INSTRUMENTATION AND METHODOLOGY

An Electrocardiogram-Based Technique to Assess Cardiopulmonary Coupling During Sleep

Robert Joseph Thomas, MD, MMSc; Joseph E. Mietus, BS; Chung-Kang Peng, PhD; Ary L. Goldberger, MD
1Division of Pulmonary, Critical Care and Sleep Medicine, 2Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA

Study Objectives: To evaluate a new automated measure of cardiopulmonary coupling during sleep using a single-lead electrocardiographic signal.

Design: Using training and test datasets of 35 polysomnograms each, we assessed the correlations of an electrocardiogram-based measure of cardiopulmonary interactions with respect to standard sleep staging, as well as to the cyclic alternating pattern classification. The pattern of coupling in 15 healthy individuals was also assessed.

Setting: American Academy of Sleep Medicine Accredited Sleep Disorders Center.

Interventions: None.

Measurements and Results: From a continuous, single-lead electrocardiogram, we extracted both the normal-to-normal sinus interbeat interval series and a corresponding electrocardiogram-derived respiration signal. Employing Fourier-based techniques, the product of the coherence and cross-power of these 2 simultaneous signals was used to generate a spectrographic representation of cardiopulmonary coupling dynamics during sleep. This technique shows that non-rapid eye movement sleep in adults demonstrates spontaneous abrupt transitions between high- and low-frequency cardiopulmonary coupling regimes, which have characteristic electroencephalogram, respiratory, and heart-rate variability signatures in both health and disease. Using the kappa statistic, agreement with standard sleep staging was poor (training set 62.7%, test set 43.9%) but higher with cyclic alternating pattern scoring (training set 74%, test set 77.3%).

Conclusions: A sleep spectrogram derived from information in a single-lead electrocardiogram can be used to dynamically track cardiopulmonary interactions. The 2 distinct (bimodal) regimes demonstrate a closer relationship with visual cyclic alternating pattern and non-cyclic alternating pattern states than with standard sleep stages. This technique may provide a complementary approach to the conventional characterization of graded non-rapid eye movement sleep stages.

Keywords: Cyclic alternating pattern, Fourier analysis, heart-rate variability, non-REM sleep, sleep-disordered breathing

Citation: Thomas RJ; Mietus JE; Peng CK et al. An electrocardiogram-based technique to assess cardiopulmonary coupling during sleep. SLEEP 2005;28(9): 1151-1161.

INTRODUCTION

THE DEVELOPMENT OF A READILY OBTAINED, SURROGATE MARKER OF SLEEP QUALITY HAS POTENTIALLY IMPORTANT CLINICAL IMPLICATIONS, AS STANDARD polysomnography is expensive and encumbering. Conventional sleep stages are scored as wake, rapid eye movement (REM) sleep, and an approximate continuum of depth (stages 1-4) during non-REM (NREM) sleep, which comprises about 80% of the average night. However, stages 3 and 4 decrease across the lifespan, and the majority of adult NREM sleep is stage 2, thus reducing the value of the conventional system as a precise measure of sleep quality: Enhanced quantitative assessments of sleep quality, especially if measurable in a simple and inexpensive manner such as from an electrocardiographic (ECG) signal, could have substantial clinical utility.

Autonomic nervous system dynamics, as measured by heart-rate variability, respiration, and related variables, have characteristic behaviors that vary according to sleep depth and type: Sleep-disordered breathing (SDB) is associated with predictable characteristics, such as the periodic cycling of respiration and heart rate. A number of methods to detect SDB from the surface ECG have been proposed. However, these methods, primarily based on detection of cardiac interbeat (R-R) interval dynamics, are of limited use in subjects with reduced heart-rate variability.

A complementary type of information independent of R-R variability, which can also be extracted from the surface ECG, is a surrogate respiration signal referred to as ECG-derived respiration (EDR). The EDR technique is based on the observation that the positions of the ECG electrodes on the chest surface move relative to the heart, and transthoracic impedance varies as the lungs fill and empty. Thus, the lead axes vary at different points in the respiratory cycle, and a sufficiently precise measurement of the mean cardiac electrical axis shows variations that are correlated with respiration. A detailed description of this technique, as well the source code for the algorithm, is available at http://www.physionet.org/physiotools/edr/.

The EDR signal, however, is difficult to quantify in long, typically noisy, clinical records. In preliminary observations, we have found that we could overcome the limitations and extend the utility of these previous approaches to ECG-based analyses during sleep by simultaneously incorporating both R-R and EDR information. Information related to simultaneous heart-rate and respiratory dynamics is readily extractable from a continuous single-lead ECG and can be used to generate a new spectrographic measure of cardiopulmonary coupling.

The purpose of the present study was (1) to evaluate this spectrographic representation of cardiopulmonary coupling obtained solely from a single-lead ECG and (2) to quantify the relation-
ship of the observed high- and low-frequency coupling regimes to standard sleep staging and to cyclic alternating pattern (CAP), a measure of sleep instability. In the CAP classification, unstable sleep is characterized by recurrent phasic electroencephalogram (EEG) complexes (CAP), a low threshold for arousal, and the predominance of periodic behaviors, such as SDB. Stable sleep is characterized by absence of recurrent phasic EEG complexes (non-CAP), elevated arousal thresholds, and minimal periodic behaviors, such as an absence of progressive flow abnormality.

METHODS

Training and Test Datasets

The technique was trained on data from patients with SDB because the states of unstable and stable NREM sleep, typically associated with the CAP and non-CAP EEG patterns, are especially distinct in these subjects (Figure 1, 2). We then evaluated the accuracy of the cardiopulmonary coupling measure in a test set of data from patients with SDB. In addition, we assessed cardiopulmonary coupling states in healthy adults, using a normative ECG database. The following 2 digital databases were used.

1. A total of 70 polysomnograms were acquired from the American Academy of Sleep Medicine-accredited Sleep Disorders Center at the Beth Israel Deaconess Medical Center and affiliated sleep laboratories for the period between December 2003 and July 2005. During this period, 900 polysomnograms were performed. The studies analyzed here were selected using the following criteria: (1) subjects were free of comorbid disease (diabetes, hypertension, heart failure, renal failure, stroke) and use of neuroactive medications such as benzodiazepines; (2) absence of respiratory-sway artifact on the EEG; and (3) low amounts of wake during sleep (< 15% total sleep time) and delta/slow-wave sleep (< 15% of NREM sleep time). The most common reasons to reject a study were neuroactive drug use (44%) and increased wake during the recordings (36%). EEG, electromyogram, eye movements, ECG, body position (direct observation and a position sensor), finger pulse oximetry, respiratory effort by piezo bands, and airflow with thermistors and nasal pressure were standard. During air-pressure titration, airflow was monitored with an in-line pneumotachograph. The training dataset consisted of polysomnograms from 35 adults (20 men) aged 46 ± 12 years, with a mean body mass index of 28 ± 4 kg/m². The distribution of study types was as follows: 22 diagnostic, including 11 without nocturnal hypoxia as defined by oxygen saturations remaining > 90%, and 13 titrations or combined diagnostic + titrations. A separate set of polysomnograms from 35 adults (28 men) was utilized as a test set. The mean age was 49 ± 18 years, with a mean body mass index of 31 ± 5 kg/m². The distribution of study types was as follows: 25 diagnostic, including 12 without hypoxia as defined above, and 10 positive pressure titration sleep studies. 2. The normative test set consisted of 15 subjects (9 men, 6 women, aged 20-41 years) recruited for a separate protocol. All subjects were disease and medication free, had regular sleep-wake schedules, and were nonobese (body mass index 24±2 kg/m²). The purpose of this additional test data was to demonstrate that the cardiopulmonary coupling states are not restricted to disease but are also a feature of sleep in healthy individuals. Visual CAP scoring was not done on the normative data, as we did not intend to evaluate a “CAP detector” but, rather, a sleep-state-stability estimator.

Polysomnogram Scoring and Data Export

Manual stage scoring used the standard method to first identify NREM stages 1-4, REM sleep, and wakefulness. Respiratory-event scoring rules were as follows. (1) Obstructive apnea was defined as an absence of airflow on the nasal cannula and a reduction in the oral thermistor signal to < 10% of baseline, with continued respiratory effort. Central apneas were scored when there was no evidence of effort. (2) Hypopnea was defined as any...
clearly evident reduction in amplitude of the nasal pressure signal, or flattening of the inspiratory flow profile, for 3 or more consecutive breaths, abruptly terminated with a return to a rounded or sinusoidal flow profile or a large recovery breath. Hypopneas were scored with and without 4% desaturation. The apnea-hypopnea index (AHI)-4% (apneas + hypopneas with 4% desaturation per hour of sleep) and AHI-0% (apneas + hypopneas regardless of desaturation per hour of sleep) reflect scores with and without desaturation. This scoring captured the entire spectrum of respiratory abnormality seen in clinical practice. The AHI-4% is the United States Medicare clinical criteria, while the AHI-0% utilizes the research recommendations of the American Academy of Sleep Medicine.27,28

Raw ECG signals (sampled at 64, 85.3, or 120 Hz) and EEG (sampled at 120 or 256 Hz) for delta frequencies (≤4 Hz) were exported in ASCII format using the relevant modules within the polysomnographic software (Sandman, Mallinckrodt, St. Louis, MO). Sampling rates varied at different affiliated sleep laboratories.

**CAP Scoring**

This classification, scored independently of the polysomnogram scoring, was based on the EEG alone, according to the CAP Atlas.29 The standard epoch duration to score CAP is 60 seconds. To improve state detection, the scoring was modified to allow 30-second designations by viewing the polysomnogram screen in 30-second epochs and designating each epoch as CAP or non-CAP. If there was ambiguity or difficulty with designation, the epoch duration was changed to 60 seconds to make a state determination. (CAP scoring is graphed along with the classic sleep stages in Figure 4-6 to allow a direct visual comparison.)

**Summary of Standard Scoring Rules for CAP**

1. Each CAP cycle consists of 2 components: phase A consisting of EEG transients, and phase B, defined as the interval of delta/theta activity that separates 2 successive A phases. The duration of each phase ranges from 2 to 60 seconds.
2. A CAP sequence includes at least 2 consecutive cycles.
3. Phase A characteristics are
   a. Intermittent alpha rhythm and sequences of vertex sharp waves in stage 1 sleep
   b. Sequences of 2 or more K-complexes, with or without alpha and beta rhythms
   c. Delta bursts showing a difference in amplitude of at least one-third compared with background activity
   d. Transient activation phases of microarousals in stage 1 and 2 or at the end of stage 3 and 4, characterized by an increase in EEG frequency with decreased amplitude, disappearance of sleep spindles and delta activity when occurring in slow wave sleep, transitory enhancement of muscle tone or appearance of electromyography activity, body movements, postural changes, and acceleration of heart rate.

A1 CAP is dominated by synchronized EEG patterns, A2 has evidence of both synchronization and desynchronization, and A3 shows predominantly EEG desynchronization.30 We visually rec-
recognized but did not differentiate among A1 to A3 types for this study, since, in the setting of SDB, A1 is rare, and the focus was detection of periods of CAP and non-CAP periods rather than individual phases.

ECG-Derived Cardiopulmonary Coupling Assessment

To estimate the degree of cardiopulmonary coupling between heart rate and respiration, we employed Fourier-based techniques to analyze the R-R interval series and its associated EDR signal. Using the Fourier transform, the R-R interval time series and EDR signals were first decomposed into a set of sinusoidal oscillations with specific amplitudes and phases at each frequency. Two key factors need to be considered in evaluating the strength of the coupling between these 2 signals. (1) If, at a given frequency, both signals have relatively large oscillation amplitudes, then it is likely that these 2 signals are coupled with each other. This effect can be measured by computing the cross-spectral power, ie, the product of the powers of the 2 individual signals at a given frequency. (2) If 2 oscillations at a given frequency are synchronized with each other (ie, they maintain a constant phase relationship), this effect can be measured by computing the coherence of these signals. We used the product of the coherence and the cross-spectral power to weight these 2 effects in order to quantify the degree of the cardiopulmonary coupling. Technical details are discussed in the Appendix.

The sequential steps in the derivation of the cardiopulmonary coupling measure are diagrammed in Figure 3. Using a single-lead ECG, an automated beat detection algorithm was used to detect beats and classify them as either normal or ectopic, based on their morphology and timing. Approximately 2% of all beats were classified as ectopic. In addition, amplitude variations in the QRS complex due to shifts in the cardiac electrical axis relative to the electrodes during respiration and changes in thoracic impedance were determined. These fluctuations in the mean cardiac electrical axis (typically between 1° and 12° peak-to-peak) correlate with phasic changes in the respiratory cycle. From these amplitude variations, a surrogate EDR was obtained as previously described. A time series of normal-to-normal sinus (N-N) intervals and the time series of the EDR associated with these N-N intervals was then extracted from the R-R interval time series. Outliers due to false or missed R-wave detections were removed using a sliding window average filter with a length of 41 data points. Central points lying outside 20% of the window average were rejected. The resulting N-N interval series and its associated EDR signal were then linearly resampled at 2 Hz. The cross-spectral power and coherence of these 2 signals were calculated over a 1024-sample (8.5-minute) window using the fast Fourier transform applied to the 3 overlapping 512-sample subwindows within the 1024 coherence window. In each subwindow, the data were first linearly detrended and windowed using the Hanning
We also observed that the ratio of the sum of the 2 maximal peaks in the very low-frequency band was associated with wake/REM periods while excess power in the high-frequency band is associated with physiologic respiratory sinus arrhythmia and deep sleep. Inspection of the cardiopulmonary coupling spectrograms suggested that the low- and high-frequency coupling regimes had only weak correlation with standard sleep staging but did follow CAP scoring where low-frequency coupling was associated with CAP and high-frequency coupling with non-CAP. We also observed that the ratio of the sum of the 2 maximal peaks in the very low-frequency band was associated with wake/REM periods. Using appropriate thresholds for these power ratios, sleep demonstrating non-CAP, CAP, and wake/REM states could be identified. Because sleep stages were scored in 30-second epochs and the ECG-derived coherent cross power calculated every 2.1 minutes, 30-second linear interpolation between the consecutive 2.1-minute measurements was used to calculate spectral power corresponding to each scored epoch. For each of the 3 sleep states of non-CAP, CAP, and combined wake/REM sleep, separate receiver-operator curves were calculated over a range of power thresholds, and the thresholds giving the maximum combined sensitivities and specificities for that state were selected as optimal for the detection of that state.

We first detected non-CAP using power thresholds giving the maximal sensitivity and specificity for non-CAP epoch-by-epoch detection. Specifically, we required a given minimum high-frequency power (> 0.02 normalized units) and a low-to-high ratio below a set value (< 2.0). If an epoch was not detected as non-CAP, we next applied CAP-detection criteria, again using thresholds giving maximal sensitivities and specificities for epoch-by-epoch detection. Here we required a given minimum low-frequency power (> 0.2 normalized units) and a low-to-high ratio above a set value (> 2.0). Finally, if an epoch was not detected as either non-CAP or CAP, we detected wake/REM sleep using thresholds giving maximal sensitivity and specificity for its epoch-by-epoch detection. For this detection, we required a minimum very low-frequency power (> 0.05 normalized units) and a minimum ratio of very-low to combined low- and high-frequency power (> 0.2). A small percentage of epochs (approximately 4%) were not detected as non-CAP, CAP, or wake/REM sleep and were classified as “indeterminate.”

Statistical Methods

Database characteristics are summarized as means, ranges, and SD; summary statistics for cardiopulmonary coupling detection of state include sensitivity, specificity, and positive predictive value. We also quantified the statistical agreement between automated ECG-based detections of low- and high-frequency coupled states with epoch-by-epoch scorings of standard sleep stages and visual scoring of CAP/non-CAP states. To this end, we considered each set of methods as “independent scorers” and evaluated “interscorer agreement” using the kappa statistic (STATA 8, StataCorp LP, College Station, Texas). For the comparison between ECG-based detection and standard stages, we restricted the calculation to stages 2 to 4 because stage 1 is always CAP on visual scoring and REM sleep in patients with SDB is indistinguishable physiologically from CAP. If the agreement between ECG-based detection of sleep state with either standard scoring or CAP scoring is high, the corresponding kappa value will be closer to 1. If the agreement is low, the corresponding kappa value will be closer to 0.

RESULTS

Data and Subject Characteristics

Tables 1 and 2 summarize subject and data characteristics. The training dataset had 35 polysomnograms that provided a total of 12,464 minutes of data with 10.5% wake, 14.8% REM, 49.0% CAP, and 25.8% non-CAP (visual EEG CAP scoring). The respiratory scoring summary was a mean AHI-4% of 26 ± 12, and a mean AHI-0% (of 46 ± 12, range: 8-76), and a mean AHI-0% (of 46 ± 12, range: 22-84). Lowest sleep oxygen saturation was 74 ± 12%. All patients had obstructive disease, although 6 showed significant amounts of pe-
riodic breathing. No patient had dominant or pure central sleep apnea. The test dataset also had 35 polysomnograms and provided a total of 11,461 minutes of data with 6.3% wake, 14.3% REM, 36.8% CAP, and 42.5% non-CAP. The respiratory scoring summary was a mean AHI-4% of 22 ± 7 (range: 0 - 53) and a mean AHI-0% of 36 ± 16 (range: 13 - 65). The lowest sleep oxygen saturation was 81% ± 9%. All patients had obstructive disease. The normative dataset was comprised of 15 polysomnograms that provided a total of 6474 minutes of data with 10.5% wake, 21% REM, 10.2% stage 1, 52.1% stage 2, 4.1% stage 3, and 1.9% stage 4. The respiratory scoring summary was a mean AHI-4% of 0 and a mean AHI-0% of 9 ± 8 (range: 2-23). Virtually all scored events were of the mild flow-limitation type. The lowest sleep oxygen saturation was 94% ± 2%.

ECG-Based Cardiopulmonary Coupling Analysis

SDB Training Dataset

Visual inspection of the spectrograms revealed that ECG-based low- and high-frequency coupling states did not correlate strongly with standard sleep stages. For example, both these coupling behaviors occurred in studies that had no scored slow-wave sleep. Quantitative analyses, however, revealed that these ECG-based states did track the course of sleep scoring in the CAP /non-CAP domains. Visually scored CAP versus ECG-coupling sleep state sensitivities and specificities were as follows: CAP: 58% and 68%; non-CAP: 62% and 81%; wake/REM: 37% and 85%, respectively (Table 2). Forty-five percent of sleep was detected as CAP, 30% as non-CAP, and 21% as wake/REM, with 4% indeterminate. Twenty-one REM-sleep fragments (537 minutes from 12 of the above polysomnograms) were then evaluated separately. The cardiopulmonary coupling detector performed consistently in detecting REM sleep with overt apneas and hypopneas as low-frequency coupled sleep CAP (92% of 250 minutes). In contrast, when the sole abnormality was flow limitation with arousals, detection dropped to 60% of 287 minutes.

Test Datasets

SDB Test Database

The ECG-based technique detected clearly separable states of high- and low-frequency coupling, with minimal overlap between states. Visually scored CAP stage versus ECG-detected coupling state sensitivities and specificities were as follows: CAP: 40% and 84%, non-CAP: 81% and 68%, and wake/REM: 37% and 86%, respectively. The percentage of sleep detected as CAP, non-CAP, and wake/REM was 25%, 53%, and 18%, respectively, with 3% indeterminate.

Normative dataset

In this data set, cardiopulmonary analysis detected 17% CAP, 56% non-CAP, and 19% wake/REM, with 3% classified as indeterminate.

Figure 7—Spectrographic representation of sleep-disordered breathing treated by positive airway pressure. Left panel shows sustained periodic breathing and predominant cyclic alternating pattern (CAP) physiology associated with low-frequency (0.01-0.1Hz) cardiopulmonary coupling (arrow) while on positive airway pressure (PAP) alone. Right panel shows that the addition of 100 mL of dead space to PAP using a nonvented oronasal mask and additional tubing results in a marked improvement in cardiorespiratory control, evidenced by the emergence of non-CAP activity (arrow) with high-frequency (0.01-0.4Hz) cardiopulmonary coupling. The 3 top traces of the figure (from top to bottom) show conventional sleep stages, 30-second averaged electroencephalogram delta power (µV2/Hz), and CAP and non-CAP sleep state obtained using the electrocardiogram-derived cardiopulmonary coupling method. The spectrogram shows the magnitude of the cardiopulmonary coupling at each frequency over the course of the study. Black triangles below the spectra indicate individual periodic breathing events. Note that these events correlate with the pathologic, sustained, low-frequency cardiopulmonary coupling associated with aroused (CAP) sleep. W refers to wake; R, rapid eye movement sleep; WR, wake or REM; Lo/Hi Ratio, low-/high-frequency coupling ratio.
Epoch-by-Epoch Comparison of NREM Sleep-Stage Scoring and ECG-Based Detection

The kappa statistic, a measure of inter-rater reliability, showed higher agreement between the ECG-based detector and visual scoring of CAP/non-CAP (training set: 74%, 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%).

Spontaneous Coupling Shifts

All subjects demonstrated spontaneous shifts between low- and high-frequency coupling regimes that occurred independent of body position, age, conventional sleep staging, and delta power, as shown in Figures 4 and 5. These distinct states have characteristic and predictable EEG, respiratory, and heart-rate variability signatures and occur independently of standard sleep staging but correlate with CAP scoring.

Detection of SDB Treatment Effects

Successful treatment of SDB was associated with a switch from low-frequency to high-frequency coupling, as seen in the example from a combined diagnostic and therapeutic (split-night) study (Figure 6). In Figure 7, right panel, low-frequency coupling continues despite positive airway pressure plus oxygen therapy in a patient with congestive heart failure. Application of a technique to add physiologic dead space to positive airway pressure therapy results in the emergence of high-frequency coupling and non-CAP EEG (Figure 7, left panel).

DISCUSSION

This study had 5 key findings. (1) The ECG contains “hidden” information about cardiopulmonary interactions. Fourier techniques that combine analysis of beat-to-beat heart-rate variability and breath-to-breath dynamics based on an EDR signal can extract this information and generate a spectrogram of cardiopulmonary coupling. (2) Application of this new spectrographic method reveals abrupt shifts between low- and high-frequency cardiopulmonary coupling modes during sleep in both health and disease. (3) This bimodal-type pattern correlates reasonably with visually determined CAP/non-CAP in adults. (4) Healthy subjects show a predominance of high-frequency coupling, while those with untreated SDB show a predominance of low-frequency coupling. (5) Sleep stability states are not dependent on conventionally scored slow-wave sleep or delta EEG power and seem to offer a complementary view of sleep regulation and physiology.

Heart-Rate Dynamics and Sleep Physiology

Heart-rate variability has been evaluated for decades as a marker of sleep physiology. Traditionally, high-frequency power dominates in slow-wave sleep and low-frequency power in REM sleep, as approximate indicators of parasympathetic and sympathetic activity. Cyclic variations in heart rate have been used in relatively similar ways to obtain correlations with manually scored respiratory-event counts in patients with SDB.33 Sleep-related modulation of heart-rate variability has been used as an index of physical training effects.34 The impact of respiratory and nonrespiratory arousal on kinetics of sympathetic activity can be quantified.35 The autonomic drive to the heart in cardiac transplant patients may be assessed, using the paradigm of arousal associated with the emergence from slow-wave sleep.36 In sleep apnea, increased vagal modulation of heart rate during sleep can be shown with the use of positive airway pressure therapy.37 Effects of altitude and acclimatization can be assessed by analysis of heart-rate variability during sleep.38,39 Associations between CAP and heart-rate variability have been described. Specifically, the low-frequency component is increased in CAP, while the high-frequency component is increased in non-CAP.40

However, analysis of heart-rate (R-R) variability alone has salient limitations in assessing sleep physiology. Certain disease conditions (eg, congestive heart failure or autonomic neuropathy) and drugs (parasympatholytics) are associated with a marked reduction in variability. Heart-rate variability also varies considerably between individuals and is affected by age and physical conditioning. The EDR signal, a complementary method designed to assess breathing dynamics more directly from QRS axis shifts, is by itself relatively noisy. The new method we describe here is unique in that it measures coupling between heart-rate variability and respiration-driven ECG amplitude modulations and thresholds this behavior to correlate with sleep stability states. Therefore, this combined approach has the potential to extract more information than either technique alone by minimizing limitations noted above and amplifying the common frequency components of the 2 signals. For example, even if R-R variability is low, R-wave amplitude modulation in the EDR signal driven by respiration can be detected, and the coupling between heart-rate variability and breathing can be quantified.

Cardiopulmonary Coupling During Sleep

The lack of overlap between the 2 states of stable (high-frequency coupled) and unstable (low-frequency coupled) sleep in health and disease is striking (Figures 4-7). Stable sleep is characterized by the absence of respiratory abnormality or progressive flow limitation and usually demonstrates non-CAP EEG, while unstable sleep is characterized by sequences of progressive flow limitation, arousals, recovery breaths, and usually CAP-EEG. These 2 described states are not unique to SDB but are also present in healthy subjects. While increased delta power or conventionally staged slow-wave sleep is usually associated with a non-CAP state, this association is not required because the majority of non-CAP sleep seen clinically in adults occurs in stage 2 sleep. In those without SDB, it is likely that small increases in tidal volume that accompany arousals or the A-phases of CAP generate the low-frequency EDR component. Such subtle fluctuations in tidal volume may or may not be visually obvious on the polysomnogram.

Correlations of EEG power and heart-rate variability dynamics have been previously described, with a clear association of increasing delta power with reduced heart-rate variability.51,52 However, EEG morphologies vary significantly from individual to individual, and medication effects may introduce additional variations that increase the difficulty of accurately detecting CAP and non-CAP. The ECG-based coupling determinations in this study were made in an automated way completely independent of EEG morphology, standard staging, or the exact morphology.
of the A-phase of the CAP complex. This consideration may be especially important when the EEG is altered by a drug (eg, benzodiazepines) or disease (eg, dementia).

CAP was originally described exclusively as an EEG pattern. Our results may help extend the concept of CAP in a broader multivariable context. The first night of positive airway pressure titration is associated with a rebound of high-frequency coupling behavior, regardless of conventional stage or delta power. The low- and high-frequency cardiopulmonary coupling regimes may reflect fundamentally distinct physiologic states resulting from an interplay between sleep homeostatic and disruptive mechanisms. These findings suggest that current approaches to sleep staging may not capture all of the sleep regulatory responses. Further, the bimodal “switching” behavior described here suggests that the division of NREM sleep into two primary cardiopulmonary coupling regimes may complement the traditional depth staging and have advantages in certain settings, for example in older individuals with low percentages of slow-wave sleep.

### Potential Applications

Since CAP-type sleep physiology is induced or amplified by a range of sleep-disrupting stimuli and non-CAP is a marker of sleep stability, the correlative ECG-based cardiopulmonary coupling measure could have utility in a wide range of settings using a noninvasive, inexpensive, and readily repeatable technique. These include (1) facilitating diagnostic screening for SDB in high-risk populations, tracking disease severity, following compliance with treatment, and assessing treatment effects; (2) assessing sleep quality in disorders known to have intrinsically abnormal sleep and increased CAP as a percentage of NREM sleep, such as in primary insomnia, depression and fibromyalgia; (3) tracking sleep quality in hostile environments, such as microgravity, in submarines, in combat, and in assessing the effect of environmental noise during sleep.

### Limitations

This ECG-based technique is not a sleep-stage or respiratory-event detector but does provide a dynamic measure of cardiopulmonary coupling during sleep. Tight correlations with visually scored sleep states, therefore, would not be expected, since (1) the time scales are different; (2) visual CAP and non-CAP rules are difficult to apply and likely imprecise at shifting boundaries of wake to sleep and NREM to REM sleep and during periods of switching from CAP to non-CAP; (3) severely disrupted REM sleep takes on low-frequency coupled CAP-type features; and (4) severe NREM sleep apnea may occur in epochs scored as wake by standard criteria but detected by the present method as an excess of power in the low-frequency range. In spite of these limitations, the reliability of ECG-based CAP detection (kappa > 0.75) compares favorably with what was considered excellent inter scorer reliability (>0.80) after extensive training in the Sleep Heart Health study. However, it should be emphasized that this technique of cardiopulmonary coupling detection is most appropriately applied as a continuous dynamic estimator of sleep physiology rather than a “CAP scorer.”

Since this technique is based on normal sinus-to-sinus beat variability, application in the presence of atrial or ventricular bigeminy is not feasible. Application in the presence of other cardiac arrhythmias such as ventricular trigeminy or atrial fibrillation was not tested. In the setting of SDB, high-frequency coupling that correlates with non-CAP may not necessarily mean normal physiology, as seen in subjects with persistent flow limitation. In this instance, significant hypoventilation may occur, a pattern especially common in the pediatric age group. The time window of assessment of this technique is 8 minutes, with overlapping windows and interpolation techniques that result in a smoothing of the coherence profile. This could be a disadvantage because rapid alterations in state will be blurred, and improvements in algorithm will determine if this is a significant practical problem. However, the transition of sleep states, as determined by sleep-stability scoring, occurs over a period of several minutes, and it is possible that the current window of assessment may be optimal.

In summary, we present a spectrographic method derived solely from a single-lead ECG that dynamically tracks changes in cardiopulmonary coupling during sleep. Spontaneous shifts are observed between high- and low-frequency coupling states in both health and disease. These 2 ECG-derived states have highly characteristic and predictable EEG, respiratory, and heart-rate signatures and show a closer relationship with CAP/non-CAP rather than conventional NREM-stage scoring. Besides its potential for clinical use, the results also encourage a reconsideration of sleep staging and typing in the “stability domain” that may complement traditional sleep-scoring systems.

### ACKNOWLEDGEMENTS

This work is supported by the NIH/NCRR P41RR13622, the G. Harold and Leila Y. Mathers Foundation, the James S. McDonnell Foundation, and NIH/NIA P60 AG08812. We thank Janet Mullington, PhD, and David Paydarfar, MD, for helpful comments.

### REFERENCES


APPENDIX

The Cardiopulmonary Coupling Algorithm: Mathematical and Technical Considerations

Two physiologic time series are derived from the electrocardiogram (ECG) signal: (1) the fluctuations of the cardiac interbeat interval (RR) as a function of time, denoted as \( R(t) \), and (2) a surrogate respiration signal, termed the ECG-derived respiratory (EDR) time series,\(^1\)\(^2\) denoted as \( E(t) \). The variable \( t \) is often considered as continuous for analytical purposes. However, the actual data are collected discretely in time. These data are further numerically resampled at a given rate (eg, 2 Hz) to facilitate the application of the discrete Fourier transform. To indicate the discreteness of the data, we denote the resampled time series as \( R_k \) and \( E_k \), where the index \( k \) corresponds to the discrete sample number. Note that \( R_k = R(t_k) = R(k \Delta t) \) and \( E_k = E(t_k) = E(k \Delta t) \), where \( 1/\Delta t \) is the sampling frequency.

The cardiopulmonary coupling (CPC) index described here is defined as the product of the coherence and cross-spectral power of the time series \( R_k \) and \( E_k \). Computationally, the following procedures are carried out:

The discrete Fourier transform of these two time series, denoted as \( \hat{R}_n \) and \( \hat{E}_n \), are calculated by

\[
R_k e^{i2\pi f_n t_k} \quad \text{and} \quad \hat{E}_n = \sum_{k=0}^{N-1} E_k e^{i2\pi f_n t_k} \quad (1)
\]

where \( f_n = \frac{n}{N\Delta t} \), \( n = 0, 1, 2, \ldots, N-1 \) and \( i = \sqrt{-1} \).

The cross-spectrum, denoted as \( \Gamma_n(R,E) \), is computed as

\[
\Gamma_n(R, E) = \hat{R}_n^* \hat{E}_n = A_n B_n e^{i(\Phi_{R,n} - \Phi_{E,n})} \quad (2)
\]

where \( A_n \) and \( B_n \) are the amplitudes and \( \Phi_{R,n} \) and \( \Phi_{E,n} \) are the phases of the Fourier components.

The coherence, denoted as \( \Lambda_n \), is defined as the squared average cross-spectrum divided by the product of the average spectral power of the individual signals, i.e.,

\[
\Lambda_n = \frac{\langle \Gamma_n(R, E) \rangle^2}{\langle \hat{R}_n^2 \rangle \langle \hat{E}_n^2 \rangle} \quad (4)
\]

where the \( \langle > \) represents averaging over frequencies in the raw spectrogram and/or averaging over multiple measurements at a given frequency. Note that the coherence is derived from the normalized cross-spectral power. It is critical to take a statistical average of the cross-spectrum from multiple samples (or multiple frequencies in a given frequency band). It is straightforward to show mathematically that the coherence = 1 if spectral estimates are used without averaging. This result is due to the fact that Fourier analysis assumes stationarity of the data; therefore, at any given frequency, the phase difference between the corresponding Fourier components of 2 signals is a constant (ie, stationary in time).

In our implementation of the coherence measurement, we divided each segment of data (observation window) into \( m \) subsegments (subwindows). Therefore, each subsegment was treated as an independent measurement, and the average of coherence as defined in Equation 4 was computed over these subsegments. For the results reported here, each window of 1024 points (about 8.5 minutes of data sampled at 2 Hz) was divided into 3 overlapping subwindows of 512 points (neighboring subwindows overlapped by 50%) for averaging.

The quantitative index we defined here for measuring CPC from a single-lead ECG combines both cross-spectral power and coherence. Specifically, we define

\[
\text{CPC}(\Gamma_n) \equiv \langle \Gamma_n(R, E) \rangle^2 \Lambda_n \quad (5)
\]

This combination takes into account 2 important factors: (1) the power at the given frequency \( f_n \) of both heart-rate variability and respiratory-related oscillation in QRS amplitude (as evaluated by the cross-spectral power) and (2) the consistency with which these 2 signals track each other (as evaluated by the coherence).

In theory, assuming a coherence window of infinite length, if either the heart-rate variability or the EDR signal does not show a corresponding oscillation at a given frequency, the coherence will be 0 and, therefore, the coherent cross-power product will also be 0. In practice, however, due to the statistical basis of the coherence calculation and the finite number of fast Fourier transformations included, the coherence will almost always deviate from 0. Thus, an oscillation present in only 1 of the signals will still be manifest in the coherent cross power. Under circumstances in which either the heart-rate variability response to respiration is substantially diminished (eg, due to impaired autonomic function) or the EDR signal is noisy, the coherent cross-power will still reflect cardiopulmonary oscillatory events present in either signal.

In using the EDR signal as a surrogate respiration signal, we consider that the respiration cycle is effectively sampled by the R-wave amplitude variations. In Fourier analysis, the Nyquist sampling theorem states that the sampling rate must be at least twice the frequency of the highest frequency component in the waveform being sampled, i.e., there must be at least 2 samples per cycle for any frequency component of interest. If the sampling rate is less than twice the highest frequency component, then
aliasing occurs such that the higher-frequency spectral components “wrap around” into the lower-frequency components. These considerations indicate that, in applying the ECG-derived cardiopulmonary coupling detector, reliable detection of respiration is dependent on heart rate. To meet the Nyquist frequency requirements for reliable detection of respiration and to avoid aliasing, our method requires at least 2 RR intervals (2 EDR samples) per respiration cycle. Specifically, the heart rate must be at least twice as high as the respiration rate. For example, if the respiration rate is 12 breaths per minute, then the heart rate must be at least 24 beats per minute. For the data presented in this paper, this requirement is always met.

The spectrograms plotted in Figures 4-7 are graphical representations of the CPC index as a function of time and frequency.

REFERENCES