somewhat reduced in all patients in Table 2. The best cutoff values for predicting AHI-PSG ≥ 5, AHI-PSG ≥ 15, and AHI-PSG ≥ 30 in all patients were all 9.4 for AHI-CPC. The best cutoff values for predicting AHI-PSG ≥ 5, AHI-PSG ≥ 15, and AHI-PSG ≥ 30 in patients combined with cardiovascular disease were 3, 9.9, and 9.9 by AHI-CPC, respectively. The best

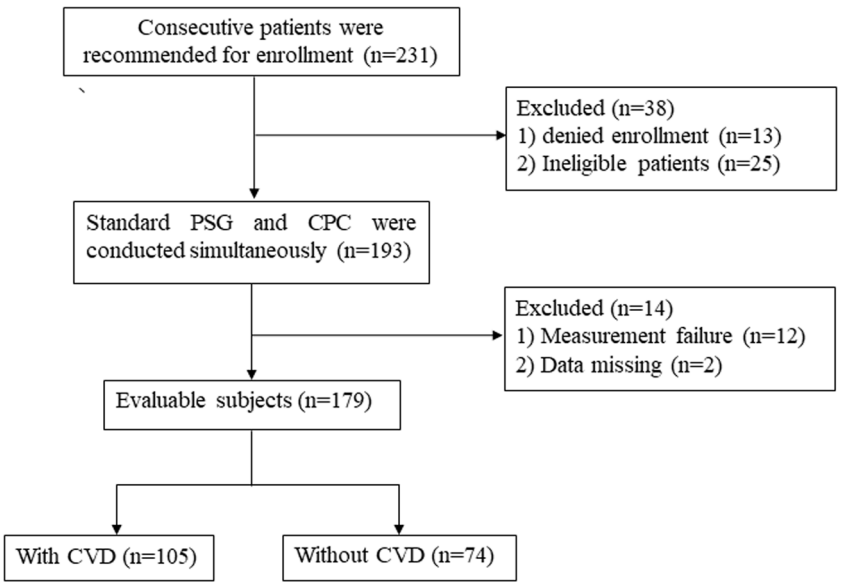

Fig. 1 Flow chart of the study design

Table 1 Characteristics of the study's cohort

Variable	All ($n = 179$)	With CVD ($n = 105$)	Without CVD ($n = 74$)
Demographic information			
Age, years	44.9 ± 11.8	48.0 ± 11.3	40.4 ± 11.2
Male, *n* (%)	152 (84.9)	92 (87.6)	60 (81.1)
Height, cm	171.3 ± 7.2	170.9 ± 6.7	171.9 ± 7.8
Weight, cm	82.1 ± 14.8	82.3 ± 15.5	81.7 ± 13.9
BMI, kg/m^2	28.0 ± 4.1	28.4 ± 3.9	27.6 ± 4.5
Neck circumference, cm	40.7 ± 3.2	41.1 ± 3.1	40.2 ± 3.3
Systolic blood pressure, mm Hg	132 ± 14	135 ± 14	127 ± 12
Diastolic blood pressure, mm Hg	81 ± 10	82 ± 10	80 ± 7
Sleep parameters			
ESS score	12.0 (8.0, 15.0)	12.0 (8.0, 15.0)	10.0 (6.0, 14.0)
Sleep efficiency, (%)	76.5 ± 13.2	76.6 ± 11.9	76.2 ± 15.0
AHI (/h)	30.1 (11.4, 49.9)	32.2 (12.2, 48.9)	20.7 (7.6, 50.4)
e-LFC(/h)	15.9 (3.9, 34.3)	17.7 (4.9, 37.6)	13.0 (1.9, 29.6)
Minimum oxygen saturation (%)	83.0 (76.0, 89.0)	81.0 (74.0, 88.0)	85.5 (77.0, 89.3)
Distribution based on OSA severity			
Mild, *n* (%)	164 (91.6)	101 (96.2)	63 (85.1)
Moderate, *n* (%)	116 (64.8)	76 (72.4)	40 (54.1)
Severe, *n* (%)	90 (50.3)	56 (53.3)	34 (45.9)

Data are presented as mean ± standard deviation or median (interquartile range). *BMI*, body mass index; *ESS*, Epworth Sleepiness Scale; *AHI*, apnea-hypopnea index; *e-LFC*, elevated low-frequency coupling; *CVD*, cardiovascular disease

cutoff values for predicting AHI-PSG ≥ 5, AHI-PSG ≥ 15, and AHI-PSG ≥ 30 in patients without cardiovascular disease were 9.4, 15.8, and 9.4 for AHI-CPC, respectively. ROC curve analysis was used to evaluate the accuracy of CPC technique in diagnosing OSA compared with PSG. Figure 2 shows the ROC curve reflecting the diagnostic capability of CPC technique in the entire cohort when the threshold of AHI-PSG was set at 5, 15, and 30 events/h, respectively. Subgroup analyses in patients with cardiovascular abnormalities are shown in Table 2 and Fig. 3, and the data for the patients without cardiovascular conditions are shown in Table 2 and Fig. 4.

Table 2 Sensitivity, specificity, PPV, NPV, +LR, −LR, and Youden index of CPC analysis according to different AHI-PSG cutoff values

Variable	Sen	95% CI		Spec	95% CI		PPV	NPV	+LR	−LR	Best cutoff value
		LL	UL		LL	UL					
The entire cohort ($n = 179$)											
AHI ≥ 5 ($n = 164$)	0.74	0.68	0.81	0.67	0.43	0.91	0.96	0.19	2.23	0.38	9.4
AHI ≥ 15 ($n = 116$)	0.75	0.64	0.85	0.66	0.58	0.75	0.55	0.83	2.22	0.38	9.4
AHI ≥ 30 ($n = 90$)	0.96	0.91	1.00	0.49	0.39	0.59	0.65	0.92	1.87	1.09	9.4
Patients with cardiovascular disease ($n = 105$)											
AHI ≥ 5 ($n = 101$)	0.76	0.68	0.84	1.00	1.00	1.00	1.00	0.14	–	0.24	3.0
AHI ≥ 15 ($n = 76$)	0.63	0.52	0.74	0.69	0.52	0.86	0.84	0.42	2.04	0.53	9.9
AHI ≥ 30 ($n = 56$)	0.50	0.37	0.63	0.92	0.84	1.00	0.88	0.62	6.13	0.54	9.9
Patients without cardiovascular disease ($n = 74$)											
AHI ≥ 5 ($n = 63$)	0.71	0.60	0.83	0.54	0.25	0.84	0.90	0.25	1.57	0.52	9.4
AHI ≥ 15 ($n = 40$)	0.73	0.59	0.86	0.79	0.66	0.93	0.68	0.93	3.52	0.35	15.8
AHI ≥ 30 ($n = 34$)	0.47	0.30	0.64	1.00	1.00	1.00	1.00	0.69	–	0.53	9.4

Sen, sensitivity; *Spec*, specificity; *CI*, confidence interval; *LL*, lower limit; *UL*, upper limit; *PPV*, positive predictive value; *NPV*, negative predictive value; *+LR*, positive likelihood ratio; *−LR*, negative likelihood ratio; *AHI*, apnea-hypopnea index

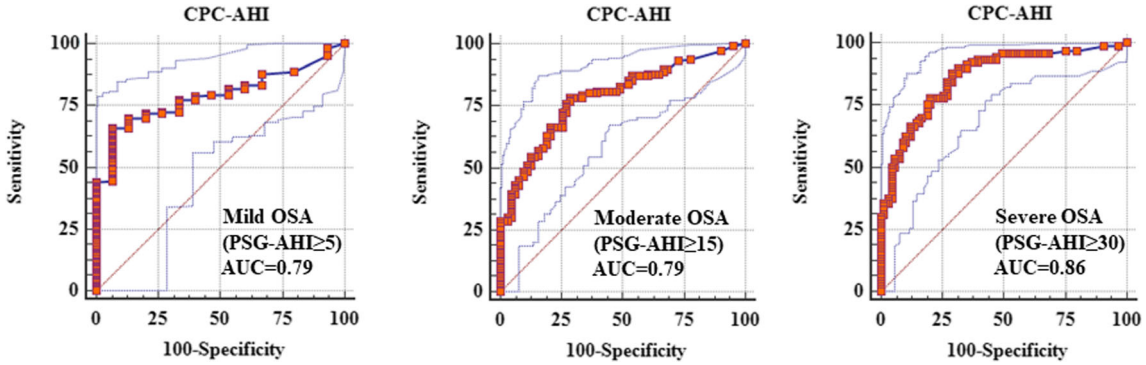

Fig. 2 ROC curves of different AHI-PSG cutoff values for the entire cohort (all $p < 0.0001$). AUC, area under the ROC curve

Agreement between CPC and PSG

The Bland-Altman agreement plots for AHI measured by PSG and CPC in the whole group are presented in Fig. 5a, where the mean difference was − 11.5 events/h and 92.7% (166/179) scatters were in the limits of agreement. The Bland-Altman agreement plots for patients with cardiovascular conditions are shown in Fig. 5b, where the mean difference was − 11.5 events/h and 92.4% (97/105) scatters were in the limits of agreement. For patients without cardiovascular conditions, the mean difference was − 11.4 events/h and 93.2% (69/74) scatters were in the limits of agreement (Fig. 5c). The ICC for AHI between CPC and PSG was 0.68 (95% CI, 0.59–0.75).

Discussion

This study evaluated the accuracy of CPC analysis for screening OSA in a sleep clinic population, especially those with cardiovascular diseases. We found that this device had a moderate sensitivity for mild OSA diagnosis, with higher sensitivity for severe OSA. Thus, the overall performance of the CPC technique is acceptable for OSA screening, especially for those with severe OSA.

To our knowledge, this is the first attempt to validate the CPC technique against PSG in OSA patients with cardiovascular disease. Of note, the sensitivity of the CPC technique decreased when OSA severity increased. For mild, moderate, and severe OSA, the sensitivities were 0.76, 0.63, and 0.50, respectively. One possible explanation is that patients with higher AHI may have more serious cardiovascular disease, which will cause reduced heart rate variability and thus affect diagnostic accuracy [16, 21]. Hence, in OSA patients with suspected cardiovascular diseases, the CPC technique may be more appropriate in mild OSA. For severe OSA patients combined with cardiovascular diseases, CPC should be used with careful interpretation.

In patients without cardiovascular disease, the sensitivities for mild, moderate, and severe OSA were 0.71, 0.73, and 0.47, respectively. It is obvious that CPC may be more appropriate for screening mild to moderate OSA in those patients. In the group-by-group analysis, the diagnostic accuracy of the CPC technique for moderate to severe OSA was highest in patients without cardiovascular disease and lowest in patients with cardiovascular disease. Interestingly, in mild OSA patients, the aforementioned parameters were lowest in patients without cardiovascular disease and highest in patients with cardiovascular disease.

A similar study was done by Magnusdottir et al. [15] using the CPC technique. One potential limitation of their study is the small sample size which is less than 1/3 of our sample size. The main conclusion of their study was CPC + cyclic variation of heart rate could perform accurately to identify the presence of moderate to severe OSA. This is somewhat better than our results

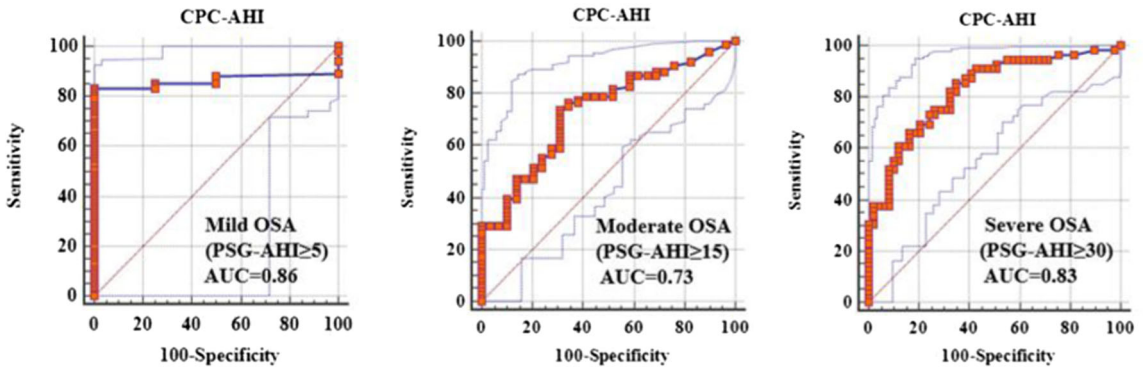

Fig. 3 ROC curves of different AHI-PSG cutoff values for patients with cardiovascular disease (all $p < 0.0001$). AUC, area under the ROC curve

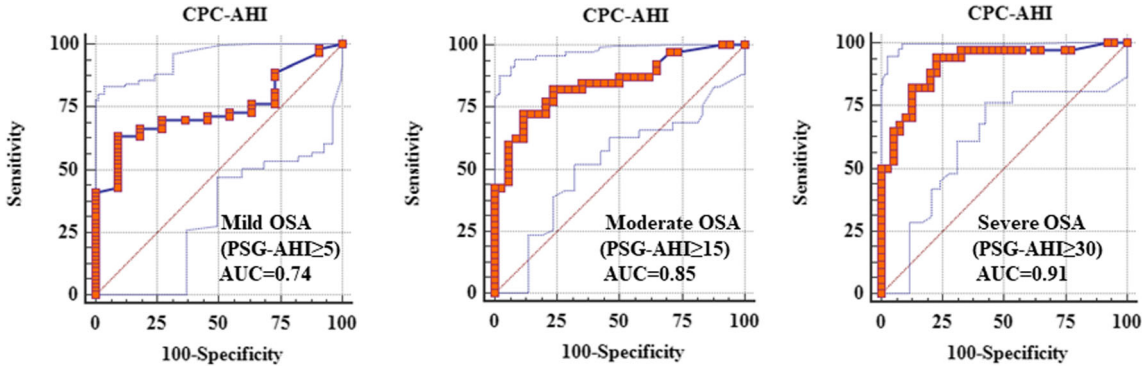

Fig. 4 ROC curves of different AHI-PSG cutoff values for patients without cardiovascular disease (all $p < 0.0001$). AUC, area under the ROC curve

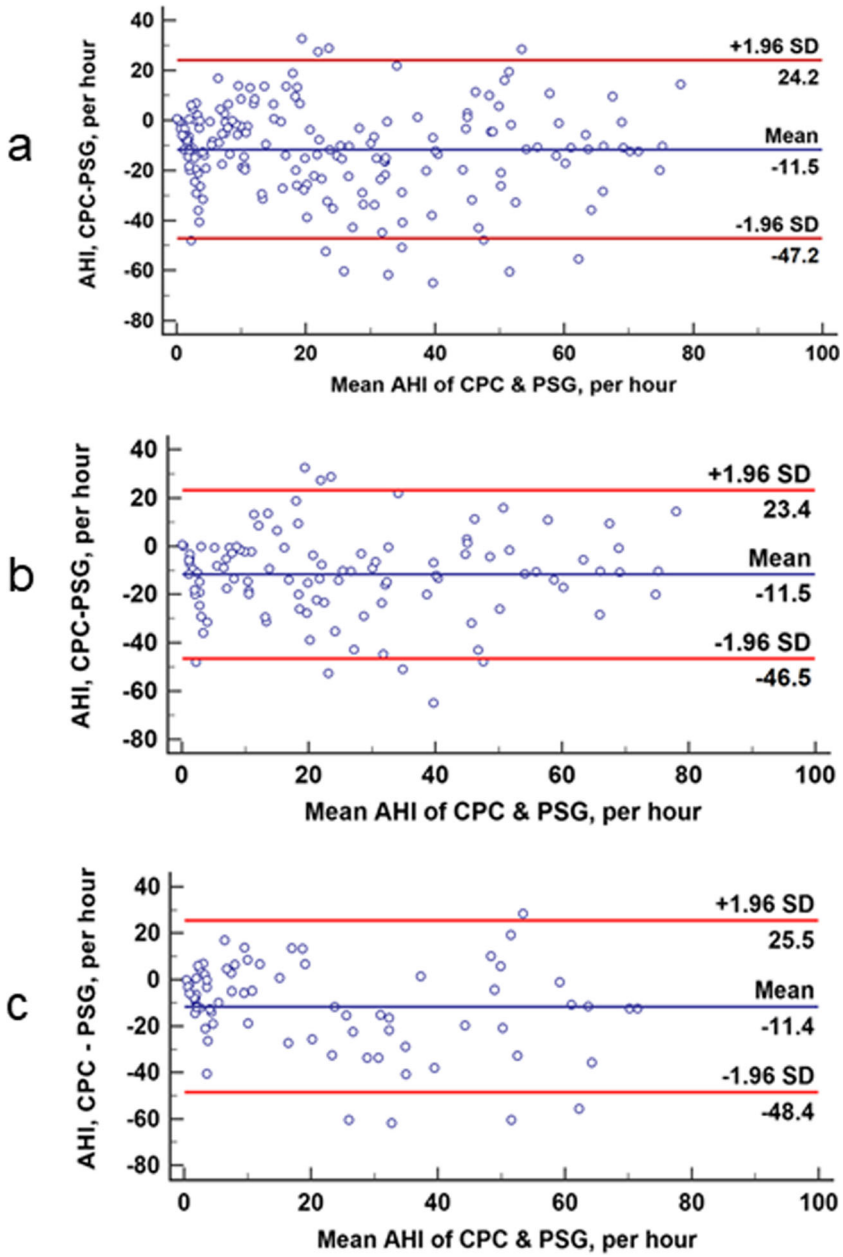

Fig. 5 Bland-Altman agreement plots for the AHI measured by PSG and CPC. **a** In the entire patients' cohort. **b** In patients with cardiovascular disease. **c** In patients without cardiovascular disease

with higher sensitivity and specificity achieved by CPC analysis. It might be due to our different study population, less obese Asian patients ($p < 0.001$). Moreover, > 50% in this study suffered from cardiovascular disease. The heart rate variability in these patients had an impact on diagnostic accuracy [22, 23]. In addition, the proportion of female of the present study was quite low (27/179, 15.1% versus 33/47, 70.2%, $p < 0.001$) and estrogen can protect the cardiovascular endothelial function [24]. However, this reflects the real-world status in China for OSA patients of female and male groups seeking medical support. It might be due to the lifestyle of male patients such as alcohol and diet. Therefore, the utility of CPC technique for female patients with cardiovascular disease warrants further study.

A major strength of our study was a relatively big sample size, which confers sufficient statistical power. In addition, simultaneous recording of PSG and CPC was achieved in patients in the sleep center, a quiet and undisturbed environment, which excluded the influence of different night effects. We also performed subgroup analyses to evaluate the impact of cardiovascular conditions on the diagnostic accuracy of CPC technique.

Study limitations

There were several limitations in this study that merit discussion. Firstly, the influence of night-to-night variability on CPC diagnostic accuracy remains unknown because only one CPC monitoring was done for each patient. Secondly, the first night effect of PSG itself may have a detrimental impact on the diagnostic accuracy of CPC, because the patients wear many electrodes in a different environment than the usual one, which may result in worse sleep quality. Therefore, we will conduct CPC monitoring in the home environment to compare the results with the in-laboratory PSG results in our future study. Thirdly, the presence of coronary artery disease and old myocardial infarction was based on the patient's medical history instead of coronary angiography, giving a relatively subjective result. In addition, recent studies have indicated that the lowest SO_2 or hypoxic burden is more important than AHI in predicting the risk of cardiovascular disease [25, 26], and thus the addition of pulse oximetry to CPC will be studied in a further study.

Conclusions

In summary, the overall performance of a CPC technique was acceptable to detect OSA in subjects with high clinical suspicion, and it might act as a fast tool to screen for OSA. As it is a user-friendly and portable device, it is both a time- and expense-saving tool compared with PSG examination; however, for patients with cardiovascular disease who are unable to perform PSG, CPC technology should be used with careful interpretation.

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Authors' contribution Conception and design: Mi Lu, Fang Fang, and Yongxiang Wei. Collection and assembly of data: Mi Lu, Qianqian Wang, and Chenyao Ma. Data analysis and interpretation: Mi Lu and Fang Fang. PSG data scoring: Fei Xie, Lei Xiao, Hu Liu, Xiaojun Zhan, and Hongyan Liu. Manuscript writing: Mi Lu, Fang Fang, and John E. Sanderson. Revised the language/article: Mi Lu, Fang Fang, John E. Sanderson, and Xiaojun Zhan. Final approval of manuscript: all authors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This study was approved by the local institutional review board of Beijing Anzhen Hospital (Capital Medical University, Beijing, China). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Abbreviations AASM, American Academy of Sleep Medicine; AHI, apnea-hypopnea index; AUC, area under the ROC curve; BMI, body mass index; CI, confidence interval; CPAP, continuous positive airway pressure; CPC, cardiopulmonary coupling; ECG, electrocardiogram; EDR, ECG-derived respiration; EEG, electroencephalogram; EMG, electromyogram; e-LFC, elevated low-frequency coupling; EOG, electrooculogram; ESS, Epworth Sleepiness Scale; HFC, high-frequency coupling; ICC, intraclass correlation; LFC, low-frequency coupling; LL, lower limit; +LR, positive likelihood ratio; −LR, negative likelihood ratio; NPV, negative predictive value; OSA, obstructive sleep apnea; PPV, positive predictive value; PSG, polysomnography; ROC, receiver operating characteristics; SD, standard deviation; SE, sleep efficiency; Sen, sensitivity; Spec, specificity; TST, total sleep time; UL, upper limit; VLFC, very-low-frequency coupling

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