Cardiopulmonary Coupling

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Abstract

Cardiopulmonary coupling (CPC) is a technique that generates sleep spectrogram by calculating the cross-spectral power and coherence of heart rate variability and respiratory tidal volume fluctuations. There are several forms of CPC in the sleep spectrogram, which may provide information about normal sleep physiology and pathological sleep states. Since CPC can be calculated from any signal recording containing heart rate and respiration information, such as photoplethysmography (PPG) or blood pressure, it can be widely used in various applications, including wearables and non-contact devices. When derived from PPG, an automatic apnea-hypopnea index can be calculated from CPC-oximetry as PPG can be obtained from oximetry alone. CPC-based sleep profiling reveals the effects of stable and unstable sleep on sleep apnea, insomnia, cardiovascular regulation, and metabolic disorders. Here, we introduce, with examples, the current knowledge and understanding of the CPC technique, especially the physiological basis, analytical methods, and its clinical applications.

Keywords

Autonomic nervous system · Cardiopulmonary coupling · Heart rate variability · Sleep apnea · Sleep spectrogram · Insomnia

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11.1 Introduction

Everyone sleeps and sleep is essential for a variety of biological functions. However, it is estimated that nearly 2 billion people worldwide suffer from one or both of the two most common sleep disorders – sleep apnea (Benjafield et al., 2019) and insomnia (Roth et al., 2011). Most people with both diseases remain undiagnosed and untreated, thus resulting in major adverse outcomes on health, performance, and safety (Young et al., 1997). The current diagnostic approaches mainly rely on full-night polysomnography (PSG) or home sleep tests utilizing direct cardiopulmonary recording (e.g., effort,

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nasal pressure), which are relatively labor-intensive, time-consuming, expensive, and uncomfortable for patients. Moreover, both a first/lab-night effect of PSG and night-to-night variability of sleep are found during recordings (Agnew Jr. et al., 1966; Mosko et al., 1988). Therefore, to better capture the physiological and pathological dynamics of sleep, it is advisable to assess patients' sleep in a natural sleep environment over multiple nights and on multiple occasions. In addition, poor adherence to continuous positive airway pressure (CPAP) as the first-line treatment for obstructive sleep apnea (OSA) may be related to poor subjective sleep quality in patients (Cistulli et al., 2019). As such, a nimble and effective approach to help clinicians and patients evaluate, diagnose, and track sleep disorders is highly desirable.

The cardiopulmonary coupling (CPC) technique, which only requires a continuous electrocardiogram (ECG) or photoplethysmography (PPG) signal as an input, is becoming more widely used in formal medical and consumer wearable devices (Hilmisson et al., 2020; Thomas et al., 2005). The CPC technique is based on analyzing the synchronization intensity of heart rate variability (HRV) and respiration data gathered during sleep, two bio signals that are both highly modulated by the autonomic nervous system (ANS) (Thomas et al., 2005; Waxenbaum et al., 2022), which is in turn highly modulated by sleep state, type, and depth. We can observe coupling between the heart and respiratory systems when external stimuli affect the ANS during sleep, allowing us to measure sleep and sleep stages.

The conventional approach to sleep has the rapid eye movement (REM) and non-rapid eye movement (NREM) stages, with three grades of NREM sleep. However, there are several other methods of quantifying sleep, including cyclic alternating pattern (CAP, a measure of sleep electroencephalogram [EEG] stability), the Odds Ratio Product (ORP, a measure of continuous sleep depth), and fine movement analysis beyond conventional actigraphy. While type, grade, and depth are useful metrics, sleep also has spontaneously shifted bimodal characteristics, independent of conventional grading, readily evident from respiratory stability or CPC analysis (Wood et al., 2020). High-frequency coupling (HFC) is one of them, and it's linked to stable NREM sleep, while low-frequency coupling (LFC) is associated with unstable NREM sleep (Thomas et al., 2005). A third CPC form, very-low-frequency coupling (VLFC), occurs during both REM sleep and wakefulness and can be distinguished by signal quality and motion artifact analysis (Al Ashry et al., 2021). These distinct CPC patterns logically vary with disease state and treatment. For example, patients with OSA have increased LFC, whereas successful CPAP therapy decreases it (Cho & Kim, 2017). In a recent study, CPC data and oxygen desaturation data were combined to calculate the automatic apnea-hypopnea index (AHI), which has been clinically validated and FDA-approved for the diagnosis and management of OSA in both children and adults (Al Ashry et al., 2021; Hilmisson et al., 2020).

In this chapter, we will introduce the current state of knowledge and understanding of the CPC technique. A greater focus is directed on the physiological basics, standard analytical methods, and the clinical application of the CPC technique in the evaluation, diagnosis, and management of sleep disorders.

11.2 Physiological Basics

The interaction between heart rate and respiratory tidal volumes was first documented in 1733 by Stephen Hales (Hales, 1733). Subsequent studies have shown that the synchronization between HRV and respiration improves gas exchange at the lung level through efficient ventilation/perfusion matching while minimizing the workload on the heart (Ben-Tal et al., 2012; Yasuma & Hayano, 2004). Such cardiopulmonary synchronization is optimal during deep sleep, sedation, and anesthesia (Dick et al., 2014). The degree of cardiopulmonary coupling is modulated by the ANS, and its characteristics vary by the type and depth of sleep. In comparison to the waking state, normal NREM sleep is associated with reduced sympathetic-nerve activity and heart rate (Somers et al., 1993), covarying with

increased depth of sleep. High vagal tone, sinus arrhythmia, stable breathing, high relative delta power, blood pressure dipping, and stable arousal threshold are all characteristics of stable NREM sleep, whereas unstable NREM sleep has the opposite characteristics, including low-frequency tidal volume fluctuations, cyclic variation in heart rate, low relative delta power, non-dipping of blood pressure, and variable arousal thresholds. In contrast, during rapid eye movement (REM) sleep, sympathetic-nerve activity increases above that observed during wakefulness, and blood pressure and heart rates are similar to those observed during wakefulness (Somers et al., 1993). According to spectral analysis, high-frequency power components have been associated with parasympathetic activity dominance, while low-frequency power components have been associated with the dominance of sympathetic activity.

11.3 Analytical Methods for Cardiopulmonary Coupling

The CPC technique extracts HRV/pulse rate variability and an ECG/PPG-derived respiration (EDR/PDR) signal from a single-channel ECG or PPG. The cross-power and coherence of these two signals are then calculated using the Fourier transform to generate a sleep spectrogram of cardiopulmonary coupling dynamics (Thomas et al., 2005).

The following are the detailed steps in calculating the cardiopulmonary coupling measure: (1) An automated beat detection algorithm is applied to detect beats, classifying them as normal or ectopic, and to determine amplitude fluctuations in the QRS complex. An EDR was calculated using these amplitude fluctuations. (2) From the RR interval time series, the time series of the normal sinus to normal sinus (N-N) interval and its associated EDR interval are extracted. (3) A sliding window average filter is used to remove outliers resulting from false or missed R-wave detections. This filter has a window of 41 data points, and center points that lie outside 20% of the window mean are rejected. (4) A cubic spline is used to resample the resulting N-N interval sequence and its associated EDR at 2 Hz. (5) The fast Fourier transform is performed to the 3 overlapping 512 sample sub-windows within the 1024-sample coherence window to calculate the cross-spectral power and coherence of these 2 signals across a 1024-sample (8.5 min) frame. (6) After that, the 1024-sample coherence window is advanced by 256 samples (2.1 min), and the calculation is repeated until the entire N-N interval/EDR series is analyzed. For each 1024-sample window, the product of the coherence and cross-spectral power is used to calculate the ratio of coherent cross-power in the low-frequency (0.01–0.1 Hz) band to that in the high-frequency (0.1–0.4 Hz) band. The logarithm of the high- to low-frequency cardiopulmonary coupling ratio [log (HFC/LFC)] is then computed to yield a continuously varying measure of cardiopulmonary coupling. Although the ECG signal was originally utilized as an input, the CPC sleep spectrogram can now be computed using any signal recordings that include an ECG signal or a similar information-content signal, such as PPG. The steps of calculating CPC are depicted in Fig. 11.1.

11.4 Distinct Patterns of Cardiopulmonary Coupling and Its Association with CAP and PSG

High-frequency (0.1–0.4 Hz) coupled pattern appears as the (upper) dark blue peaks on the sleep spectrogram (Fig. 11.2), which represents integrated, stable NREM sleep with the characteristics of stable breathing, high vagal tone, generally a non-CAP on the EEG, high relative delta power, and blood pressure dipping. Stable NREM sleep is equivalent to part of stage 2 and usually all of stage 3 NREM sleep derived from PSG; N3 can be unstable and exhibit LFC in conditions such as epilepsy and NREM parasomnias. There is a link between stable NREM sleep (HFC) and delta waves (deep sleep). We therefore consider this pattern as “effective” NREM sleep. Effective

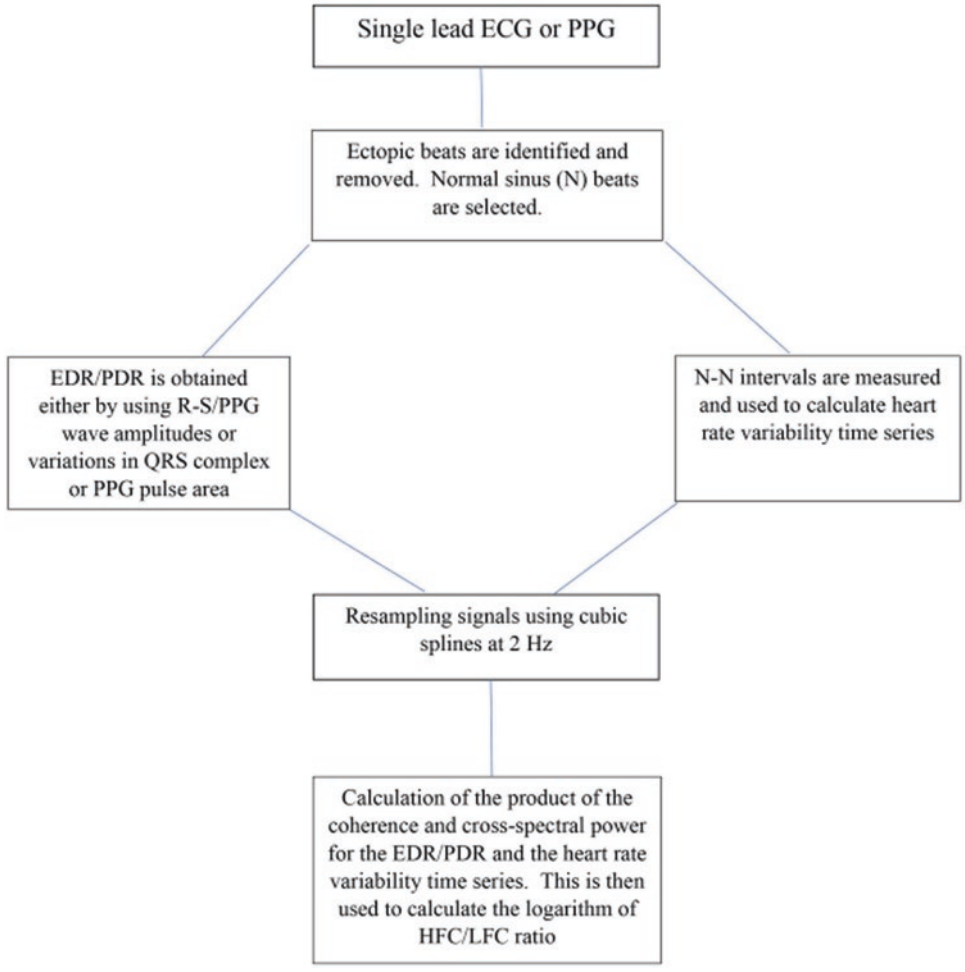

Fig. 11.1 Algorithm outline for CPC analysis. ECG electrocardiogram, PPG photoplethysmogram, EDR ECG-derived respiration, PDR photoplethysmogram-derived respiration, R-S and QRS are ECG waveforms, N-N intervals normal sinus to normal sinus intervals, Hz frequency, HFC high-frequency coupling, LFC low-frequency coupling

sleep enables the desired functions of sleep across multiple dimensions (e.g., metabolic, immune, etc.), allowing for recovery and restorative processes to occur. Low-frequency (0.01–0.1 Hz) coupled patterns appear as light blue peaks on the sleep spectrogram (Fig. 11.2), which represent unstable NREM with the exact opposite characteristics of stable sleep: low-frequency tidal volume fluctuations, cyclic variation in heart rate, CAP, EEG low relative delta power, and non-dipping of blood pressure and variable arousal thresholds. Unstable NREM sleep equates to all of stage 1 and part of stage 2 NREM sleep from PSG, and it is also considered as "ineffective" NREM sleep. Ineffective sleep fails to accomplish the functions that a healthy sleep should. A subset of LFCs called elevated low-frequency coupling (e-LFC) pattern has two further subsets: one with broad-band coupling spectra and the other with narrow-band coupling spectra (e-LFC_{BB} and e-LFC_{NB}). Very-low-frequency (0.004–0.01 Hz) coupling (VLFC), shown as orange peaks on the sleep spectrogram (Fig. 11.2), occurs during both awake and healthy REM sleep; fragmented REM sleep is characteristic of LFC.

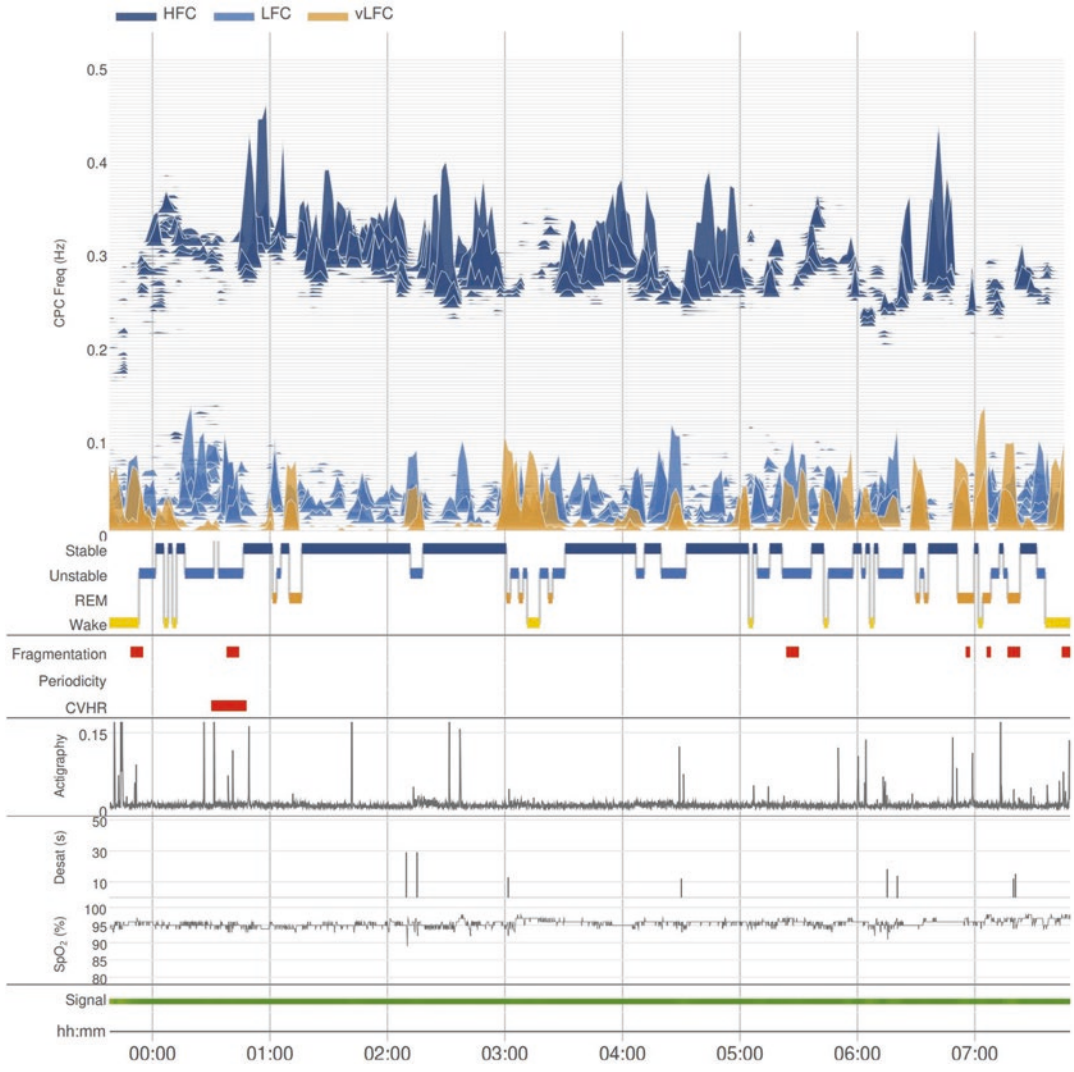

Fig. 11.2 The oximeter-extracted CPC spectrogram. The basic graphical representation of the CPC spectrogram has high-, low-, and very-low-frequency coupling (HFC, LFC, and VLFC, respectively) components

HFC and LFC are mutually incompatible and do not coexist. Some LFC, up to about 20–30% of NREM sleep in adults, is normal, occurring at sleep onset, during brief periods within a given NREM cycle, and just prior to REM sleep. These "lightening" periods may serve a biological disengagement function as sleep processes move from NREM to REM sleep and exhibit other kinetics. Sleep fragmenting disease states "hijack" LFC and increase both duration and biological hostility at the expense of HFC. Similarly, conditions that enhance sleep drive and continuity suppress LFC while amplifying HFC.

The CPC spectrogram showed a strong correlation with CAP scoring, with LFC associated with CAP and HFC with non-CAP (Thomas et al., 2005). The kappa statistic, a measure of interscorer reliability, showed higher agreement between the ECG-based detector and visual scoring of CAP/non-CAP (training set, 74%, and test set, 77.3% agreement, respectively) than between the ECG-based state estimate and standard

NREM stages (training set, 62.7%; test set, 43.9% agreement). The agreement between visual CAP/non-CAP scoring and stage 2/delta sleep (conventional stages 3 + 4) was not significantly better than chance (54%).

Even though CPC and PSG analyze and present biological activity during sleep from different brain structures (ANS regulation vs. cortical brain wave regulation, respectively), they both reflect sleep. As shown in Fig. 11.3, the two methods share important similarities but also exhibit some key differences.

11.5 Sleep Stability Is Independent of Continuous Sleep Depth

The CPC analysis provides a measure of sleep stability and complements conventional polysomnographic analysis. The 30-second epoch-based scoring of sleep heavily down-samples the relevant biology and provides a low-resolution view of the continuous nature of sleep. Stage N2 is especially problematic as this stage can show a wide range of morphologies and oscillatory information content across low amplitude slow waves, spindles, and K-complexes. The ORP is a novel approach to estimate continuous sleep depth in 3-second epochs, utilizing the power content at classic sleep-related frequencies, estimating the probability of arousability (Penner et al., 2019; Younes et al., 2015). A natural question is the correlation of while night sleep depth, especially in NREM sleep, between CPC and ORP measures – there is virtually none. This can be readily understood by consideration of what is being measured – the proportion of stable sleep vs. the overall EEG sleep depth. Stable sleep (HFC) covaries with relative slow-wave power and may be expected to align with low ORP (deeper sleep), but K-complex enriched periods of sleep, for example, can be profoundly unstable yet have increased sleep depth. Thus, in the most extreme instances, such as marked increases in slow-wave sleep or severe whole night sleep fragmentation, the measures may agree somewhat, but not across the entire range of sleep stability and sleep depth. This idea is confirmed by analysis of the Sleep Heart Health Study-I dataset (5781 subjects, age: 63.1 ± 11.2 years, 46.7% male), where all correlations between the Sleep Quality Index (a measure that integrates high- and low-frequency coupling, sleep fragmentation, and total sleep time) and HFC with NREM, REM, or whole night ORP were all statistically non-significant (all correlation coefficients <0.05). Thus, CPC and ORP provide information about non-overlapping dimensions of sleep physiology and pathology.

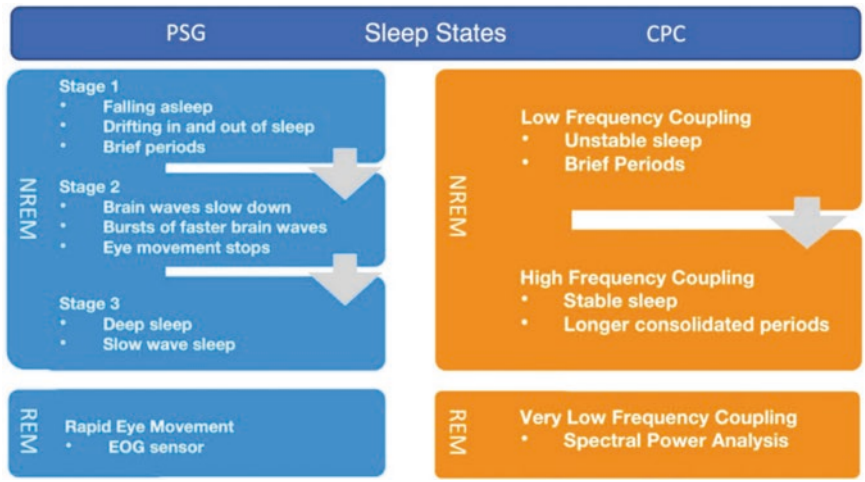

Fig. 11.3 The relationship between the CPC scoring system and conventional sleep scoring system

11.6 Clinical Application of Cardiopulmonary Coupling Technique

11.6.1 Diagnosis of Sleep Apnea

Sleep apnea disrupts rhythmic breathing and increases sympathetic-nerve activity, which results in pathological oscillations in heart rate and breathing. They are represented in the CPC sleep spectrogram as the LF-coupled band spectra. Analysis of the PhysioNet Sleep Apnea Database showed that e-LFC (a subset of LFC) coincided highly with the manually scored apneas and hypopneas. There are two further bands within e-LFC, namely, e-LFC_{BB} and e-LFC_{NB}. Given that other causes of sleep fragmentation may also contribute to the e-LFC spectrum, especially e-LFC_{NB}, the latest methods of AHI calculation have combined oxygen desaturation analysis and CPC analysis to minimize this limitation. Thus, a spectrographic apnea-hypopnea index (sAHI) is defined as (broad-band index + narrow-band index + oxygen desaturation index) per hour of sleep as determined by CPC, which has been approved by the USA FDA (K182618) in 2019 and to be accepted as comparable to manual scoring of AHI from PSG in adults and children.

Numerous studies have validated the diagnostic performance of the CPC technique against PSG in the adult populations (Table 11.1; Liu et al., 2012; Magnusdottir & Hilmisson, 2018; Hilmisson et al., 2019; Lu et al., 2019; Ma et al., 2020; Seo et al., 2021; Al Ashry et al., 2021; Xie et al., 2018; Feng et al., 2017). We further performed a meta-analysis of relevant studies published in the past 10 years, to summarize pooled diagnostic performance. The comprehensive meta-analysis of 6 validation studies (including 1524 patients) that recorded CPC and PSG simultaneously demonstrated that the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 94% (95%CI: 92–95%), 63% (95%CI: 56–71%), 2.4 (95%CI: 1.97–2.92), 0.12 (95%CI: 0.04–0.35), and 20.43 (95%CI: 6.49–64.34), respectively, when we used PSG-AHI $\geq$ 5 as the threshold. The summary receiver operating characteristic curve was shown in Fig. 11.4, and the area under the curve was 0.76. In addition, there are two validation studies performed on children (Guo et al., 2011; Hilmisson et al., 2020). The recent large study showed that the novel sAHI combining PPG data with oximetry desaturation data has a significant correlation with manually AHI derived from PSG studies (Pearson correlation = 0.954, $P < 0.0001$) (Hilmisson et al., 2020).

11.6.2 Distinguishing Sleep Apnea Types

Sleep apnea can be caused by several driver endotypes, including high loop gain, a low arousal threshold, an inadequate negative pressure reflex, and increased upper airway collapsibility. At least two types of sleep apnea can be distinguished using spectral profiles of CPC (Thomas et al., 2007). In the sleep spectrogram, the differences between OSA (broad spectral band pattern e-LFC) and CSA or periodic breathing (narrow spectral band pattern e-LFC, high loop gain sleep apnea) are both computationally and visually distinctive and easily quantifiable. As seen in Fig. 11.5a, a broad band of gray peaks suggests that the upper airway obstruction is the primary pathophysiological factor causing the patient's sleep apnea. The presence of a narrow spectral band indicates abnormal chemoreflex regulation of respiration during sleep, which is a hallmark of high loop gain expression (Thomas et al., 2007). It is represented by a narrow red peak in the 3D spectrogram view (Fig. 11.5b). Cheyne-Stokes respiration, a subtype of CSA, shows similar peaks on the CPC sleep spectrogram. As seen in Fig. 11.6, both pathologies can coexist.

11.6.3 Treatment Tracking in Sleep Apnea

Several studies were conducted to evaluate the efficacy of various treatments for OSA, such as CPAP, upper airway surgery, and mandibular

Table 11.1 Studies that used cardiopulmonary coupling to diagnose sleep apnea

Author and year	Sample size	Age, year	Male	BMI, kg/m^2	Main finding
Adults					
Al Ashry et al. (2021)	833	51 ± 13	554	NA	Receiver operating characteristic (ROC) curves demonstrated strong agreement in all OSA categories: 98.5% in mild OSA (95% CI, 97.6–99.3%), 96.4% in moderate OSA (95% CI, 95.3–97.5%), and 98.5% in severe OSA (95% CI, 97.8–99.2%)
Seo et al. (2021)	194	18–72	NA	NA	The spearman correlation coefficient showed that the sAHI was significantly positively correlated with the AHI ($r = 0.973$, $P < 0.05$)
Ma et al. (2020)	205	46.8 ± 12.8	149	27.53 ± 4.28	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 ($r = 0.840$, $P < 0.001$)
Lu et al. (2019)	179	44.9 ± 11.8	152	28.0 ± 4.1	Area under the curve (AUC) 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, AUC 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 $P < 0.0001$)
Hilmisson et al. (2019)	68	45.1 ± 10.9	55	27.6 ± 6.0	CPC identified patients with moderate to severe SA with the sensitivity of 100%, specificity of 81%, and agreement of 93% compared with manual scoring of AHI
Magnusdottir and Hilmisson, (2018)	47	48.6 ± 12.6	14	33.9 ± 9.2	Compared with the manually scored PSG, the combined CPC + CVHR algorithm had a sensitivity of 89%, a specificity of 79%, an agreement of 85%, a PPV of 0.86, an NPV of 0.83, and a Kappa of 0.70
Xie et al. (2018)	44	47.7 ± 13.3	37	25.6 ± 3.5	The corresponding areas under the ROC curves were 0.868, 0.892, 0.915, 0.942, and 0.921, respectively, when PSG-AHI ≥ 5/h, ≥10/h, ≥15/h, ≥20/h, and ≥ 30/h, respectively
Feng et al. (2017)	292	50.26 ± 13.28	212	NA	The correlation between CPC-RDI and PSG-AHI was excellent ($r = 0.801$, $P < 0.01$)
Liu et al. (2012)	69	40.4 ± 10.7	56	28.1 ± 6.5	The AUC was 0.79 when apneas and hypopneas were detected
Children					
Hilmisson et al. (2020)	805	6.81 ± 1.78	378	Z score 1.00 ± 1.27	ROC curve demonstrated strong agreement in all OSA categories (mild, moderate, severe) 91.4% [95% CI: 89.5, 93.4], 96.7% [95% CI: 95.4, 97.9], and 98.6% [95% CI: 97.8, 99.4]; sensitivities 95.4% [95% CI: 93.2, 97.0], 86.5% [95% CI: 80.3, 91.3], and 88.4% [95% CI: 78.4, 94.9]; and specificities 84.4% [95% CI: 79.7, 88.4], 99.2% [95% CI: 98.2, 99.7], and 99.6% [95% CI: 98.8, 99.9], respectively
Guo et al. (2011)	63	6.2 ± 2.5	41	NA	CPC-RDI has a strong positive correlation with the conventional nasal flow RDI (correlation coefficient 0.70)

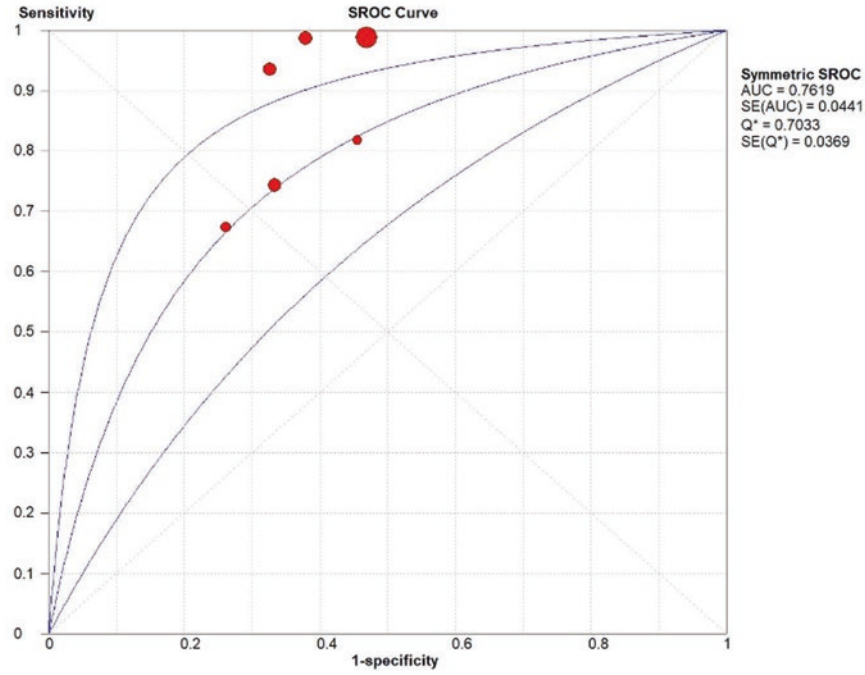

Fig. 11.4 Summary receiver operating characteristic (ROC) curves comparing CPC and PSG studies. ROC for apnea-hypopnea index ≥5 events/h

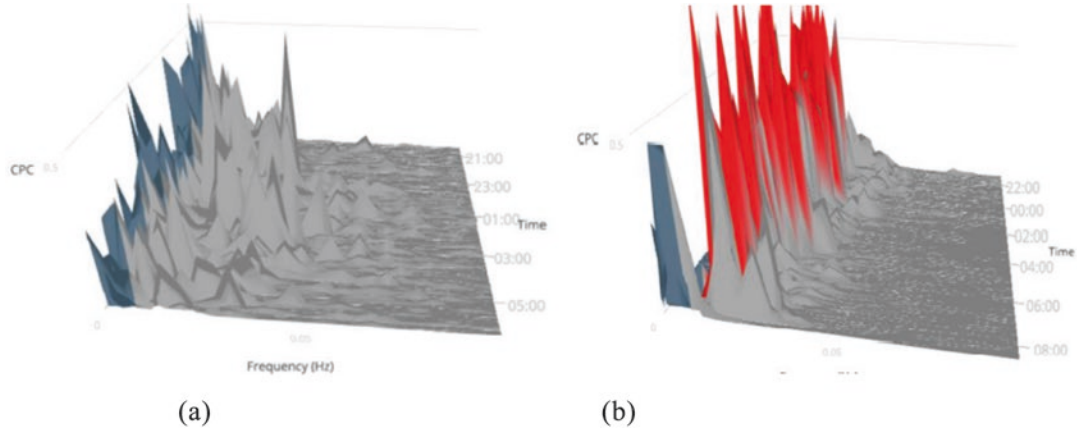

Fig. 11.5 The 3D view spectrogram – (**a**) Obstructive sleep apnea is presented as a "broad" distribution of the peaks colored gray. (**b**) Central sleep apnea is presented as a line of narrow peaks colored red

advancement (Table 11.2). Harrington et al. (2013) revealed that patients with successful CPAP therapy have more HFC, less LFC, and e-LFC_{BB} than those with unsuccessful CPAP therapy. Cho and Kim (2017) looked at how CPC variables changed after CPAP titrations and discovered that HFC increased while LFC and e-LFC decreased. Treatment of OSA with an oral appliance or upper airway surgery produces similar results (Choi et al., 2015; Lee et al., 2016). In addition, Lee et al. (2012) and Chen and He (2019) both found that adenotonsillectomy resulted in a significant change in CPC parameters (increased HFC, decreased

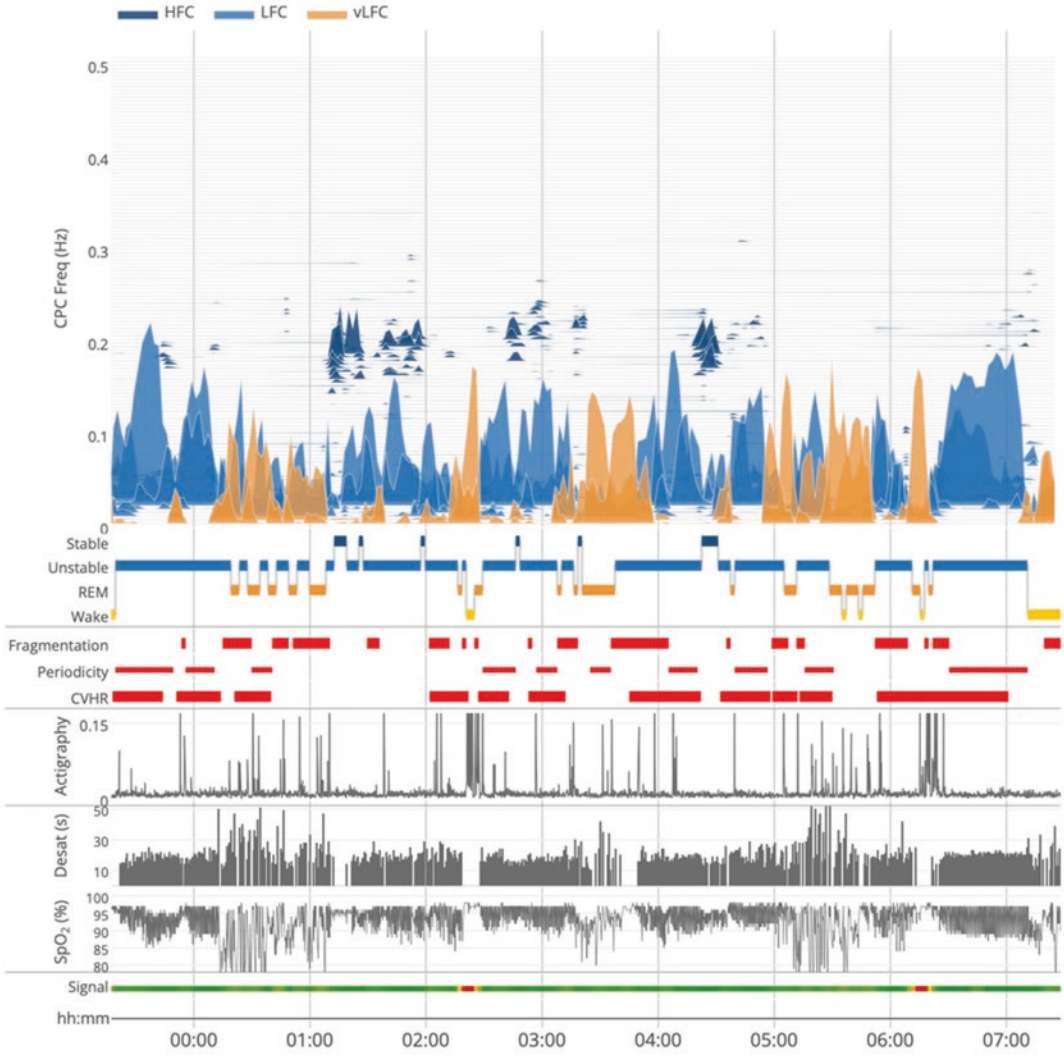

Fig. 11.6 Mixed physiology sleep apnea. A 55-year-old male with classic sleep apnea symptoms, CPC from a ring oximeter. Note (1) poor sleep quality and (2) two patterns of oxygen desaturation: V-shaped in REM sleep consistent with obstructive pathology and band-like oxygen desaturation in NREM sleep associated with detected "periodicity" (narrow-band e-LFC), consistent with additional high loop gain effects

LFC) in pediatric OSA patients. As previously mentioned, in addition to dynamically tracking the change in sleep stability after treatment, the CPC technique can also detect and phenotype residual apnea, predicting PAP failure (Thomas et al., 2007).

In the sleep apnea population, there are several advantages to using the CPC technique through wearable devices, particularly the current device of a ring-form oximeter. These include (1) easy to use, low cost, and comfortable for patients, allowing for repeated testing and ambulatory tracking of sleep apnea; (2) the automatically generated AHI reduces the scoring burdens; (3) detecting expressed high loop gain (central apnea and periodic breathing) may help improve risk stratification and capture therapy effects, such as treatment-emergent CSA; (4) aging does not appear to negatively affect the ability of CPC technology to detect OSA accurately. According to AI Ashry et al. (2021), the patients were divided into three

Table 11.2 Studies that used cardiopulmonary coupling in following treatment effect of sleep apnea

Author and year	Number of subjects	Main finding
Adults		
Lee et al. (2016)	98 OSA patients treated with surgery or with a MAD therapy	The reduction in the apnea-hypopnea index greater than 50% was significantly associated with the reduction in LFC and increment in HFC
Cho and Kim (2017)	115 OSA patients with CPAP	In the CPAP titration group, HFC increased, while LFC and e-LFC decreased linearly as AHI decreased
Choi et al. (2015)	62 OSA patients treated with surgery	Patients with surgical success were found to have a significant increase in HFC and a significant decrease in LFC compared to those without successful surgery
Lee et al. (2014)	52 OSA patients with MAD therapy	LFC decreased, while HFC increased as AHI improved by MAD therapy
Harrington et al. (2013)	24 OSA patients with CPAP	The successful CPAP therapy group had more HFC, less LFC, and e-LFC_{BB} compared to the unsuccessful CPAP therapy group
Ramar et al. (2013)	106 complex sleep apnea patients with ASV	The percentage of e-LFC_{NB} did not relate to the success of ASV treatment
Schramm and Thomas (2012)	Case report of 1 patient with mild OSA with the mandibular advancing appliance, sleep position restriction, oxygen therapy	The HFC/LFC ratio was higher on mandibular advancing appliance nights than oxygen therapy and positional therapy
Children		
Chen and He (2019)	126 children with OSA	There was an improvement in RDI collected from CPC after surgery
Lee et al. (2012)	37 children with OSA	Adenotonsillectomy significantly increased HFC and decreased LFC, which were paralleled by the improvement in the apnea-hypopnea and arousal index

groups based on their age: <45, 45–55, and >55. They discovered that none of these age groups had a significant effect on the accuracy of AHI. As a result, CPC is a desirable method for evaluating sleep apnea in elderly adults because it is not constrained by the dependence of conventionally scored slow-wave sleep which deteriorates with age when measured through EEG from the cortex; (5) it can be applied regardless of autonomic dysfunction. Even with a flat heart rate, the EDR comes through. Of course, it is also worth considering its potential limitation. CPC output is less meaningful in patients with chronic atrial fibrillation, due to complex patterns that cannot be identified and the chaos of the ANS. Therefore, the results should be interpreted cautiously. Figures 11.7, 11.8, and 11.9 show the sleep apnea and sleep quality phenotyping in apnea utility of the CPC technique.

11.7 Cardiopulmonary Coupling Spectrogram in Other Disorders

11.7.1 Insomnia/Mental Health

In the field of insomnia and related adverse mental and psychological diseases, CPC technology has been widely applied (Table 11.3). Primary insomnia patients had lower HFC and higher LFC, VLFC, and e-LFC compared to good sleepers, according to Schramm et al. (2013). A similar finding has been observed by Thomas et al. (2018), and they found that patients with insomnia had a higher e-LFC_{BB} percentage than healthy participants. Zhang et al. (2021) assessed the relationship between cognitive function and sleep stability in insomnia patients and discovered that insomnia patients with cognitive impairment had lower HFC and higher LFC than

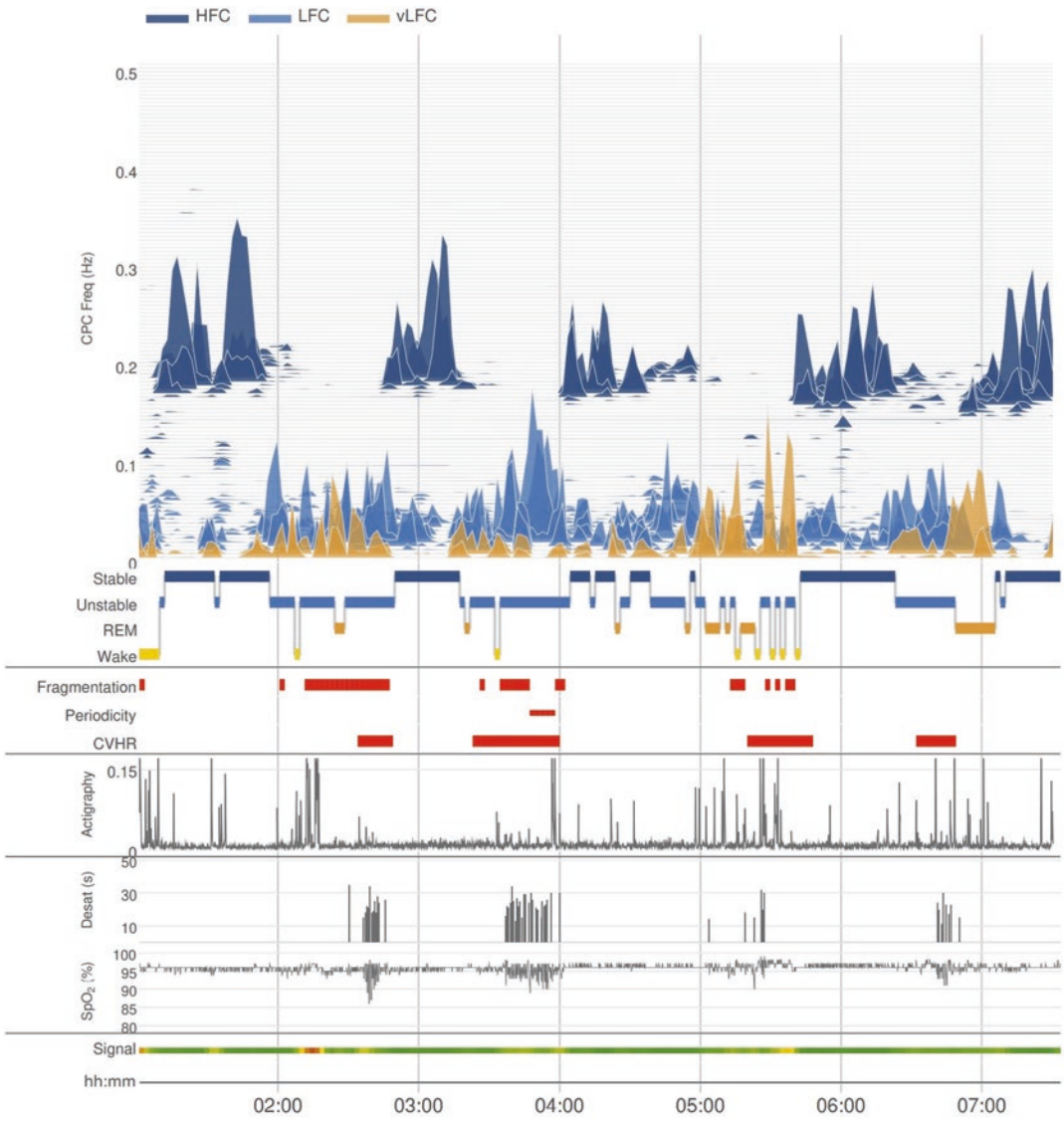

Fig. 11.7 Diagnostic assessment of milder sleep apnea. A 44-year-old male. Note generally good sleep quality but clusters of oxygen desaturation and cyclic variation in heart rate

insomnia patients with normal cognition. However, CPC characteristics did not differ substantially between participants with restless legs syndrome and those with insomnia (Na et al., 2015). Furthermore, Jarrin et al. (2016) evaluated the potential benefits of cognitive-behavioral therapy for insomnia and found that sleep improvements were related to reduced HF following therapy. Because insomnia is linked to a variety of medical and psychiatric conditions (Sivertsen et al., 2014), the CPC technique has been utilized to study and track therapy responses in these patients. In comparison to controls, unmedicated depressive patients exhibited a lower HFC and a higher LFC, according to Yang et al. (2011). Ma et al. (2018) studied the effects of tai chi training on sleep quality in patients with depression. When the patients got tai chi

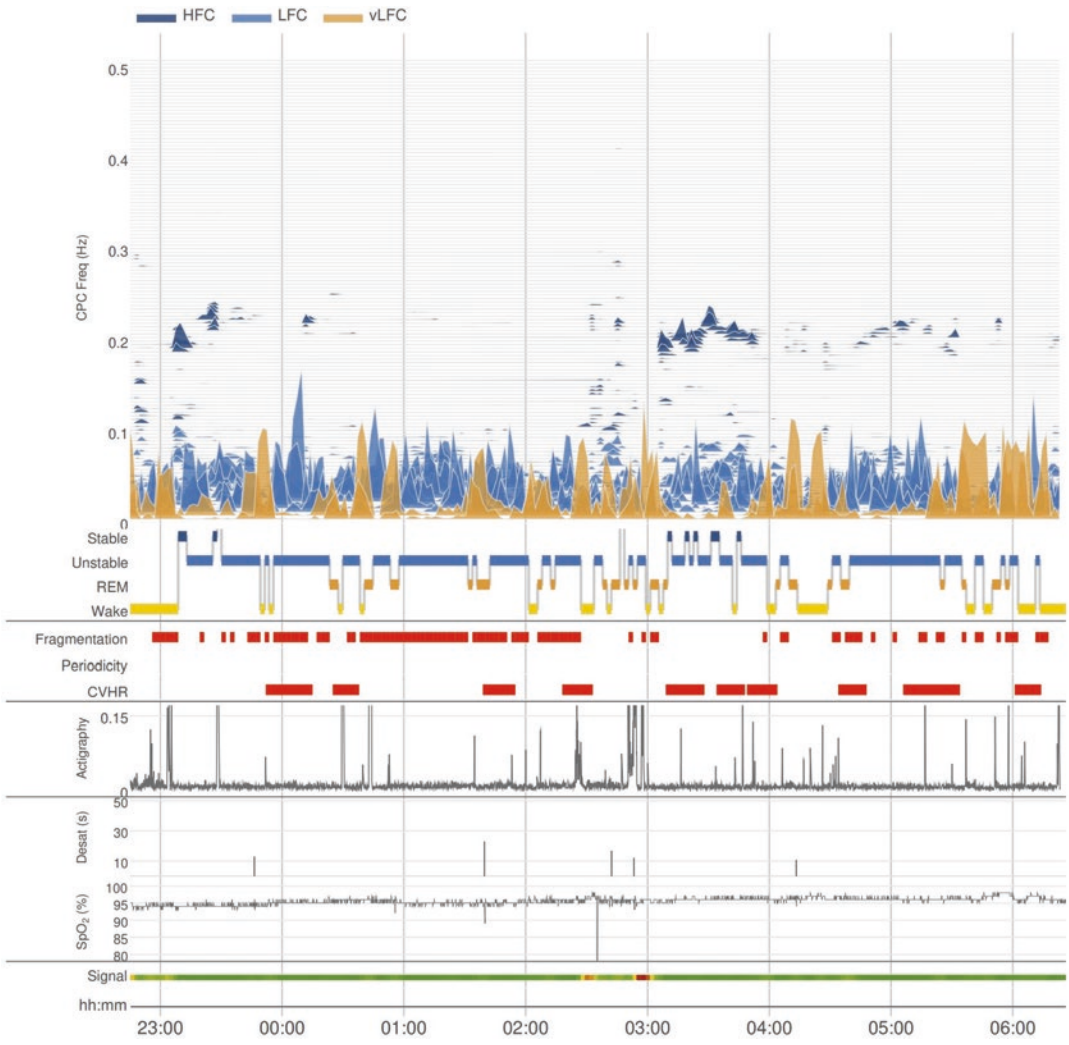

Fig. 11.8 Failure of CPAP to improve sleep quality. The same patient as in Fig. 11.6, after 3 months of CPAP, with a complaint of persistent fatigue despite good use of CPAP and low (less than 5) event index on CPAP. Note the severe loss of HFC, suggesting worse sleep quality, associated with an increase in cyclic variation in heart rate. This could be from non-apnea causes (such as anxiety) or CPAP-induced respiratory instability or sleep fragmentation

training, their CPC analysis revealed an increase in stable sleep percentages and a decrease in unstable sleep percentages. Sun et al. (2019) looked at 41 depressed patients and found that there were significant associations between CPC characteristics at baseline and depression symptom improvement after 2 weeks of antidepressant drug treatment. As sleep apnea syndromes often have comorbid insomnia and mood disorders, CPC spectrograms provide a method to assess sleep quality relatively independent of respiratory abnormality.

11.7.2 Cardio-Cerebral Metabolic Health

Sleep health, as measured by CPC analysis, including sleep duration, sleep quality, and OSA, has been linked to cardio-cerebral meta-

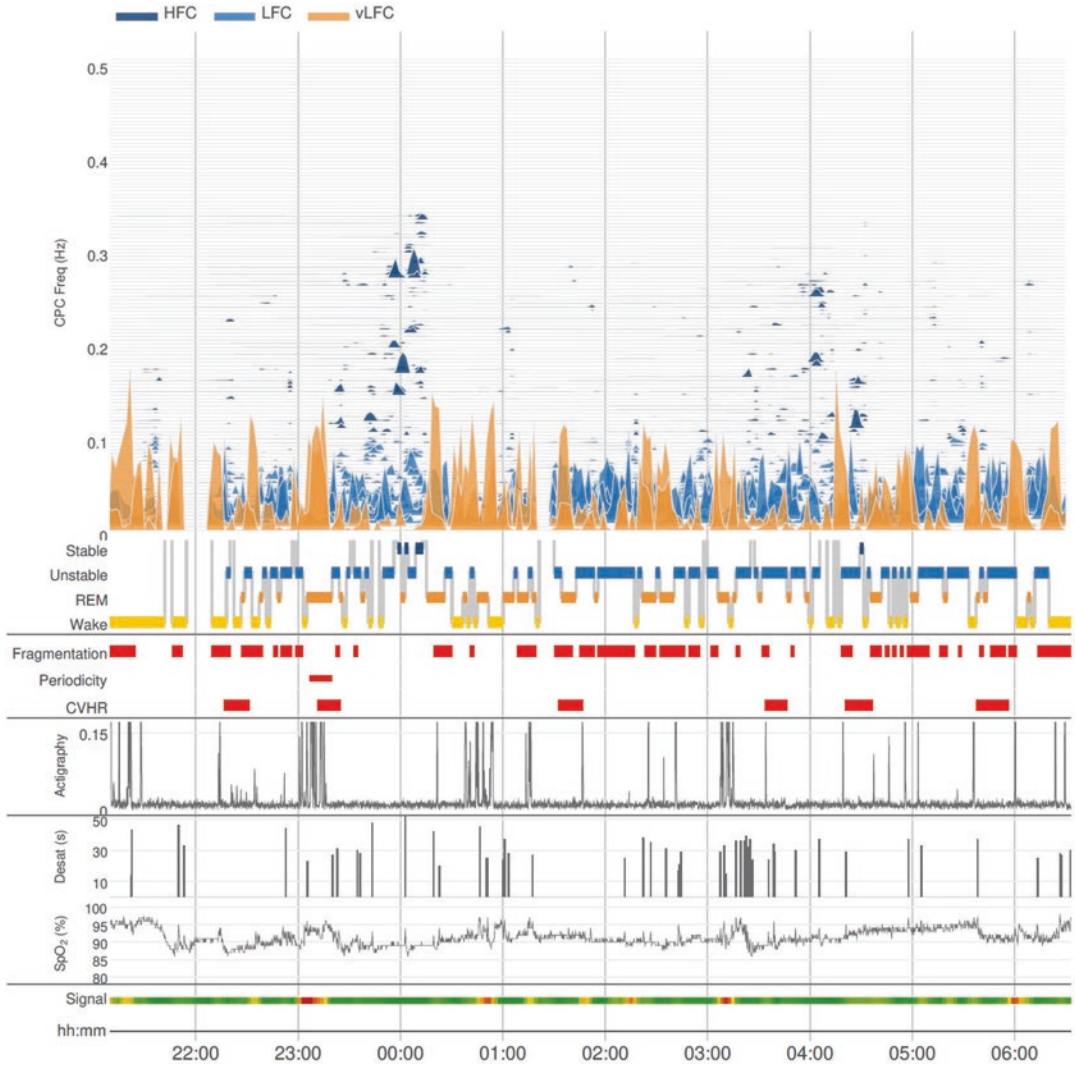

Fig. 11.9 Failure of adaptive servo-ventilation for treatment-emergent central sleep apnea**.** A 55-year-old male who has been using an ASV for over 10 years, with improvement from CPAP yet residual fatigue. Machine residual AHI is less than 1/h of sleep. Note near absence of stable NREM sleep. Note also unstable oximetry trace. Though residual machine estimated AHI is low, clearly there is ongoing sleep disruption, which can occur from excessive pressure cycling of the ventilator

bolic illnesses in numerous studies (Table 11.4). Thomas and colleagues (2009) found that e-LFC_{NB} is linked to more severe sleep apnea, as well as a higher prevalence of hypertension and stroke. Pogach et al. demonstrated that HFC is an independent driver of the glucose disposal index (Pogach et al., 2012). In a study of 615 patients with acute non-cardioembolic ischemic stroke, Kang et al. (2020) discovered narrow-band coupling could predict severe and protracted functional impairment at 3 months. Magnusdottir et al. (2020) found that CPC-derived sleep quality influenced 24-h mean arterial blood pressure and mean diastolic blood

Table 11.3 Studies that used cardiopulmonary coupling in insomnia/mental health

Author and year	Simple size	Main finding
Zhang et al. (2021)	43 patients with insomnia	Insomnia-cognitive impairment patients had lower HFC and higher LFC compared to the insomnia-normal cognition patients
Sun et al. (2019)	41 patients with depression	Significant correlations were found between CPC variables at baseline and depression symptom improvement after 2 weeks of treatment
Hilmisson et al. (2019)	110 patients with chronic insomnia	The prevalence of moderate-severe SDB (REI > 15) was 25% based on HSAT. Surrogate markers of moderate-severe SDB detected by CPC analysis identified the prevalence of 33%, with a negative predictive value of 96%
Ma et al. (2018)	12 depressed patients	CPC analysis showed decreased stable sleep onset latency, increased stable sleep percentages, and decreased unstable sleep percentages after tai chi training
Thomas et al. (2018)	20 insomnia patients, 10 healthy participants	Patients with insomnia had increased LFC duration and increased e-LFCBB percentage than healthy participants
Schramm et al. (2016)	25 chronically depressed patients	By post-treatment night 6, the Cognitive Behavioral Analysis System of Psychotherapy group had more stable sleep and less wake compared with Treatment as Usual group and less wake than Mindfulness-based Cognitive Therapy group
Jarrin et al. (2016)	65 patients with chronic insomnia	Following cognitive-behavioral therapy, sleep improvements were related to reduced HF in S2 and REM
Park et al. (2015)	200 OSA subjects divided into OSA with insomnia group and OSA without insomnia group	There was no significant difference in CPC parameters between the two groups after adjustment of AHI
Na et al. (2015)	109 subjects with restless legs syndrome and 86 with insomnia	CPC parameters were not significantly different between groups
Sylvia et al. (2014)	8 patients with bipolar disorder	SleepImage M1 device is a feasible means to obtain objective sleep quality and quantity data in individuals with bipolar disorder
Schramm et al. (2014)	19 subjects with depression	Bupropion did not impact CPC variables
Schramm et al. (2013)	50 subjects with primary insomnia and 36 good sleepers	Relative to good sleepers, primary insomnia patients on adaptation night had lower HFC and HFC/LFC ratio and higher LFC, VLFC, and e-LFC. On baseline night, the primary insomnia group had increased LFC, VLFC, and e-LFC and a lower HFC/LFC ratio. Except for HFC, good sleepers had larger CPC variable differences between adaptation and baseline nights compared to the primary insomnia group
Yang et al. (2011)	100 patients with major depressive disorder and 91 healthy controls	Relative to controls, unmedicated depressed patients had a reduction in high-frequency coupling and an increase in low-frequency coupling and very-low-frequency coupling. The medicated depressed group showed a restoration of stable sleep to a level comparable with that of the control group

pressure, as well as blood pressure during wakefulness, in a study of 241 patients with OSA at high cardiovascular risk. They also found that better sleep quality was associated with increased serum adiponectin levels and decreased insulin levels (Magnusdottir et al., 2021). For patients with chronic heart failure, tai chi training is likely to increase HFC and decrease LFC (Yeh et al., 2008). Similarly, in patients with paroxysmal atrial fibrillation, the HFC and VLFC were significantly elevated after radio-frequency catheter ablation, whereas LFC

Table 11.4 Studies that used cardiopulmonary coupling in cardio-brain-metabolic health and diseases

Author and year	Simple size	Main finding
Thomas et al. (2021)	504 patients from Offspring/Omni-1 database	Stable sleep computed using CPC was positively associated with white matter health
Magnusdottir et al. (2021)	241 patients with OSA at high cardiovascular risk	Improvements in CPC-sleep quality were associated with higher serum adiponectin levels and improved measures of glycemic metabolism
Magnusdottir et al. (2020)	241 patients with OSA at high cardiovascular risk	CPC-derived sleep quality impacted 24-h mean arterial blood pressure and mean diastolic blood pressure, as well as blood pressure during wake, in patients participating in the Heart Biomarker Evaluation in Apnea Treatment study
Kim et al. (2020)	225 patients with paroxysmal atrial fibrillation	Six months after radio-frequency catheter ablation, the HFC and VLFC were significantly increased, while LFC was decreased. The recurrence rate of atrial fibrillation was significantly lower in the patient who had unstable sleep before radio-frequency catheter ablation
Kang et al. (2020)	615 patients with acute non-cardioembolic ischemic stroke	Narrow-band coupling was an independent predictor of a higher risk of severe and persistent functional impairment at 3 months
Pogach et al. (2012)	118 nondiabetic subjects with and without SDB	HFC duration was associated with increased and VLFC was associated with reduced disposition index
Thomas et al. (2009)	5247 patients from the SHHS database	(1) Increasing age and male sex are associated with an increase in the prevalence of e-LFCNB. (2) The presence of e-LFCNB is a biomarker of severity of sleep-disordered breathing. (3) Use of diuretics, calcium blockers, and β-blockers was associated with increased e-LFCNB. (4) e-LFCNB was associated with prevalent stroke and hypertension
Yeh et al. (2008)	18 patients with chronic stable heart failure	At 12 weeks, those who participated in tai chi showed a significant increase in HFC and a significant reduction in LFC compared to patients in the control group

decreased (Kim et al., 2020). A recent study of Thomas et al. (2021) found stable sleep computed using CPC was positively associated with white matter health.

11.8 Conclusion

The CPC technique provides an accurate, practical, and low-cost alternative to traditional PSG and home sleep apnea testing for the objective assessment, diagnosis, and tracking of sleep health and disease over time. The technology may be used in both adults and children. It also offers the potential for individualized management of sleep disorders as it allows for repeatable sleep monitoring in the patient's natural sleep environment, as well as automated analysis.

11.9 Clinical Practice Points

- CPC technique generates sleep spectrograms by calculating the cross-spectral power and coherence of HRV and respiratory tidal volume fluctuations.
- The CPC spectrogram shows only a weak correlation with conventional sleep staging, but better follows CAP scoring, with LFC associated with CAP and HFC with non-CAP.
- The CPC sleep spectrogram provides a clear visual view of sleep health during the sleep period and helps healthcare providers manage sleep disorders in their patients, including evaluating sleep quality, diagnosing sleep apnea, and tracking therapy response.
- For the diagnosis of sleep apnea, the spectrographic AHI calculated combining CPC output

and hypoxic events shows strong agreement with AHI calculated manually from PSG.

11.10 Research Points

- The CPC analysis shows a fundamental sleep characteristic – that of bimodal stability, most clearly evident in NREM sleep. This dimension of sleep does not have a known neurobiological explanation, posing a unique research opportunity.
- The presence of a narrow spectral band indicates abnormal chemoreflex regulation of respiration during sleep, which is a hallmark of high loop gain expression.
- The pre- and post-treatment effects of sleep apnea with CPAP or upper airway surgery can be traced by changes in the ratio of HFC to LFC.
- e-LFC_{NB} is associated with higher prevalence of hypertension and stroke.
- HFC is an independent driver of the glucose disposal index.
- Narrow-band coupling was an independent predictor of a higher risk of severe and persistent functional impairment in acute ischemic stroke.
- Better sleep quality was associated with increased serum adiponectin levels and decreased insulin levels.
- Sleep quality and sleep hypoxia were associated with white matter injury.

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Disclosures and Conflict of Interest Dr. Robert Thomas has the following disclosures:

1. Patent for a device to regulate CO_2 in the positive airway pressure circuit, for the treatment of central/complex apnea.
2. Patent and license for an ECG-based method to phenotype sleep quality and sleep apnea (to MyCardio, LLC, through Beth Israel Deaconess Medical Center).
3. Patent, past consultant – Drive DeVilbiss, CPAP auto-titrating algorithm.
4. GLG Councils and Guidepoint Global – general sleep medicine consulting.

ML and TP have no disclosures.

Author Contributions ML and RT contributed to the study design. ML wrote the draft. ML, RT, and TP revised the manuscript.

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