Sleep and Breathing (2019) 23:125–133
https://doi.org/10.1007/s11325-018-1672-0

ORIGINAL ARTICLE

Sleep apnea detection: accuracy of using automated ECG analysis compared to manually scored polysomnography (apnea hypopnea index)

Hugi Hilmisson[1] · Neale Lange[2] · Stephen P. Duntley[3]

Received: 8 January 2018 / Revised: 9 May 2018 / Accepted: 14 May 2018 / Published online: 28 May 2018

Abstract

Introduction Adequate sleep is fundamental to wellness and recovery from illnesses and lack thereof is associated with disease onset and progression resulting in adverse health outcomes. Measuring sleep quality and sleep apnea (SA) at the point of care utilizing data that is already collected is feasible and cost effective, using validated methods to unlock sleep information embedded in the data. The objective of this study is to determine the utility of automated analysis of a stored, robust signal widely collected in hospital and outpatient settings, a single lead electrocardiogram (ECG), using clinically validated algorithms, cardiopulmonary coupling (CPC), to objectively and accurately identify SA.

Methods Retrospective analysis of de-identified PSG data with expert level scoring of Apnea Hypopnea Index (AHI) dividing the cohort into severe OSA (AHI > 30), moderate (AHI 15–30), mild (AHI 5–15), and no disease (AHI < 5) was compared with automated CPC analysis of a single lead ECG collected during sleep for each subject. Statistical analysis was used to compare the two methods.

Results Sixty-eight ECG recordings were analyzed. CPC identified patients with moderate to severe SA with sensitivity of 100%, specificity of 81%, and agreement of 93%, LR+ (positive likelihood ratio) 5.20, LR− (negative likelihood ratio) 0.00 and kappa 0.85 compared with manual scoring of AHI.

Conclusion The automated CPC analysis of stored single lead ECG data often collected during sleep in the clinical setting can accurately identify sleep apnea, providing medically actionable information that can aid clinical decisions.

Keywords Sleep apnea · Cardiopulmonary coupling · Cyclic variation of heart rate · Apnea Hypopnea Index

Introduction

Good sleep quality sleep is important and fundamental for a healthy cardiovascular system, glucose metabolism, immune function, and hormonal regulation, all of which are highly important while recovering from an illness [1, 2]. Sleep apnea (SA), the intermittent cessation or reduction in breathing sufficient to disturb sleep, is one of the most common sleep disorders among adults and is increasingly recognized as an important modifiable risk factor for cardiovascular disease (CVD). SA is prevalent in the adult population, with about 12% of adults suffering from the disease, and in the USA, it is estimated that 80% of this patient population is undiagnosed [3] and is likely to increase with increased prevalence of obesity and the aging population [4]. Obstructive sleep apnea (OSA) is the more common form of sleep apnea, is characterized by repeated partial, or complete obstruction of the upper airway during sleep, causing intermittent hypoxia and transient repetitive sympathetic arousals from sleep. The less common form, central sleep apnea (CSA), is associated with disrupted respiratory control [5]. A recent European study

Data registry
The data is obtained from an open access research database https://physionet.org/physiobank/database/apnoea-ecg/ contributed by Dr. Thomas Penzel of Philipps-University, Marburg, Germany.

✉ Hugi Hilmisson
hugi.hilmisson@sleepimage.com

[1] MyCardio-LLC, SleepImage®, 370 Interlocken Blvd., Broomfield, CO 80021, USA

[2] Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Health at Denver-Anschutz Medical Campus, Denver, CO 80045, USA

[3] Critical Care Pulmonary and Sleep Associates, 274 Union Blvd, Suite #110, Lakewood, CO 80228, USA

looking at a general population found the prevalence of OSA to be 43.1 or 19% when looking at only moderate and severe OSA [6]. Untreated, SA is potentially a lethal disease, which increases the risk of onset and progression of numerous health complications like hypertension, congestive heart failure, atrial fibrillation, coronary artery disease, obesity, type 2 diabetes, stoke, and depression [7, 8]. Data also suggests that untreated SA is associated with an increased risk of stroke and cardiovascular mortality [2].

A critical part of public health approach to CVD is to identify and treat modifiable CVD risk factors such as OSA as continuous positive airway pressure treatment (CPAP) may reduce mortality and other associated risks [9, 10] but not universally [11].

In patients with medical conditions causing hospitalization, SA has been found to be highly prevalent. Acute hospitalization is known to contribute to poor inpatient sleep quality and acute sleep loss due to environmental factors [12]. Inpatients with preexisting, undiagnosed sleep disorders like SA may experience even more sleep disruptions than patients free of SA [13, 14].

The high prevalence of SA among hospitalized patients [14, 15] suggests that hospitalization may represent a missed opportunity to identify SA and initiate appropriate treatment that might both improve patient outcomes and decrease risk of postoperative complications [15–17]. ECG data routinely collected during hospitalization can serve as a source of additional objective information to risk stratify patients that may be identified with SA and who would benefit from treatment during hospitalization for potentially faster recovery and reduced risk of readmission as research on patients identified with SA has confirmed that non-adherence to CPAP is associated with increased 30-day all-cause and cardiovascular-cause readmission [17–19]. Polysomnography (PSG) is the reference standard for diagnosis of SA, can be challenging, resource intensive, and generally not available to inpatients [20]. The methods that have been used to identify SA in hospital settings have therefore mostly been limited to subjective questionnaires: the STOP-BANG questionnaire being the most widely used to screen patients for SA [21]. Questionnaires, based on the respondents' own subjective evaluation, put clinicians in the situation of not being able to verify or validate the accuracy of the respondent's output. For these reasons, using easy to collect objective data to analyze sleep physiology to identify sleep disorders in inpatients could potentially both improve patient outcomes and reduce healthcare spending by decreasing readmission rates and postoperative complications [17, 18].

The proposed technique, cardiopulmonary coupling (CPC), evaluates the usefulness of analyzing a single lead ECG data stream to measure sleep duration, sleep quality, and sleep pathology that may be used to identify SA and guide clinical decisions and therapy management. CPC measures coupling of interactions between two physiological streams which both are strongly modulated by sleep, autonomic (heart rate variability, HRV), and respiratory (ECG-derived respiration, EDR) and identifies oscillations associated with prolonged cycles of sleep apnea (cyclic variation of heart rate, CVHR). Both methods have previously been described [22–25].

CPC is Food and Drug Administration (FDA) cleared for evaluation of sleep disorders to inform or drive clinical management and accurately identifies sleep apnea in adults [26, 27], monitors treatment efficacy in sleep apnea [28, 29], and can objectively identify insomnia based on the patients' sleep quality and architecture, to guide therapy initiation and track therapy efficacy [30, 31].

Materials and methods

Retrospectively collected, open access, de-identified data was accessed at PhysioNet (http://www.physionet.org/physiobank/database/-ecg/) [32].

Data set of 70 PSG studies including ECG signals extracted from full laboratory PSG studies of approximately 8 h of duration, digitalized at 100 Hz and a set of apnea annotations (derived by human experts on the basis of simultaneously recorded respiration and related signals). Of the 70 studies, 68 had acceptable ECG signal quality for CPC analysis.

The subjects (Table 1) are males and females with AHI ranging from 0 to 93.5, of age ranging from 27 to 63 years and weigh between 53 and 135 kg. Based on numbers of epochs containing apneas or hypopneas, PSG recordings were grouped as no disease (AHI < 5), mild SA (AHI 5–15), moderate SA (AHI 15–30), and severe SA (AHI > 30).

The CPC method is FDA approved for evaluating sleep disorders to inform or drive clinical management (SleepImage®). The technique is based on continuous ECG-data collected during sleep analyzing coupling between HRV and EDR to generate frequency maps, the ECG-derived sleep-spectrogram (Fig. 1), a detailed methodology on the basic algorithms has been published [22, 23]. During periods of prolonged SA, changes in heart rate dynamics have been described where heart rate typically shows cyclic increases and decreases associated with apneic phase and resumption of breathing (CVHR) [24, 25]. CPC output is presented as the Sleep Quality Index (SQI) providing a summary index of an automated measure of sleep duration, sleep stability (stable sleep (high-frequency coupling, HFC), unstable sleep (low-frequency coupling, LFC)), sleep fragmentation, and sleep pathology (elevated low-frequency coupling broad band ($eLFC_{BB}$) and elevated low-frequency coupling narrow band ($eLFC_{NB}$)), to generate a number between 0 and 100.

The sleep pathology markers of elevated low-frequency coupling broad band ($eLFC_{BB}$) and elevated low-frequency coupling narrow band ($eLFC_{NB}$) aid in distinguishing

Table 1 Characteristics of the study cohort

	All	Female ($n = 13$)	Male ($n = 55$)	p value
Age	45.1 (± 10.9)	32.8 (± 0.1)	48.1 (± 9.6)	0.00
Height (cm)	175.9 (± 5.6)	171.3 (± 0.6)	176.9 (± 4.2)	0.00
Weight (kg)	85.4 (± 19.4)	65.6 (± 0.2)	90.1 (± 17.2)	0.00
BMI	27.6 (± 6.0)	22.1 (± 0.1)	28.8 (± 5.7)	0.00
AHI	28.7 (± 27.7)	12.8 (± 0.1)	32.4 (± 25.7)	0.03

BMI body mass index, *AHI* Apnea-Hypopnea Index

between sleep disordered breathing caused by upper airway anatomical obstruction and respiratory dyscontrol [26, 33].

Sleep Apnea Indicator (SAI) is an automated measure detecting oscillations in heart rate often associated with prolonged cycles of sleep apnea showing abrupt tachycardia on the cessation of the apneic event and return to baseline occurring during periods of unstable breathing (tidal volume fluctuations in breathing). Displaying SAI based on these oscillations in the cardiovascular system as a consequence of drop in oxygen saturation during unstable breathing (LFC) helps to identify sleep-disordered breathing. Using SAI together with SQI, $eLFC_{BB}$, and $eLFC_{NB}$, it is possible to identify the presence of SA and to categorize SA as obstructive, central, or complex sleep apnea [26, 33].

The CPC analysis automatically generates an ECG-derived sleep spectrogram (Fig. 1), presenting a distinct bimodal-type of sleep periods during non-rapid eye movement sleep (NREM), alternating between high- and low-frequency cardiopulmonary coupling (CPC). High-frequency coupling, HFC (stable sleep), occurs during part of stage N2 and all of N3 NREM sleep. During stable sleep periods, desirable sleep features dominate (periods of stable breathing, strong sinus arrhythmia, blood pressure dipping, non-cyclic alternating pattern (non-CAP) electroencephalogram (EEG)). Conversely, during low-frequency coupling, LFC (unstable sleep) periods of less desirable sleep features dominate (variability of tidal volumes, non-dipping of blood pressure, and cyclic alternating pattern (CAP) EEG). Normal rapid eye movement sleep and wake show very low-frequency coupling signature (vLFC) while fragmented REM sleep is part of LFC (Fig. 2) [23, 26].

Being based on analyzing ECG data and not relying on EEG amplitudes, the CPC method is not constrained by the "loss" of slow wave sleep associated with aging and apparent in individuals over the age of 40–50 years for whom stage N3 makes up less than 20% of the sleep period [23, 34] eliminating reliance on absolute delta power for detecting sleep apnea. Increase in the CPC $eLFC_{NB}$ index has been associated with hypertension and stroke [35], unstable sleep negatively affects glucose disposal characteristics [36], and stable sleep is reduced in cases of depression [37, 38] and heart failure [39].

Clinical diagnosis of sleep apnea is currently primarily based on the Apnea Hypopnea Index (AHI). This study examines the feasibility of analyzing single lead ECG data and applying the SQI and SAI together with the underlying CPC parameters of high-frequency coupling (HFC), low-frequency coupling (LFC), and markers of sleep pathology, $eLFC_{BB}$, and

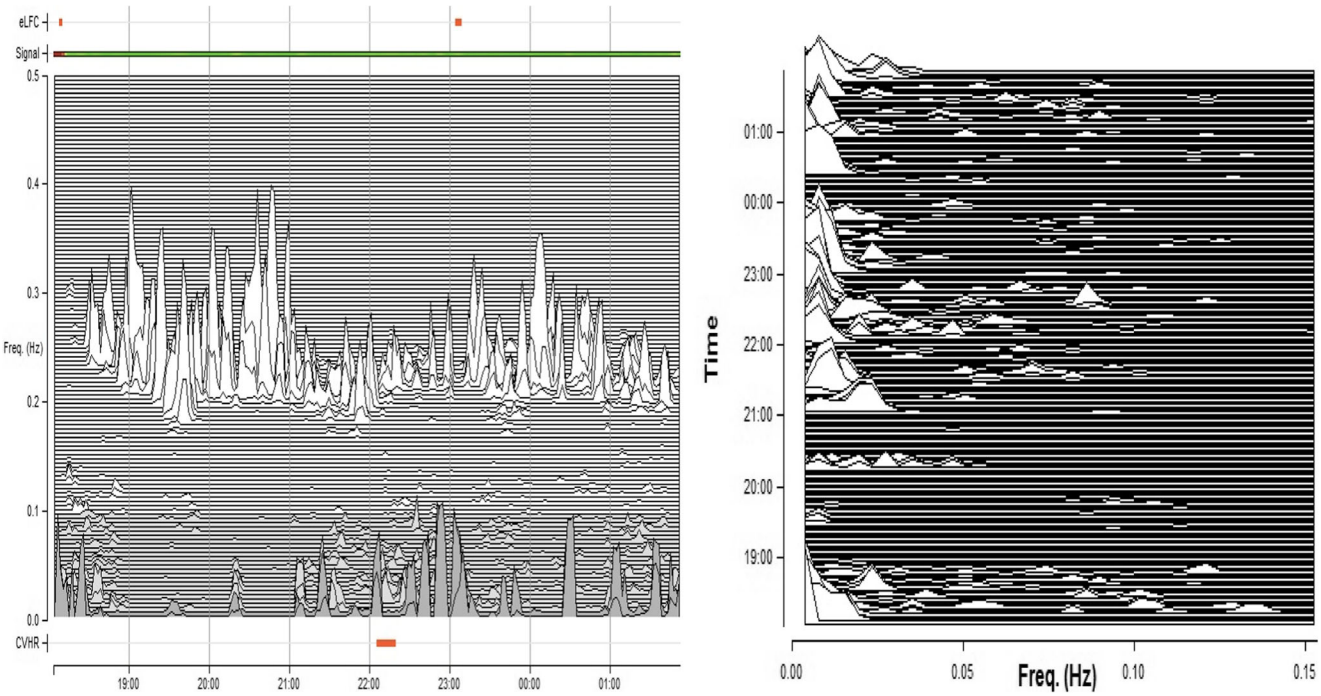

Fig. 1 Sleep spectrogram-healthy sleep (patient-c01); front view spectrogram (left) and 90-view spectrogram (right). SQI = 84, HFC = 82%, LFC = 8%, $eLFC_{BB} = 1\%$, $eLFC_{NB} = 0\%$, SAI = 0, AHI = 0

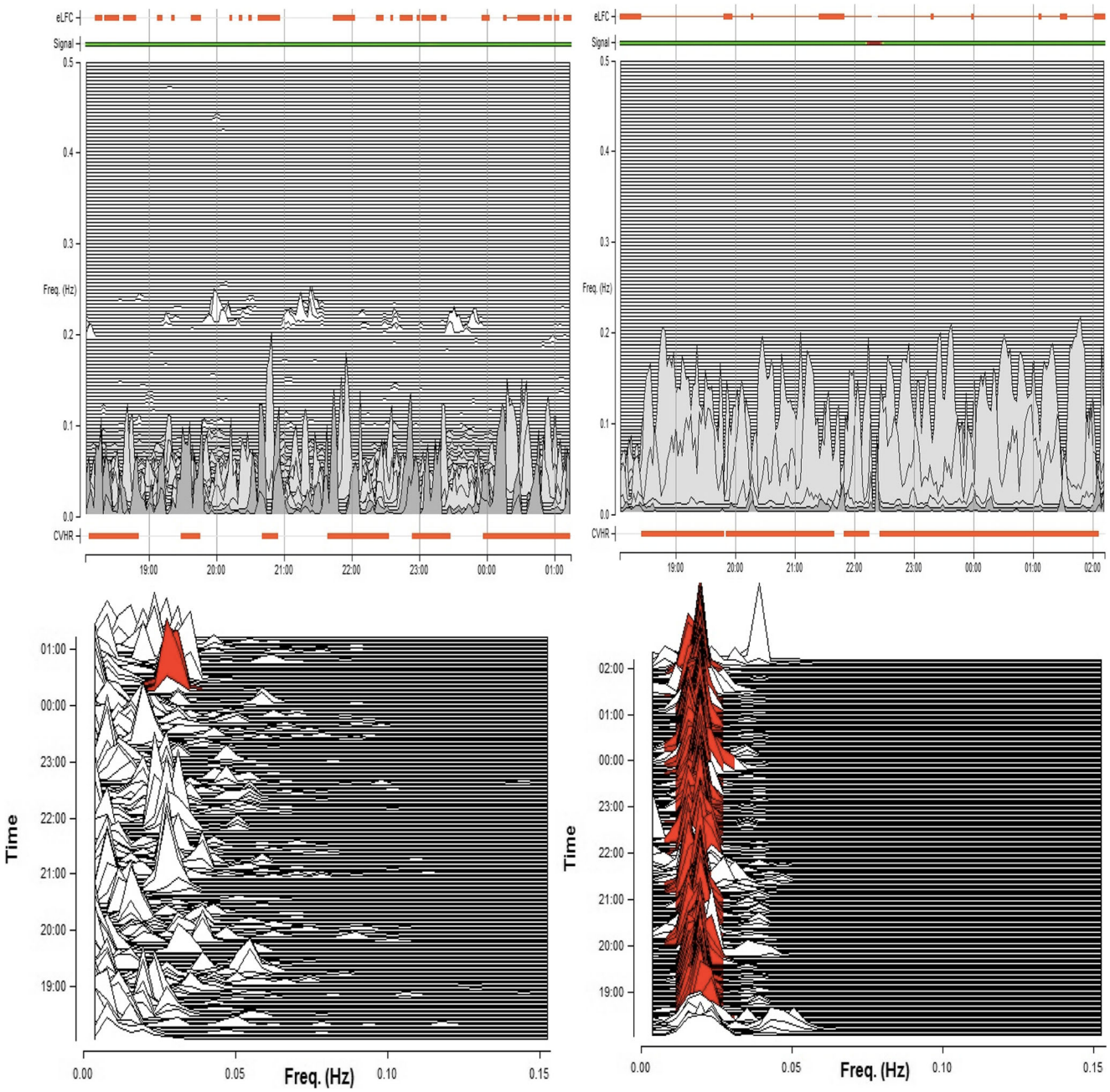

Fig. 2 Front view sleep spectrogram-left (patient-b03); obstructive sleep apnea (AHI = 24) (left); SQI = 21, HFC = 7%, LFC = 76%, $eLFC_{BB}$ = 40%, $eLFC_{NB}$ = 2%, SAI = 56. Sleep spectrogram (× 27); front view sleep spectrogram—right; central sleep apnea (AHI = 75) (right). SQI = 17, HFC = 0%, LFC = 99%, $eLFC_{BB}$ = 17%, $eLFC_{NB}$ = 82%, SAI = 89. Note the lack of stable sleep and increase in unstable sleep in both cases and the difference between when looking at the 90-view spectrograms below with respect to $eLFC_{BB}$, a marker of obstructive sleep apnea and $eLFC_{NB}$, a marker of periodic breathing

$eLFC_{NB}$ to establish criteria to aid clinical evaluation of SA to diagnose and better guide therapy management during hospitalization [15–19].

We hypothesized that the CPC metrics may aid in detecting SA in at-risk patients with at least the same degree of accuracy as is commonly accepted for clinical diagnosis-based AHI values and may offer guidance to therapy initiation during hospitalization for potentially faster recovery and reduced risk of readmission (the reference inter-agreement standard for scoring PSG studies is 80%) [40–42].

Outcome measures

The CPC parameters of interest to identify SA are SQI and SAI combined with either $eLFC_{BB}$, correlating with sleep

fragmentation or $eLFC_{NB}$, correlating with periodic breathing and central sleep apnea. These outputs from the automated analysis of CPC are compared with a manually scored PSG-derived AHI to distinguish moderate to severe SA.

Statistical analysis

The data was categorized based on clinical diagnostic criteria determined by the manual scoring of the PSG studies using the AHI. Results between patient groups were presented as means with the associated standard deviations and compared for each category (no disease, mild disease, or severe disease) for PSG versus CPC variables separately. Statistical significance was rejected for p values > 0.01, and receiver operating characteristics were calculated for comparison between the two outcome metrics of CPC and AHI. Stata 12.0 was used for the analysis [43].

Results

Study sample allocation

ECG signal from 68 studies from the PhysioNet database was analyzed. The data is grouped based on AHI scoring, no-mild SA (n = 26), moderate SA (n = 11), and severe SA (n = 31). Sleep time, sleep quality (SQI), and CPC sleep pathology markers of SAI, $eLFC_{BB}$, and $eLFC_{NB}$ were compared to AHI. Table 1 summarizes the cohorts' characteristics; of the total of 68 patients, there were 13 females (F) (19.1%) and 55 males (M) (80.8%) with a mean age of 45.1 ± 10.9 (F 32.8 ± 0.1 vs. M 48.1 ± 9.6) and range of 27–63 years. The mean body mass index (BMI) was 27.6 ± 6.0 (F 22.1 ± 0.1 vs. M 28.8 ± 5.7).

PSG parameters

Of the total of 68 patients, the manually scored AHI identified a total of 42 patients with SA. Patients identified with no or mild SA (n = 26), moderate SA (n = 11), and severe SA (n = 31).

CPC parameters

The CPC parameters are summarized in Table 2. Patients identified with no or mild SA (n = 26) were identified to have statistically significant (p < 0.01) shorter sleep duration (CPC period), higher SQI, a lower SAI, less unstable sleep (LFC), and lower $eLFC_{BB}$ and $eLFC_{NB}$, when compared to both the group identified with moderate (n = 11) and severe SA (n = 31).

Receiver operating characteristics comparing CPC vs. AHI are summarized in Table 3. Of the total of 68 patients when combining SQI, SAI and the sleep pathology markers $eLFC_{BB}$ and $eLFC_{NB}$ for SA identification, the system identified a total

Table 2 Multivariate analysis of variance comparing variables between sleep apnea categories

	p value					
	(α) Normal-mild (n = 26)	(β) Moderate (n = 11)	(δ) Severe (n = 31)	α vs β	α vs δ	β vs δ
Age	36 (± 0.18)	55.5 (± 5.57)	49.1 (± 8.34)	0.00	0.00	0.00
Height (cm)	175 (± 0.87)	175.7 (± 2.61)	176.6 (± 3.74)	0.76	0.00	0.00
Weight (kg)	70 (± 0.36)	88.9 (± 9.82)	97.1 (± 14.46)	0.06	0.00	0.00
BMI	22.8 (± 0.12)	28.8 (± 3.31)	31.1 (± 4.54)	0.06	0.00	0.00
AHI	1.4 (± 0.02)	20.1 (± 3.21)	54.6 (± 18.18)	0.00	0.00	0.00
Duration (min)	441(± 2.22)	497.6 (± 22.86)	497.3 (± 23.72)	0.01	0.00	0.00
SAI	7.1 (± 0.05)	34.1 (± 22.03)	65.5 (± 21.42)	0.00	0.00	0.00
SQI	54.7 (± 0.28)	31.6 (± 13.41)	19 (± 7.71)	0.00	0.00	0.00
HFC (%)	46.9 (± 0.25)	24.9 (± 16.3)	9.8 (± 10.08)	0.02	0.00	0.00
LFC (%)	27.5 (± 0.15)	65.2 (± 15.35)	82.2 (± 13.53)	0.00	0.00	0.00
vLFC (%)	21.3 (± 0.11)	9.4 (± 2.55)	7.1 (± 4.6)	0.00	0.00	0.00
$eLFC_{BB}$(%)	10 (± 0.06)	31.8 (± 13.18)	35.2 (± 17.38)	0.00	0.00	0.00
$eLFC_{NB}$(%)	0.9 (± 0.02)	12.8 (8.16)	31.9 (21.08)	0.00	0.00	0.00
HFC ↔ vLFC	14 (± 0.07)	3.5 (± 2.5)	2.5 (± 2.26)	0.00	0.00	0.00
HFC ↔ LFC	12.9 (± 0.07)	17.5 (± 7.94)	7.8 (± 7.21)	0.02	0.00	0.00
vLFC ↔ LFC	21.7 (± 0.12)	19.5 (± 5.54)	13.5 (± 7.84)	0.28	0.00	0.00

BMI body mass index, *AHI* Apnea-Hypopnea Index, *SAI* Sleep Apnea Index, *SQI* Sleep Quality Index, *HFC* high-frequency coupling, *LFC* low-frequency coupling, *vLFC* very low-frequency coupling, *eLFCbb* elevated low-frequency coupling broad band, *eLFCnb* elevated low-frequency coupling narrow band, *HFC ↔ vLFC* sum of CPC transactions between HFC and vLFC, *HFC ↔ LFC* sum of CPC transition between HFC and LFC, *vLFC ↔ LFC* sum of CPC transitions between vLFC and LFC

Table 3 Receiving operating characteristics

		AHI^	
		1	0
SAI &	1	42	5
CPC*	0	0	21
		Sensitivity	100%
		Specificity	81%
		PPV	89%
		NPV	100%
		Agreement	93%
		PABAK	0.85
		LR+	5.20
		LR−	0.00

PPV positive predictive value, *NPV* negative predictive value, *PABAK* prevalence and bias adjusted kappa, *LR+* positive likelihood ratio, *LR−* negative likelihood ratio

*SAI = > 15 I eLFCbb > 18% I eLFCnb ➔ positive sleep disorder breathing

^AHI = > 15 ➔ positive sleep disorder breathing

of 47 patients with moderate to severe SA compared to 42 patients identified by the AHI.

The automated system identified patients with moderate to severe SA with sensitivity of 100% ($CI_{95\%}$ 1.0, 1.0), specificity of 81% ($CI_{95\%}$ 0.656, 0.959), agreement of 93%, LR+ (positive likelihood ratio) of 5.20 and LR− (negative likelihood ratio) of 0.00 and kappa 0.85 when compared with the manual scoring of AHI.

Discussion

The PhysioNet database is scored using AASM scoring rules 1999 [44] which are based on more stringent scoring guidelines than the current AASM scoring rules that now include scoring of hypopneas [45]. The CPC algorithms are, however, designed to work with the current AASM scoring rules, which may explain why 5 out of the 26 individuals who were identified as normal or having a mild sleep apnea in the PhysioNet database (AHI < 15) were identified with moderate to severe sleep disorder breathing symptoms. The CPC algorithms, based on low sleep quality (SQI < 55), increased unstable breathing (LFC > 30%), increased markers of sleep fragmentation and obstructive sleep apnea ($eLFC_{BB} > 15\%$) or periodic breathing ($eLFC_{NB} > 2\%$) and sleep apnea indicator (SAI > 15) in this analysis have shown consistency with AASM current scoring rules for moderate-severe sleep apnea as in similar clinical studies [26].

A fundamental assumption in comparing two methods is that the test results are compared to an error-free reference standard. To diagnose SA, the reference standard is human scored PSG data. A wide body of literature has documented that expert human scoring has substantial inter-rater and intra-rater variability and is therefore an imperfect standard to compare to. As there is no anatomic or physiologic "gold standard" for the diagnosis of SA, in contrast to conditions where a tissue biopsy result can serve as the definitive reference standard, which makes true sensitivity and specificity analysis of PSG in diagnosing not straightforward and poses a practical difficulty in diagnosing SA [40–42]. Assessing validity of a new method to identify SA, it should not only be based on how well it compares the results of the reference standard, but also how comparable it is to agreement between currently used methods for clinical diagnosis. Our analysis demonstrates a high concordance between the CPC method when compared to manually scored AHI from PSG studies, to determine the presence or absence of SA. Sensitivity of 100%, specificity of 81%, a low NPV (negative predictive value, 100%), a good PPV (positive predictive value, 89%), and agreement with PSG diagnostic studies of 93%, rendering it sufficiently reliable compared to currently accepted methods to aid clinical diagnosis and guide clinical management in the hospital.

Several publications have looked at algorithms for automated ECG detection of SA based on wavelet analysis of R-R intervals classifying minute-by-minute apnea/hypopnea periods to discriminate SA patients from normal subjects [46–50] and found that these methods tend to overestimate AHI in central apnea patients and patients with periodic leg movements (PML). Autonomic activations and heart rate changes are known to happen during PLM episodes consistent with CVHR [51, 52] although they have been reported to have a briefer duration and shorter cycle length than those associated with SA causing an overlap between CVHR accompanied by PLM and CVHR accompanied by SA.

The CPC analysis incorporates an automated method to distinguish between CVHR happening during stable breathing (HFC) and CVHR that happens during unstable breathing (LFC), thus automatically excluding CVHR events happening during stable breathing from being included in sleep disordered breathing calculations that would overestimate sleep apnea episodes. The CPC spectral analysis automatically displays a subset of data in the low-frequency band (LFC), an elevated-low frequency (eLFC), enabling clear and easily observed differentiation between obstructive breathing and central or periodic breathing. Sleep apnea caused by respiratory control dysfunction shows almost metronomic characteristics of oscillations, presented as elevated-low frequency narrow band coupling ($eLFC_{NB}$) on the sleep spectrogram detecting sustained periods of central apnea (CSA) or periodic breathing vs. apneas driven by upper airway anatomical obstruction (OSA) presenting more variable patterns of oscillations, presented as elevated-low frequency coupling broad-band ($eLFC_{BB}$) correlating with sleep fragmentation and obstructive apnea-hypopnea [22, 26, 33]. CPC is thus able to

distinguish between unstable breathing directly reflected in the SAI and pure PLMs that would show up in the SAI to be < 15 and a high total CVHR. The relationship between PLMs vs. both arousals and respiratory events during PSG recordings and clinical evaluation is complex. When they ultimately coexist, either clinical correlation or follow-up reassessment is required.

These results indicate that when compared to manually scored PSG studies, the automated CPC technology can be applied to existing ECG data to accurately identify patients that may test positive for SA, thus providing a powerful ECG-based tool to risk stratify patients and improve clinical decision-making based on data that is already collected but not currently analyzed for sleep pathology. ECG is a widely collected signal to monitor CVD patients using both Holter and hospital monitors representing a missed opportunity to identify sleep apnea and initiate treatment when appropriate, given the positive impact SA management can have on chronic care of CVD patients. Abundant evidence exists that confirms a pathophysiologic link between OSA and CVD and that CPAP treatment benefits certain CVD patient populations [9–11], although further studies of this question are still required to fully comprehend this question 53.

There are several limitations to this study. The demographic heterogeneity within the small study sample is significant representing both a strength and a weakness. The small population sample contained within the database limits generalizability of the actual findings to any given population. This study demonstrates a potential application of the CPC algorithms to a clinical sample of stored ECG data. The lack of subjects with CSA is reinforced as an additional limitation acknowledging the rates of CSA in any given sample would be highly dependent on presence or absence of discreet CSA risk factors.

PLMs may have been present in this cohort; hence, to mitigate overdiagnosis, we have confined this automated analysis to moderate and severe OSA.

These findings might have implications for future clinical interventions. Using CPC to analyze ECG data that is already collected during sleep such as in hospital settings, to accurately and cost-effectively identify SA may deliver output that can be reliably used to identify sleep apnea at the point of care. This method will need to be tested in additional environments.

Acknowledgements Dr. Thomas Penzel of Philipps-University, Marburg, Germany who provided the data for this analysis, PhysioBank Database https://www.physionet.org/physiobank/database/apnea-ecg/ (assessed November 2016).

Author's contribution Neale Lange: Drafting and final approval of the manuscript.

Hugi Hilmisson: Analysis of data, initial drafting, and final approval of the manuscript.

Stephen P Duntley: Final approval of the manuscript.

Compliance with ethical standards

Formal consent was not required for this analysis, as the data had already been de-identified.

Conflict of interest Lange, Neale, MD:

Assistant Clinical Professor of Medicine, University of Colorado Health Sciences Center, Denver, CO; Partner Critical Care Pulmonary and Sleep Associates.

Dr. Lange declares no conflict of interest.

Hilmisson, Hugi, MA works as a data Analyst, MyCardio LLC. SleepImage is the brand name of MyCardio LLC, a privately held entity. MyCardio LLC is a licensee of the CPC algorithm, a method using ECG recordings during sleep to phenotype sleep and sleep apnea, from the Beth Israel Deaconess Medical Center, Boston, MA, USA.

Stephen P Duntley, MD declares no conflict of interest.

Abbreviations AASM, American Academy of Sleep Medicine; AHI, Apnea Hypopnea Index; CAP, Cyclic alternating pattern; CPC, Cardiopulmonary coupling; CPAP, Continuous positive airway pressure; CVD, Cardiovascular disease; CVHR, Cyclic variation of heart rate; EDR, ECG-derived respiration; ECG, Electrocardiogram; EEG, Electroencephalogram; $eLFC_{BB}$, Elevated low-frequency broad-band; $eLFC_{NB}$, Elevated low-frequency narrow-band; HRV, Heart rate variability; HFC, High-frequency coupling; LFC, Low-frequency coupling; NREM, Non-rapid eye movement sleep; non-CAP, Non-cyclic alternating pattern; PABAK, Prevalence adjusted and bias adjusted kappa; REM, Rapid eye movement; SAI, Sleep Apnea Indicator; SQI, Sleep Quality Index; VLFC, Very low frequency coupling

References

1. Gallicchio L, Kalesan B (2009) Sleep duration and mortality: a systematic review and meta-analysis. J Sleep Res 18:148–158. https://doi.org/10.1111/j.1365-2869.2008.00732.x2
2. Young T, Finn L, Peppard PE et al (2008) Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohorts. Sleep 31:1071–1078
3. Frost & Sullivan. Hidden Health Crisis Costing America Billions. American Academy of Sleep Medicine 2016 http://www.aasmnet.org/Resources/pdf/sleep-apnea-economic-crisis.pdf (assessed March 2017).
4. Peppard PE, Young TE, Barnet JH et al (2013) Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 177(9):1006–1014. https://doi.org/10.1001/jama.2014.17822
5. Leung RS, Comodore VR, Ryan CM et al (2012) Mechanisms of sleep-disordered breathing: causes and consequences. Pflugers Arch 463(1):213–230. https://doi.org/10.1007/s00424-011-1055-x
6. Arnardottir ES, Bjornsdottir E, Olafsdottir KA, Benediktsdottir B, Gislason T (2016) Obstructive sleep apnea in the general population: highly prevalent but minimal symptoms. Eur Respir J 47(1): 194–202. https://doi.org/10.1183/13993003.01148-2015
7. Beuters F, Reitzschel ER, Hertegonne KB, Chirinos JA (2016) The link between obstructive sleep apnea and cardiovascular disease. Curr Atheroscler Rep 18(1):1. https://doi.org/10.1007/s11883-015-0556-z
8. Khayat R, Pleister A (2016) Consequences of Obstructive Sleep Apnea: Cardiovascular Risk of Obstructive Sleep Apnea and Whether Continuous Positive Airway Pressure Reduces that Risk. Sleep Med Clin 11(3):273–286. https://doi.org/10.1016/j.jsmc.2016.05.002

9. Punjabi NM (2008) The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 5(2):136–143. https://doi.org/10.1513/ats/200709-155MG.
10. Fu Y, X Xia Y, Yi H, Xu H, Guan J, Yin S (2017) Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment. Sleep Breath 21(1):181–189. https://doi.org/10.1007/s11325-016-1393-1
11. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E (2016) Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. Am J Respir Crit Care Med 194(5):613–620. https://doi.org/10.1164/rccm.201601-0088OC
12. Costa SV, Ceolim MF (2013) Factors that affect inpatients' quality of sleep. Rev esc enferm 47(1):46–52. https://doi.org/10.1590/S0080-62342013000100006
13. Elliott R, McKinley S, Cistulli P, Fien M (2013) Characterization of sleep in intensive care using 24-hour polysomnography: an observational study. Crit Care 17(2):R46. https://doi.org/10.1186/cc12565
14. Shear TC, Balachandran JS, Mokhlesi B, Spampinato LM, Knutson KL, Meltzer DO, Arora VM (2014) Risk of sleep apnea in hospitalized older patients. Journ Clin. Sleep Med 10(10):1061–1066. https://doi.org/10.5664/jcsm.4098
15. Lockhart EM, Willingham MD, Abdallah AB, Helsten DL, Bedair BA, Thomas J, Duntley S, Avidan MS (2013) Obstructive sleep apnea screening and postoperative mortality in a large surgical cohort. Sleep Med 14:407–415. https://doi.org/10.1016/j.sleep.2012.10.018
16. Mokhlesi B, Hovda MD, Vekhter B, Arora VM, Chung F, Meltzer DO (2013) Sleep disordered breathing and postoperative outcome after elective surgery: analysis of a nationwide inpatient sample. Chest 144:903–914. https://doi.org/10.1378/chest.12-2905
17. Kaula S, Keenan B, Goldberg L et al (2014) Diagnosis and treatment of sleep disordered breathing in hospitalized cardiac patients: a reduction in 30-day hospital readmission rates. Journ Clin. Sleep Med 10(10):1051–1059. https://doi.org/10.5664/jcsm.4096
18. Truong K, Jardin R, Massoudi N, Hashemzedeh M, Jafari B (2018) Nonadherence to CPAP associated with increased 30- day hospital readmissions. J Clin Sleep Med 14(2):1–7. https://doi.org/10.5664/jcsm.6928
19. Sharma S, Chowdhury A, Tang L, Willes L, Glynn B, Quan SF (2016) Hospitalized patients at high risk for obstructive sleep apnea have more rapid response system events and intervention is associated with reduced events. PLoS One 11:e0153790
20. Kapur VK, Auckley DH, Chowdhuri S (2017) Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of sleep medicine clinical practice guide. J Clin Sleep Med 13(3):479–504. https://doi.org/10.5664/jcsm.6506
21. Chung F, Abdullah H, Liao P et al (2016) STOP-Bang questionnaire: a practical approach to screen for obstructive sleep apnea. Chest 149(3):631–638. https://doi.org/10.1378/chest.15-0903
22. Thomas RJ (2016) CardioPulmonary coupling sleep spectrograms. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine, 6th edn. Elsevier, Inc, Philadelphia, pp 1615–1623
23. Thomas RJ, Mietus JE, Peng CK, Guo D, Gozal D, Montgomery-Downs H, Gottlieb DJ, Wang CY, Goldberger AL (2014) Relationship between delta power and the electrocardiogram-derived cardiopulmonary spectrogram. Possible implications for assessing the effectiveness of sleep. Sleep Med 15(1):125–131. https://doi.org/10.1016/j.sleep.2013.10.002
24. Mietus JE, Peng CK, Ivanov PC, Goldberger AL (2000) Detection of obstructive sleep apnea from cardiac interbeat interval time series. Comput Cardiol 27:753–758. https://doi.org/10.1109/CIC200
25. Guilleminault C, Connolly S, Winkle R, Melvin K, Tilkian A (1984) Cyclical variation of the heart rate in sleep apnea syndrome: mechanisms, and usefulness of 24h electrocardiography as a screening technique. Lancet 1:126
26. Magnusdottir S, Hilmisson H (2017) Ambulatory screening tool for sleep apnea: analyzing a single-lead electrocardiogram (ECG). Sleep Breath; E-Pub September 22:421–429. https://doi.org/10.1007/s11325-017-1566-6
27. Lee WH, Hong SE, Kim HJ et al (2016) A Comparison of Different Success Definitions in Non-Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea Using Cardiopulmonary Coupling. J Clin Sleep Med 1:35–41. https://doi.org/10.5664/jcsm.5388
28. Lee WH, Ahn JC, We J, Rhee CS, Lee CH, Yun PY, Yoon IY, Kim JW (2014) Cardiopulmonary coupling analysis: changes before and after treatment with mandibular advancement device. Sleep Breath 18(4):891–896. https://doi.org/10.1007/s11325-014-0961-5
29. Choi JH, Thomas RJ, Suh SY, Park IH, Kim TH, Lee SH, Lee HM, Yun CH, Lee SH (2015) Sleep quality changes after upper airway surgery in obstructive sleep apnea. Electrocardiogram-based cardiopulmonary coupling analysis. Laryngoscope 125(7):1737–1742. https://doi.org/10.1002/lary.25101
30. Schramm PJ, Thomas R, Feige B (2013) Et.al. Quantitative measurement of sleep quality using cardiopulmonary coupling analysis: a retrospective comparison of individuals with and without primary insomnia. Sleep Breath 17:713–721. https://doi.org/10.1007/s11325-012-0747-6
31. Thomas RJ, Wood C, Bianchi M (2018) Cardiopulmonary coupling spectrogram as an ambulatory clinical biomarker of sleep stability and quality in health, sleep apnea and insomnia. Sleep 41(2):1–11. https://doi.org/10.1093/sleep/zsx196
32. Goldberger AL, Amaral LAN, Glass L, Hausdorff JM, Ivanov PCH, Mark RG, Mietus JE, Moody GB, Penc CK, Stanley HE (2000) PhysioBank, PhysioToolkit and PhysioNet: components of a new research resource for complex physiologic signals. Circulation 101(23):e215–e220. https://doi.org/10.1161/01CIR10123.e215
33. Thomas RJ, Mietus JE, Peng CK et al (2007) Differentiation obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. Sleep 30(12):1756–1759
34. Ancoli-Israel S (2009) Sleep and its disorders in aging populations. Sleep Med 10(Suppl 1):S7–S11. https://doi.org/10.1016/jsleep.2009.07.004
35. Thomas RJ, Weiss MD, Mietus JE et al (2009) Prevalent hypertension and stroke in the Sleep Heart Health Study: association with an ECG-derived spectrographic marker of cardiopulmonary coupling. Sleep 32(7):897–904
36. Pogach MS, Punjabi NM, Thomas N et al (2012) Electrocardiogram-based sleep spectrogram measures of sleep stability and glucose disposal in sleep-disordered breathing. Sleep 35:139–148. https://doi.org/10.5665/sleep.1604
37. Yang AC, Yang CH, Hong CJ et al (2011) Sleep state instabilities in major depressive disorder: Detection and quantification with electrocardiogram-based cardiopulmonary coupling analysis. Psychophysiology 48(2):285–291. https://doi.org/10.1111/j.1469-8986.2010.01060.x
38. Schramm PJ, Polland RE, Rao U et al (2014) Bupropion response on sleep quality in patients with depression: implications for increased cardiovascular disease risk. Eur Neuropsychopharmacol 24(2):207–214. https://doi.org/10.1016/j.euroneuro.2013.09.007
39. Yeh GY, Mietus JE, Peng CK et al (2008) Enhancement of sleep stability with Tai Chi exercise in chronic heart failure: preliminary findings using and ECG-based spectrogram method. Sleep Med 9(5):527–536. https://doi.org/10.1016/j.sleep.2007.06.003
40. Magalang UJ, Chen NH, Cistulli PA et al (2013) Agreement in the scoring of respiratory events and sleep among international sleep centers. Sleep 36:591–596. https://doi.org/10.5665/sleep.2552
41. Ho V, Crainiceanu C, Punjabi N et al (2015) Calibration model for apnea-hypopnea indices: impact of alternative criteria for hypopneas. Sleep 38(12):1887–1892. https://doi.org/10.5665/sleep.5234

42. Centers for Medicare and Medicate Services https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=227&ver=11&NcaName=Sleep+Testing+for+Obstructive+Sleep+Apnea+(OSA)&CoverageSelection=National&KeyWord=sleep+testing&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAACAAEAAA& (accessed Jan 2017)
43. StataCorp (2011) Stata statistical software: release 12. StataCorpLP, College Station
44. American Academy of sleep Medicine Task Force (1999) Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 22(5):667–689
45. Kapur V, Auckley D, Chowdhuri S et al (2017) Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of sleep medicine clinical practice guideline. J Clin Sleep Med 13(3):479–504. https://doi.org/10.5664/jcsm.6506.
46. Penzel T, McNames J, Murray A et al (2002) Systematic comparison of different algorithms for apnoea detection based on electrocardiogram recordings. Med Biol Eng Comput 40(4):402–407
47. Varon C, Caicedo A, Testelmans D, Buyse B, van Huffel S (2015) A novel algorithm for the automatic detection of sleep apnea from single-lead ECG. IEEE Trans Biomed Eng 62(9):2269–2278. https://doi.org/10.1109/TBME.2015.2422378
48. Hayano J, Watanabe E, Saito Y, Sasaki F, Fujimoto K, Nomiyama T, Kawai K, Kodama I, Sakakibara H (2011) Screening for obstructive sleep apnea by cyclic variation of heart rate. Circ Arrythym Electrophysiol 4(1):64–72. https://doi.org/10.1161/CIRCEP.110.958009
49. Mendez MO, Cortbout J, van Huffel S, Matteucci M, Penzel T, Cerutti S, Bianchi AM (2010) Automatic screening of obstructive sleep apnea from the ECG based on empirical mode decomposition and wavelet analysis. Physiol Meas 31:273–289
50. Khandoker AH, Palaniswami M, Karmakar CK (2002) Support vector machines for automated recognition of obstructive sleep apnea syndrome from ECG recordings. Med Biol Eng Comput 40:402–407
51. Sforza E, Pichot V, Barthelemy JC, Haba-Rubio J, Roche F (2005) Cardiovascular variability during periodic leg movements: a spectral analysis approach. Clin Neurophysiol 116(5):1096–1104. https://doi.org/10.1016/j.clinph.2004.12.018
52. Gugisberg AG, Hess CW, Mathis J (2007) The significance of the sympathetic nervous system in the pathophysiology of periodic leg movements in sleep. Sleep 30:755–766. https://doi.org/10.1213/ane.0b013e318187c83a
53. McNicholas (2016) Continuous positive airway pressure therapy and cardiovascular outcomes in obstructive sleep apnoea syndrome: where are we now? J Thorac Dis 8(12):E1644–E1646. https://doi.org/10.21037/jtd.2016.12.36