



# Cardiopulmonary Coupling (CPC) Published Papers & Case Studies

<b>Author(s)</b>		<b>Title</b>	
Thomas RJ, Mietus JE, Peng CK, Goldberger AL		An Electrocardiogram-based Technique to Assess Cardiopulmonary Coupling During Sleep	
<b>Journal</b>	<b>Summary (Objective and Conclusions)</b>		<b>Practical Significance</b>
SLEEP 2005;28:1151-1161	<p>O: Evaluate a new automated measure of CPC during sleep using a single-lead electrocardiographic (ECG) signal</p> <p>C: 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 (CAP) 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 (NREM) sleep stages</p>		This seminal work establishes the link between High Frequency CPC with good sleep quality, and Low Frequency CPC with poor quality sleep
<b>Author(s)</b>		<b>Title</b>	
Thomas RJ, Mietus JE, Peng CK, Gilmartin G, Daly RW, Goldberger AL, Gottlie DJ.		Differentiating Obstructive from Central and Complex Sleep Apnea Using an Automated Electrocardiogram-based Method	
<b>Journal</b>	<b>Summary (Objective and Conclusions)</b>		<b>Practical Significance</b>
SLEEP 2007;30:1756-1769.	<p>O: Complex sleep apnea is defined as sleep disordered breathing secondary to simultaneous upper airway obstruction and respiratory control dysfunction. The objective of this study was to assess the utility of an electrocardiogram (ECG) based CPC technique to distinguish obstructive from central or complex sleep apnea</p> <p>C: ECG based spectral analysis allows automated, operator-independent characterization of probable interactions between impaired respiration and upper airway anatomical obstruction. The clinical utility of spectrographic classification, especially in predicting failure of positive airway pressure therapy, remains to be more thoroughly tested</p>		Using the Heart Health Study population of 3989 subjects, this study shows that CPC not only differentiated obstructive vs. central vs. complex sleep apnea, but it positively correlated with periodic breathing episodes in PSG and was the strongest predictor of success or failure with PAP titration.



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Ibrahim LH, Jacono FJ, Patel SR, Thomas RJ, Larkin EK, Mietus JE, Peng CK, Goldberg AL, Redline S		Heritability of Abnormalities in Sleep Apnea: Use of an Electrocardiogram-based Technique	
<b>Journal</b>	<b>Summary (Objectives and Conclusions)</b>		<b>Practical Significance</b>
SLEEP 2010;33(5):643-646	<p>O: To evaluate the familial aggregation of distinctive spectrographic biomarkers of unstable sleep, related to elevated-low frequency (e-LFC), and to assess their utility in genetic studies.</p> <p>C: Approximately 30% of the variability of e-LFC, measured from a continuous ECG during sleep is explained by familial factors other than BMI. ECG-based spectrographic measures of heart rate variability &amp; breathing rate may provide novel markers for characterizing subgroups of individuals with different propensities and genetic etiologies for sleep apnea or for other conditions associated with sleep fragmentation.</p>		This study suggests that CPC provides an objective measure aimed to enhance our understanding of the genetics of OSA by identifying intermediate traits with high heritability.
<b>Author(s)</b>		<b>Title</b>	
Thomas RJ, Weiss MD, Mietus JE, Peng CK, Goldberger AL, Gottlieb DJ.		Prevalent Hypertension and Stroke in the Sleep Heart Health Study: Association with an ECG-derived Spectrographic Marker of Cardiopulmonary Coupling	
<b>Journal</b>	<b>Summary (Objective and Conclusions)</b>		<b>Practical Significance</b>



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<p>SLEEP 2009;32(7):897-904</p>	<p>O: The ECG-based sleep spectrogram generates a map of CPC based on heart rate variability and respiration derived from QRS amplitude variations. A distinct spectrographic type, designated as elevated Low Frequency Coupling Narrow Band (e-LFC<sub>NB</sub>), has been associated with central apneas and periodic breathing and predicts failure of CPAP therapy. This study assesses, at a population level, the associations of this spectrographic biomarker with prevalent cardiovascular disease using the Sleep Heart Health Study (SHHS)-I dataset.</p> <p>C: An ECG derived spectrographic marker related to low frequency is associated with greater sleep apnea severity. Whether this biomarker is solely a sign of more severe disease or whether it reflects primary alterations in sleep apnea pathophysiology, which may either cause or result from sleep apnea, is unknown. This ECG-based spectral marker is associated with a higher prevalence of hypertension and stroke.</p>	<p>The presence of e-LFC<sub>NB</sub> represents for the first time a biomarker for sleep disordered breathing independent of age, sex and body mass has been described.</p>
<p><b>Authors</b></p>		<p><b>Title</b></p>
<p>Thomas RJ, Mietus JE, Peng CK, Goldberger AL, Crofford LJ, Chervin RD</p>		<p>Impaired Sleep Quality in Fibromyalgia: Detection and Quantification with ECG-based Cardiopulmonary Coupling Spectrograms</p>
<p><b>Journal</b></p>	<p><b>Summary (Objectives and Conclusions)</b></p>	<p><b>Practical Significance</b></p>
<p>Sleep Med. 2010;11(5): 497-8.</p>	<p>O: To employ the use of CPC to retrospectively analyze polysomnogram (PSG) ECG data from patients with fibromyalgia compared with matched controls.</p> <p>C: Both ECG and EEG approaches yield consistent findings in this syndrome, further solidifying the hypothesis of altered sleep stability in fibromyalgia.</p>	<p>This study shows the favorable comparison of CPC findings over time with traditional PSG findings and the pain diaries of patients suffering from fibromyalgia.</p>
<p><b>Author(s)</b></p>		<p><b>Title</b></p>
<p>Thomas RJ, Mietus JE, Peng CK, Goldberger AL</p>		<p>An Electrocardiogram-based Technique to Assess Cardiopulmonary Coupling During Sleep</p>



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<p>SLEEP 2010;33(5):643-646</p>	<p>O: To evaluate the familial aggregation of distinctive spectrographic biomarkers of unstable sleep, related to elevated-low frequency (e-LFC), and to assess their utility in genetic studies.</p> <p>C: Approximately 30% of the variability of e-LFC, measured from a continuous ECG during sleep, is explained by familial factors other than BMI. ECG-based spectrographic measures of may provide novel markers for characterizing subgroups of individuals with different propensities and genetic etiologies for sleep apnea or for other conditions associated with sleep fragmentation.</p>	<p>This study suggests the opportunity that CPC provides to enhance our understanding of the genetics of OSA by identifying intermediate traits with high heritability.</p>
<b>Author(s)</b>		<b>Title</b>
<p>Yang AC, Yang CH, Hong CJ, Tsai SJ, Kuo CH, Peng CK, Mietus JE, Goldberger AL, Thomas RJ.</p>		<p>Sleep State Instabilities in Major Depressive Disorder: Detection and Quantification with Electrocardiogram-based Cardiopulmonary Coupling Analysis</p>
Journal	Summary (Objectives and Conclusions)	Practical Significance
<p>Psycho-physiology. 2011;48(2):285-291</p>	<p>O: To evaluate the utility of electrocardiogram (ECG)-based analysis to quantify physiologic sleep stability in patients with major depression</p> <p>C: Relative to controls, non-medicated depressed patients had a reduction in High-Frequency Coupling (HFC; index of stable sleep), an increase in Low Frequency Coupling (LFC; index of unstable sleep), and an increase in very Low Frequency Coupling (vLFC; index of wakefulness/REM sleep).</p>	<p>ECG-based analysis can offer a simple, cost-efficient point-of-care method to quantify sleep quality/stability and to objectively evaluate the severity of insomnia in patients with major depression.</p>
<b>Author(s)</b>		<b>Title</b>
<p>Harrington J, Schramm PJ, Davies CR, Lee-Chiong TL Jr.</p>		<p>An Electrocardiogram-based Analysis Evaluating Sleep Quality in Patients with Obstructive Sleep Apnea.</p>



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Sleep Breath 2013:1-8	<p>O: Using the M1 sleep recorder, determine that 1) CPC is equal to PSG in discriminating between an apnea hypopnea index above or below 5 events/hour, 2) PSG with successful CPAP titration is distinguishable from titration studies with AHIs &gt;5 events/hour 3) CPC variables simultaneously recorded ECG collected via M1 and PSG will correlate highly; and 4) High Frequency Coupling (HFC) cutoff of &lt;50% will demonstrate clinical utility in identifying the presence of a sleep disorder.</p> <p>C: High sensitivity and mutual agreement to clinical diagnosis for the presence of a sleep disorder was found. Elevated-LFC<sub>NB</sub> was associated with SDB severity. CPC variables differentiated successful from unsuccessful CPAP therapy using an AHI cutoff of ≤4 events/ hour of sleep compared to standard PSG variables.</p>	The results support the use of the SleepImage system to investigate and objectively measure sleep quality in patients complaining of a sleep disorder.
<b>Author(s)</b>		<b>Title</b>
Schramm PJ, Thomas RJ, Feige B, Spiegelhalder K, Riemann D.		Quantitative Measurement of Sleep Quality Using Cardiopulmonary Coupling Analysis: A Retrospective Comparison of Individuals With and Without Primary Insomnia.
Journal	Summary (Objectives and Conclusions)	Practical Significance
Sleep Breath. 2013; 17(2):713-721	<p>O: To determine the utility of an objective measure of sleep physiology based on CPC analysis in patients with primary insomnia vs. good sleepers.</p> <p>C: On adaptation nights, primary insomniacs had poor sleep quality, captured well by conventional and CPC sleep spectrogram techniques. Good sleepers showed the biggest improvement in sleep quality, as identified only by CPC</p>	Novel insights into physiology and pathology of sleep can be obtained through the coupling of ECG and respiratory signal influences on the ECG R wave.
<b>Author(s)</b>		<b>Title</b>
Thomas RJ, Mietus JE		Mapping Sleep Using Coupled Biological Oscillations
Journal	Summary (Objectives and Conclusions)	Practical Significance
Conf. Proc IEEE Eng Med	<p>O: To examine the utility of an electrocardiogram-derived sleep spectrogram to provide a different view of sleep</p>	Novel insights into physiology and pathology of sleep can be obtained



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<p>Biol. Soc. 2011;201 1:1479-82.</p>	<p>C: Non-electroencephalogram (EEG) recordings can provide an alternative approach to viewing sleep quality.</p>	<p>through the coupling of ECG and respiratory signal influences on the ECG R wave.</p>
<p><b>Author(s)</b></p>		<p><b>Title</b></p>
<p>Pogach, MD; Naresh M. Punjabi, MD, PhD; Neil Thomas; Robert J. Thomas, MD</p>		<p>Electrocardiogram-Based Sleep Spectrogram Measures of Sleep Stability and Glucose Disposal in Sleep Disordered Breathing</p>
<p><b>Journal</b></p>	<p><b>Summary (Objectives and Conclusions)</b></p>	<p><b>Practical Significance</b></p>
<p>SLEEP 201235(1):139-148</p>	<p>O: This analysis explored associations between glucose metabolism and an EEG-independent measure of sleep quality, the sleep spectrogram, which maps coupled oscillations of heart-rate variability and electrocardiogram (ECG)-derived respiration.  C: The ECG-spectrogram analysis of sleep quality may provide information beyond that obtained by conventional polysomnography (PSG) in relationship to glucose metabolism</p>	<p>Experimental sleep fragmentation can impair insulin sensitivity. ECG-derived sleep-spectrogram measures of sleep quality are associated with alterations in glucose-insulin homeostasis.  This could improve our understanding of sleep and sleep-breathing effects on glucose metabolism.</p>
<p><b>Author(s)</b></p>		<p><b>Title</b></p>
<p>Guo D, Peng CK, Wu H, L,Mietus JE, Liu Y, Sun RS, Thomas RJ</p>		<p>ECG-derived Cardiopulmonary Analysis of Pediatric Sleep-Disordered Breathing</p>
<p><b>Journal</b></p>	<p><b>Summary (Objectives and Conclusions)</b></p>	<p><b>Practical Significance</b></p>



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<p>Sleep Medicine 2011;12(4): 384-389</p>	<p>O: An ECG-derived sleep spectrogram, based on CPC analysis previously described in adults, can provide information about the severity of sleep disordered breathing (SDB) and coupled interactions of sleep modulated autonomic drive and respiration. We hypothesized that CPC algorithm-derived metrics will correlate with nasal pressure-based apnea-hypopnea scoring in pediatric population.</p> <p>C: ECG-derived sleep spectrogram metrics are correlated with nasal flow-derived respiratory abnormality in pediatric SDB. In suitable clinical contexts, this method may have screening utility and possibly allow tracking of treatment effects, specifically in children with severe SDB</p>	<p>The high correlation between CPC metrics and nasal flow derived metrics in pediatric SDB patients demonstrates an opportunity to screen for SDB and track treatment effects.</p>
<p><b>Author(s)</b></p>		<p><b>Title</b></p>
<p>Schramm PJ, Neville AG, Madison S, Thomas RJ, Baker DN</p>		<p>Cardiopulmonary Coupling Measures Correlate to Standard Sleep Variables in a Random Clinical Sample of Patients Suspected with Sleep Disordered Breathing (SDB)</p>
<p><b>Journal</b></p>	<p><b>Summary (Objective and Conclusions)</b></p>	<p><b>Practical Significance</b></p>
<p>SLEEP 2009;32:A373</p>	<p>O: To determine the correlation of Cardiopulmonary variables to standard sleep variables in a random clinical sample.</p> <p>C: The RemLogic CPC analysis variables correlate with standard sleep metrics in a clinical population suspected with OSA, and seem to detect complementary aspects of sleep physiology.</p>	<p>Some of these variables were reported in subjects selected from the Sleep Heart Health study in addition to CPC measures.</p> <p>CPC variables compliment various aspects of sleep physiology obtained using standard sleep metrics</p>
<p><b>Author(s)</b></p>		<p><b>Title</b></p>
<p>Baker D, Schramm PJ, Neville AN, Thomas R., Madison S</p>		<p>An Assessment of Sleep Quality Using Validation in Patients Suspected with Sleep Disordered Breathing</p>



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SLEEP 2009;32:A82 <a href="http://www.journalsleep.org/PDF/AbstractBook2009.pdf">http://www.journalsleep.org/PDF/AbstractBook2009.pdf</a>	O: To assess automated sleep quality analysis software using CPC from one ECG channel polysomnography from 69 patients suspected of sleep disordered breathing (SDB).  C: The RemLogic CPC analyzer accurately reproduces sleep quality data obtained from patient results collected at Beth Israel Deaconess Hospital and is comparable to the work of Thomas et al. 2007	The RemLogic CPC tool is validated against the CPC algorithm created by Dr. Robert Thomas of Beth Israel University, a teaching school of Harvard University, as seen in the 2007 study differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method.
<b>Author(s)</b>		<b>Title</b>
SchrammPJ, Thomas RJ		Assessment of Therapeutic Options for Mild Obstructive Sleep Apnea Using Cardiopulmonary Coupling Measures
Journal	Summary (Objectives and Conclusions)	Practical Significance
Journal of Clinical Sleep Medicine, 2012;8(3):?	O: To examine the efficacy of a number of therapeutic modalities for mild obstructive sleep apnea using Cardiopulmonary variables of sleep quality.  C: Objective measurements of sleep quality using CPC variables differentiated the efficacy of various therapeutic options for mild obstructive sleep apnea.	Clinicians can obtain objective, reliable information about sleep quality using CPC when assessing efficacy of therapeutic interventions in patients with sleep disordered breathing
<b>Author(s)</b>		<b>Title</b>
Schramm PJ.		An Early Indicator of Complex Sleep Apnea





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Advance for Respiratory Care and Sleep Medicine June 2010	<p>O: Demonstration of the impact on a Complex Sleep Apnea patient's sleep quality with CPAP versus ASV using CPC to detect stable and unstable sleep.</p> <p>C: CPC variables indicated that the patient's sleep quality had improved objectively. Subjectively, the patient reported his sleep more restful when using the combination of ASV at 9cm H<sub>2</sub>O and added dead space compared to CPAP.</p>	<p>This study highlights that the presence of e-LFC<sub>NB</sub> can help identify complex sleep apnea both before and after initiation of PAP therapy. A second CPC study following the application of ASV with dead space showed improved quality of sleep in the form of increased HFC, which corresponded well with the patients subjective findings.</p>
<b>Author(s)</b>		<b>Title</b>
Schramm PJ, Neville AN, Baker D,		The Sleep Quality Recovery of a Snorer's Bed Partner
Journal	Summary (Objectives and Conclusions)	Practical Significance
Respiratory Therapy Magazine June/July 2010 Volume 5	<p>O: To demonstrate, through the use of CPC technology, the negative impact of snoring and Obstructive Sleep Apnea (OSA) and the response to PAP initiation the bed partner's sleep quality.</p> <p>C: Both the snorer and his bed partner's sleep quality improved significantly with the application of PAP therapy.</p>	<p>Proof to a reticent CPAP user of the benefit of CPAP compliance to their bed partner as well as themselves</p>