





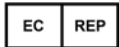


## **Introduction to SleepImage®**

## Introduction to SleepImage®

This document is only available in an electronic format, as a PDF document, on [www.sleepimage.com](http://www.sleepimage.com). This document is updated periodically, identified by a sequential revision number. The contents of this document refer to the SleepImage System, a prescription Software as a Medical Device (SaMD), which is identified by the following:

	<b>Manufacturer</b>	MyCardio LLC, dba SleepImage 3003 E 3 <sup>rd</sup> Ave., Suite 201 Denver, CO 80206, USA <a href="mailto:support@sleepimage.com">support@sleepimage.com</a> <a href="http://www.sleepimage.com">www.sleepimage.com</a>
	<b>Instructions for Use Version Number</b>	Please read Instructions for Use carefully and periodically as it is updated from time to time. The <a href="#">current version</a> (Instructions for Use, Rev. 12) was issued on June 11, 2021 – Previous editions are not applicable, as all users always use a current version of the cloud-based SleepImage System. Printed copy will be provided within 7 calendar days if requested at no additional cost. Please contact <a href="mailto:support@sleepimage.com">support@sleepimage.com</a>
	<b>Prescription Use Only</b>	FDA-cleared <a href="#">K182618</a> : Federal law restricts sales of this device as “by or on the order of a licensed healthcare practitioner”. The FDA Unique Device Identifier (UDI) is *+B315sleepimage.com0.*
 0413	<b>CE Mark</b>	The CE mark is a declaration that the SleepImage System is in compliance with the EU Medical Device Directive.



European Representative

Emergo Europe  
Prinsessegracht 20  
2514 AP The Hague  
The Netherlands

Singapore Sponsor  
BMEC Sleep Care Ltd  
82 Ubi Avenue 4  
#07-03 Edward Boustead Centre  
Singapore 408832

Australian Sponsor  
Emergo Australia Level 20  
Tower II, Darling Park  
201 Sussex Street Sydney  
NSW 2000 Australia

Africa Representative  
SleepFit Pty Ltd  
323 Lynnwood Road  
Menlo Park, Pretoria, Gauteng 0102  
South Africa

## **Copyright © Notice and Disclaimer**

No part of this publication may be reproduced, transmitted, transcribed, stored in a retrieval system, or translated into any language or computer language, in any form, or by any means, electronic, mechanical, optical, chemical, manual, or otherwise, without the prior written consent of MyCardio. Copyright © 2021 MyCardio. All rights reserved. MyCardio™ and SleepImage® are registered trademarks of MyCardio LLC. Introduction to SleepImage, Rev 12. Published June 11, 2021.

This document may contain technical inaccuracies or typographical errors. Changes are periodically made to the information herein; these changes will be incorporated in future revisions of this document.

## **Patent Marking**

SleepImage (MyCardio LLC) is a provider of medical systems and services intended to establish sleep quality, evaluate sleep disorders and aid in diagnosis and management of sleep disorder breathing.

The technology in SleepImage's systems and services is covered by patents owned and/or licensed in the United States and/or in other countries. This marking is intended to serve as notice under 35 U.S.C. § 287(a).

The following patents apply to SleepImage systems and services, including but not limited to the SleepImage System:

U.S. Patent Number(s): 7,324,845; 7,734,334; 8,401,626; 8,403,848. Other patent(s) pending.

Australian Patent Number(s): 2006269263. Other patent(s) pending.

Canadian Patent Number(s): 2566193; 2619617. Other patent(s) pending.

European Patent Number(s): 1765156; 1906817. Validated in France, Germany, Italy, Spain, United Kingdom. Other patent(s) pending.

Japanese Patent Number(s): 5005539; 5005687. Other patent(s) pending.

## **Patents Pending:**

WO2019246234A1; WO2020061014A1; WO2021055943A1

# Contents

<b>Introduction.....</b>	<b>5</b>
Understanding the SleepImage Benefits .....	5
The SleepImage System Features and Benefits are summarized as follows: .....	6
Understanding the SleepImage Science .....	7
SleepImage Output Parameters .....	11
SleepImage in Sleep (Disorder) Management .....	14
Expected Values - Sleep Quality and Sleep Pathology .....	15
Children .....	15
Adults.....	16
Understanding the SleepImage Spectrogram.....	17
Full View Spectrogram.....	17
Stable Sleep or High Frequency Coupling - HFC.....	18
Unstable Sleep or Low Frequency Coupling - LFC.....	18
Wake & REM sleep or Very Low Frequency Coupling - vLFC .....	18
<b>The SleepImage Report &amp; Graphics .....</b>	<b>19</b>
The SleepImage Report.....	19
Reviewing SleepImage Report Output.....	20
Clinician Notes .....	21
<b>Reviewing SleepImage Graphics for Associations &amp; Patterns.....</b>	<b>22</b>
Distinguishing Sleep Disordered Breathing Types .....	23
3D Spectrogram - Obstructive Sleep Apnea .....	23
3D Spectrogram - Central Sleep Apnea .....	23
3D Spectrogram - Mixed Sleep Apnea .....	24
<b>CPC Publications .....</b>	<b>25</b>
Books .....	25
Published papers .....	25
Technique.....	25
Relationship between CPC and PSG.....	25
Sleep Quality .....	26
Sleep Disordered Breathing .....	26
Sleep Disordered Breathing - Therapy .....	27
Cardiovascular and Cardiometabolic .....	28
Pediatric .....	28
Insomnia/Mental Health .....	29
Pain .....	29
Other .....	29
<b>References .....</b>	<b>30</b>
<b>Glossary .....</b>	<b>34</b>

## Introduction

The SleepImage® System is in compliance with the EU Medical Device Directive and is U.S. Food and Drug Administration (FDA) cleared Software as a medical Device (SaMD) that establishes Sleep Quality.<sup>1</sup> The technology, Cardiopulmonary coupling (CPC), is based on calculations and spectral analysis of cardiovascular- and respiratory data typically collected during sleep. CPC technology is based on patented algorithms developed and validated by sleep researchers, using continuous, evenly sampled, normal sinus rhythm ECG- or PLETH (Plethysmogram from a PPG sensor) signal as the only input requirement.

The SleepImage System is FDA-cleared to aid clinical diagnosis of Sleep Disordered Breathing (SDB) in children, adolescents and adults. The output from the SleepImage System present various sleep related output metrics such as sleep duration (SD), total sleep time (TST), wake after sleep onset (WASO) and sleep quality (SQI) and sleep disordered breathing (SDB) related output metrics that include an Oxygen Desaturation Index (ODI), an Apnea Hypopnea Index (sAHI), a Respiratory Disturbance Index (sRDI) and the Sleep Apnea Indicator (SAI) that is derived from Cyclic Variation in Heart Rate (CVHR).

The SleepImage System is patented, Health Insurance Portability and Accountability Act (HIPAA) compliant cloud-based system. It is intended for use by, or on the order of, a Healthcare Professional to establish sleep quality, aid in the evaluation of sleep disorders to inform or drive clinical management, as well as to aid in diagnosis and management of SDB. The SleepImage System is [FDA-cleared](#) for use with children from age 2, adolescents and adults.

The validation of CPC utilized clinical Polysomnography (PSG) as the standard upon which it was compared. Data presenting periods of sleep identified by both systems were compared for validation and published. Please refer to [Publications Reference List](#) which can be found on the last few pages of this document.

The SleepImage System is cleared for use in various countries around the world. This document is intended to be relevant for clinical users in all countries where the SleepImage System is cleared for use, it is available in the English language only and is intended for general educational purposes. It is not intended to be Instructions for Use of the SleepImage System, for that please refer to [SleepImage System Instructions for Use](#). For information on where the SleepImage System is available and contact information for SleepImage representatives in different countries, please contact [support@sleepimage.com](mailto:support@sleepimage.com).

## Understanding the SleepImage Benefits

Good sleep quality is crucial for good physical and mental health. One of the key benefits of using the SleepImage system in clinical practice is, that unlike most clinical sleep measurements, it is not restricted to evaluate only SDB. SleepImage is a comprehensive measure based on collecting and analyzing signals controlled by the autonomic nervous system (ANS).<sup>2-5</sup> The data is automatically calculated, and the output is presented through easy-to-understand biomarkers, that are displayed with expected normative thresholds and color-coded results for each biomarker. The SleepImage FDA-clearance states that (1) SleepImage establishes Sleep Quality based on the Sleep Quality Index (SQI), a summary biomarker of sleep health cleared as a unit of measure, presented on a scale of 0 – 100. The SQI has demonstrated a direct relationship with health outcomes in clinical studies,<sup>6-9 10-18</sup> (2) the SleepImage Apnea Hypopnea Index (sAHI) has been clinically validated and FDA-cleared for children, adolescents and adults for diagnosis and management of Sleep Disordered Breathing (SDB).<sup>19, 20</sup>

Everyone sleeps and SleepImage is a tool that can enhance clinical practice across all medical specialties. Sleep is an important modulator of various biological functions. Prior to the onset of a chronic disease, symptoms may be present, and prior to symptoms there are reflections of changes in ANS regulation that are not obvious. The SleepImage System is based on coupling heart rate variability (HRV) and respiration data collected during sleep, bio signals both highly influenced by the ANS (sympathetic and parasympathetic influence). Observing the synchronization between the cardiovascular- and respiratory systems during sleep when there are minimum environmental stimuli that can affect the ANS as happens during wake, allows for measures of sleep and sleep staging.<sup>2, 3 4</sup> SpO<sub>2</sub> data is used with CPC data to calculate the SleepImage Apnea Hypopnea Index (sAHI) and the SleepImage Respiratory Disturbance Index (sRDI).

The sleep period, on average represents one third of a person's life and getting sufficient good quality sleep at the right circadian times is vital for good health and well-being as during sleep, muscles and tissues are rebuilt, neuroendocrine- and metabolic functions are regulated, information collected during the waking hours are reorganized and consolidated for learning and memory, and the immune system is strengthened.<sup>21, 22</sup> These benefits of sleep can only happen when sleep is dominated by parasympathetic activity (good quality sleep). The SleepImage output clearly distinguishes between parasympathetic and sympathetic dominance and present the output as 'Stable' and 'Unstable' sleep reflecting sleep health. That is why SleepImage brings value beyond the focus on diagnosis of SDB.

The SleepImage System Features and Benefits are summarized as follows:

		SleepImage	PSG	HSAT
<b>Patient Populations</b>	Asymptomatic	✓		
	Symptomatic	✓	✓	✓
	Children	✓	✓	
	Adults	✓	✓	✓
<b>Types of Testing</b>	Sleep Disorder Evaluation <sup>1</sup>	✓		
	Sleep Disorder Screening	✓		
	OSA Diagnosis in Children	✓	✓	
	OSA Diagnosis in Adults	✓	✓	✓
	Treatment Tracking <sup>2</sup>	✓		
<b>Test Output</b>	Sleep Quality	✓	✓	
	Sleep Duration	✓	✓	
	NREM & REM Sleep	✓	✓	
	Phenotype OSA vs. CSA <sup>3</sup>	✓	✓	

<sup>1</sup> To evaluate clinical symptoms of Insomnia or Sleep Apnea, <sup>2</sup> To track if treatment is improving objective sleep parameters

<sup>3</sup> OSA = Obstructive Sleep Apnea; CSA = Central Sleep Apnea

For the purpose of diagnosing SDB, the US FDA-clearance for SleepImage states the following: *“Clinical evaluation has confirmed that the SleepImage System auto-scoring algorithms calculating the SleepImage Apnea Hypopnea Index (sAHI) generate comparable output to human manual scoring of an Apnea Hypopnea Index (AHI) from Polysomnography (PSG) studies, using American Academy of Sleep Medicine (AASM) scoring guidelines for children and adult patients.”* <sup>2</sup>

## Understanding the SleepImage Science

The SleepImage System is based on Cardiopulmonary Coupling (CPC) calculations and spectral analysis of continuously and evenly sampled data from electrocardiogram (ECG) or photoplethysmogram (PPG) sensors (Figure 1). The data collected contains information on heart (pulse) rate, heart (pulse) rate variability (HRV/PRV), as well as tidal volume fluctuations in respiration, called Electrocardiogram Derived Respiration (EDR) and Plethysmograph Derived Respiration (PDR) respectively and oxygen levels (SpO<sub>2</sub>).

The data is automatically analyzed and generates a sleep report. The SleepImage System provides clinical users with access to the raw data collected during the recording period for manual interpretation of the study output if desired.

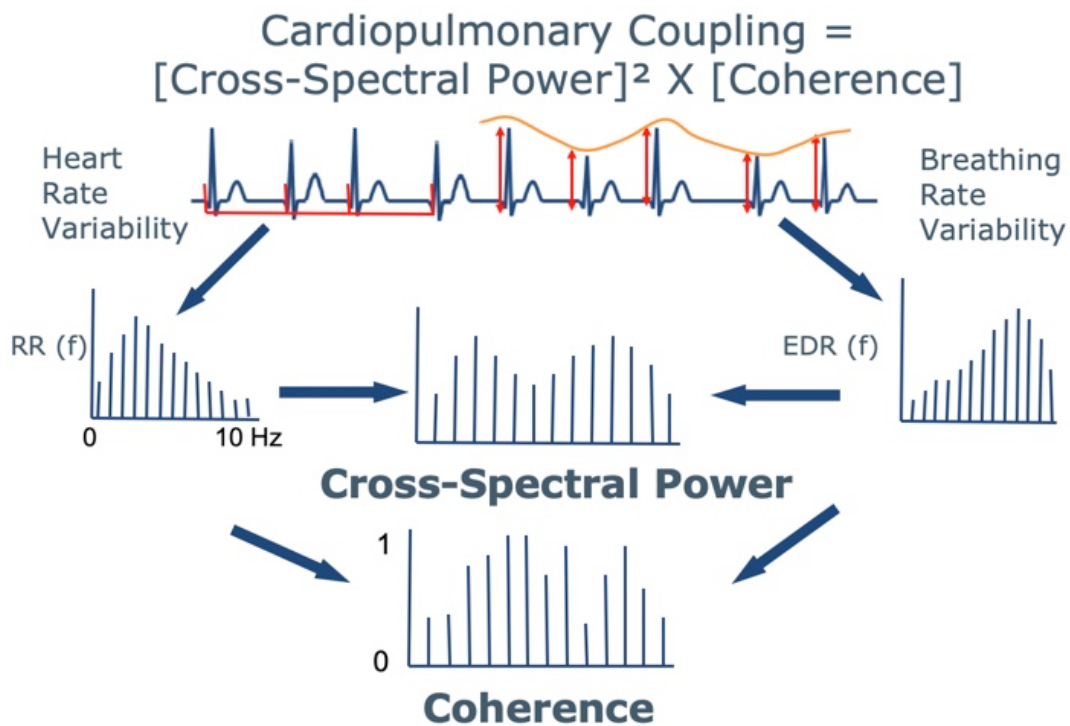


Figure 1. Cardiopulmonary Coupling.

The SleepImage System utilizes mathematical and frequency analysis to calculate synchronization between HRV/PRV and respiration to provide numerical and visualization of sleep states and sleep pathologies. The Sleep Spectrogram demonstrates that there are clear boundaries with sleep-stage transition from parasympathetic dominance (Stable sleep or High Frequency Coupling (HFC)) to sympathetic dominance (Unstable sleep or Low Frequency Coupling (LFC) and Rapid Eye Movement (REM) sleep and wake. <sup>2-4</sup> The spectrogram provides a clear visual view of sleep health during the sleep period and is useful for healthcare providers in sleep disorder evaluation of their patients, to diagnose sleep disorders and to monitor therapy success for any disease or condition that affects sleep. (Figure 2)

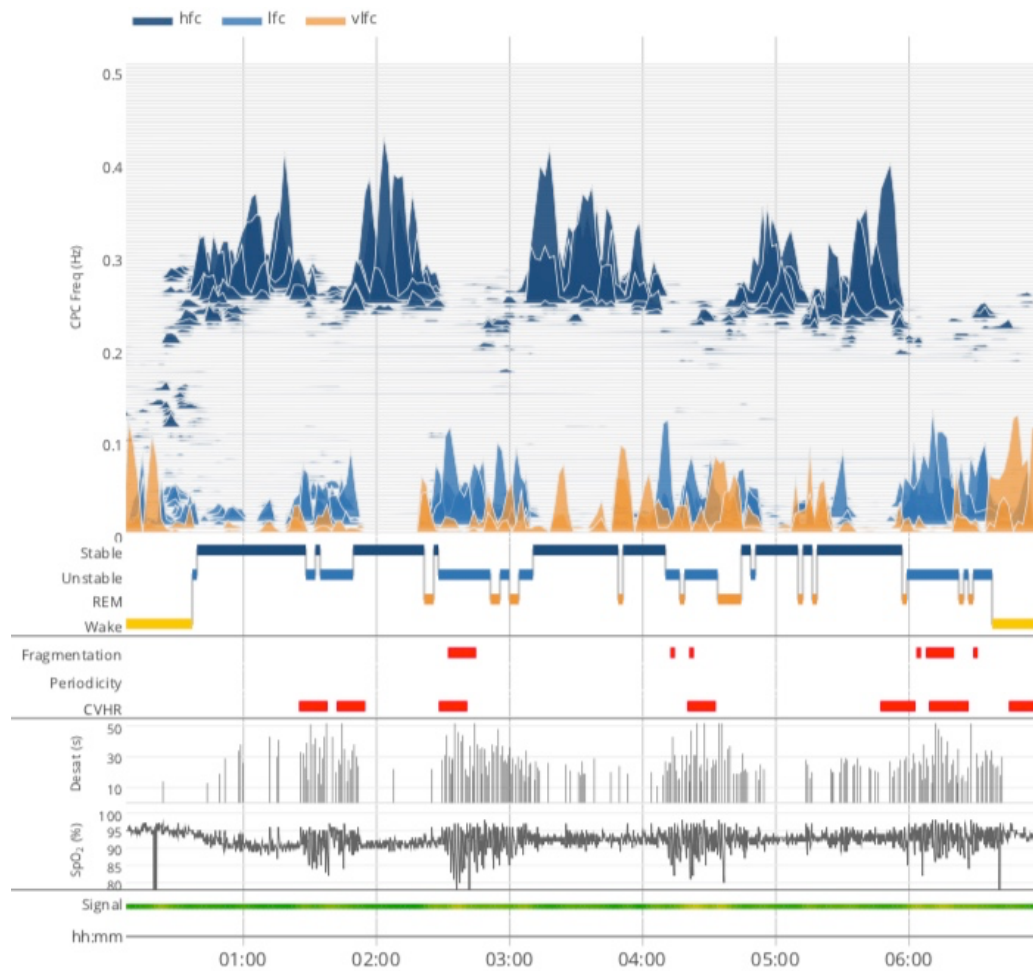


Figure 2. The sleep spectrogram reveals that NREM sleep has a distinct bimodal-type structure marked by distinct alternating and abruptly varying periods of strong high and low frequency cardiopulmonary coupling (HFC and LFC, respectively). These CPC states are separated widely in signal space with no overlap – that is, the boundaries are clean.

The medical literature historically divided sleep into Non-Rapid-Eye-Movement (NREM) sleep and REM sleep, with NREM-sleep having four stages, that later were reduced to three stages (by combining Stage 3 and 4). Stage 3 represents “deep sleep” or “slow wave sleep” a stage where the brain almost exclusively produces slow delta waves. Stage 1 is usually a short period, a transition stage between wake and sleep. Stage 2 is defined as a state when cortical brain waves slow down and eye movements stop, but still with an occasional burst of faster brain waves, sleep spindles and K-complexes. How the biologic role of NREM sleep is associated with delta power is unclear. Restricting such periods produces adverse consequences similar to those of total sleep deprivation, including sleepiness and metabolic dysregulation. Delta power as a proportion of total EEG power is highest during the initial cycles of NREM sleep, and gradually decreases across the biological night and shows rebound effects after a period of sleep deprivation.

It is important to note that CPC does not rely on the same data input streams as PSG. Rather than the primary dependence on PSG and interpretation of EEG morphology, CPC utilizes the physiological changes that occur with sleep via changes in the Autonomic Nervous System (ANS) signaled through the “lower” brain centers and networks (including thalamus, hypothalamus, and hippocampus, all brain centers highly involved in sleep regulation). It integrates information from brain electrical activity on ANS and changes that occur in respiration and cardiac output to capture the ebb and flow of sleep, making traditional “sleep staging” comparison a misnomer. The CPC-method is based on evaluating the strength of synchronization of HRV and respiration and is independent of absolute EEG amplitudes. The degree of this synchronization dramatically changes with sleep stages, offering sleep-stage identification of NREM-sleep as Stable and Unstable and REM-Sleep.<sup>3, 4, 16</sup> This synchronization/coupling is most prominent in healthy children. Starting in adolescence, the coupling reduces but remains



relatively stable across subjects through adulthood, suggesting that sleep regulation has a significantly stronger effect on cardiopulmonary coupling than aging. Cardiopulmonary coupling thus may provide a more meaningful method to evaluate sleep in elderly adults as the method is not constrained by the dependence of slow wave sleep that when measured through EEG from the cortex show deterioration with age.<sup>3,4</sup>

While PSG requires interpretation of observations (manual or automated) from EEG morphology to determine stages of NREM-sleep (stage, 1,2 and 3) and REM-sleep, SleepImage displays sleep stages based on ANS-regulation on the cardiovascular- and respiratory system during sleep. Based on CPC-analysis sleep has a distinct bi-modal structure demonstrating NREM-sleep as two distinct sleep stages, displaying distinct alternating and abruptly varying periods of strong high and low frequency cardiopulmonary coupling as Stable sleep (High Frequency Coupling, HFC) and Unstable sleep (Low Frequency Coupling, LFC). This concept is supported by various biological system behaviors, like being either awake or asleep and when sleeping, being either in NREM-sleep or in REM- sleep and during REM-sleep in either phasic- or tonic-REM.

When comparing Stable NREM-sleep using SleepImage to traditional sleep staging from PSG, Stable NREM sleep is equivalent to part of Stage 2 and all of Stage 3 NREM sleep derived from PSG. Research has demonstrated the correlation between Stable sleep (HFC) and Delta Waves (deep sleep).<sup>2,4</sup> In this state, desirable sleep features dominate, including high vagal tone/sinus arrhythmia, blood pressure dipping, high slow wave power, and stable breathing. Unstable sleep (LFC) equates to the part of NREM sleep that is unstable, meaning all of Stage 1 and part of Stage 2 NREM sleep. In this stage, generally less desirable features dominate, such as cyclic variation in heart rate, absence of blood pressure dipping, tidal volume fluctuations (with sleep apnea of a degree exceeding clinical thresholds) and lower delta power. REM sleep and Wake are detected and separated through SleepImage's spectral power analysis (Very Low Frequency Coupling; vLFC). During REM-sleep the person is near motionless or in state of "skeletal muscular paralysis" where the primary mechanical motion is in the eyes. The EEG physiology of REM sleep and Wake is closely linked from the standpoint of EEG, with the electrooculography (EOG) as the main tool for distinguishing between the two states. SleepImage defines REM sleep into Stable and Unstable REM sleep based on frequency analysis of how the dominant sleep state has been classified as vLFC, where fragmented REM sleep is often accompanied by elevated Low Frequency Coupling.<sup>16</sup>

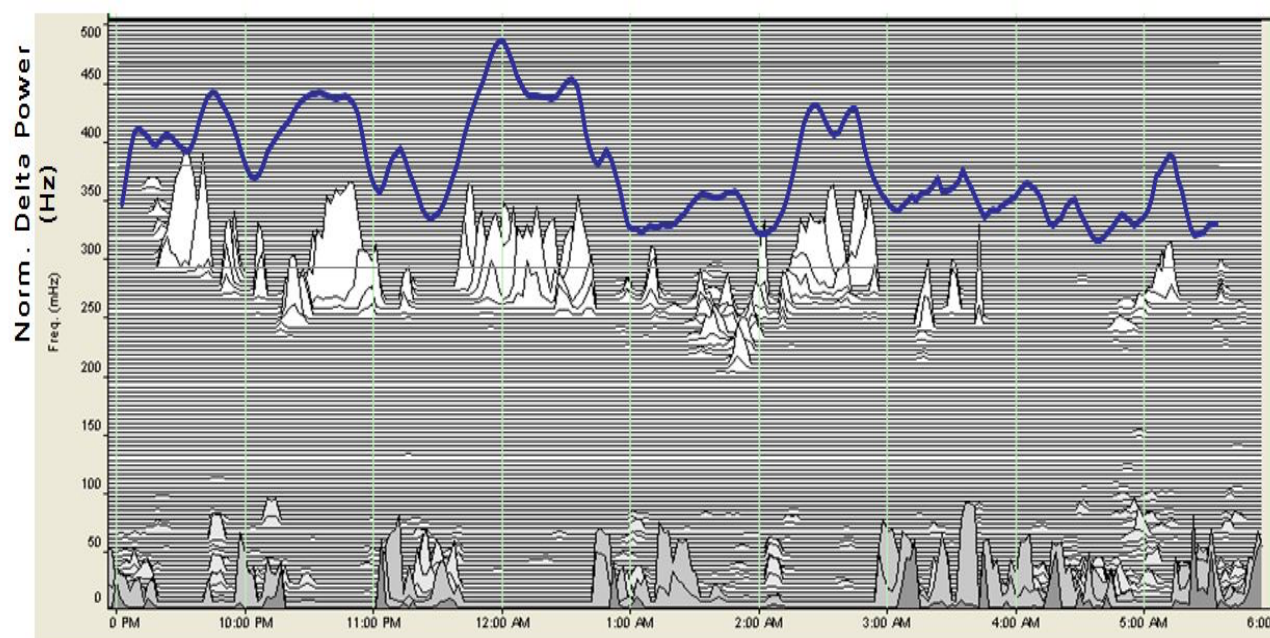


Figure 3. The figure above reveals the relationship between HFC and normalized delta power (blue line) during simultaneous data collection using CPC and PSG as discussed in the paper "Relationship between delta power and the electrocardiogram-derived CPC Spectrogram: possible implications for assessing the effectiveness of sleep". Dr. Robert Joseph Thomas et al. Sleep Med.2014 Jan; 15(1): 125-131.

During the validation of the SleepImage technology, output comparison to tens of thousands of PSG sleep-recordings were performed and a high level of correlation with PSG sleep power mapping has been confirmed. The ebb and flow of slow wave

power is the accepted marker of sleep drive in humans and in non-human species. Delta power measured from surface EEG correlates with ECG- or PLETH-derived Cardiopulmonary Coupling high-frequency power (Figure 3, blue line), further supporting a link between cortical EEG electrical activity and brainstem-related cardiorespiratory functions.<sup>3, 4</sup> For diagnosis of SDB the Sleep Image Apnea Hypopnea Index (sAHI) has a strong agreement with AHI calculated from PSG<sup>20, 23</sup> and the method is also able to differentiate between obstructive and central sleep apnea.<sup>24, 25</sup>

While SleepImage and PSG analyze and present biological activity during sleep from different brain structures (Autonomic Nervous System regulation vs. Cortical Brain Wave regulation, respectively), they both reflect sleep. The two methods (CPC and PSG) do therefore not vary as much as it may seem at first, as is demonstrated in Figure 4.

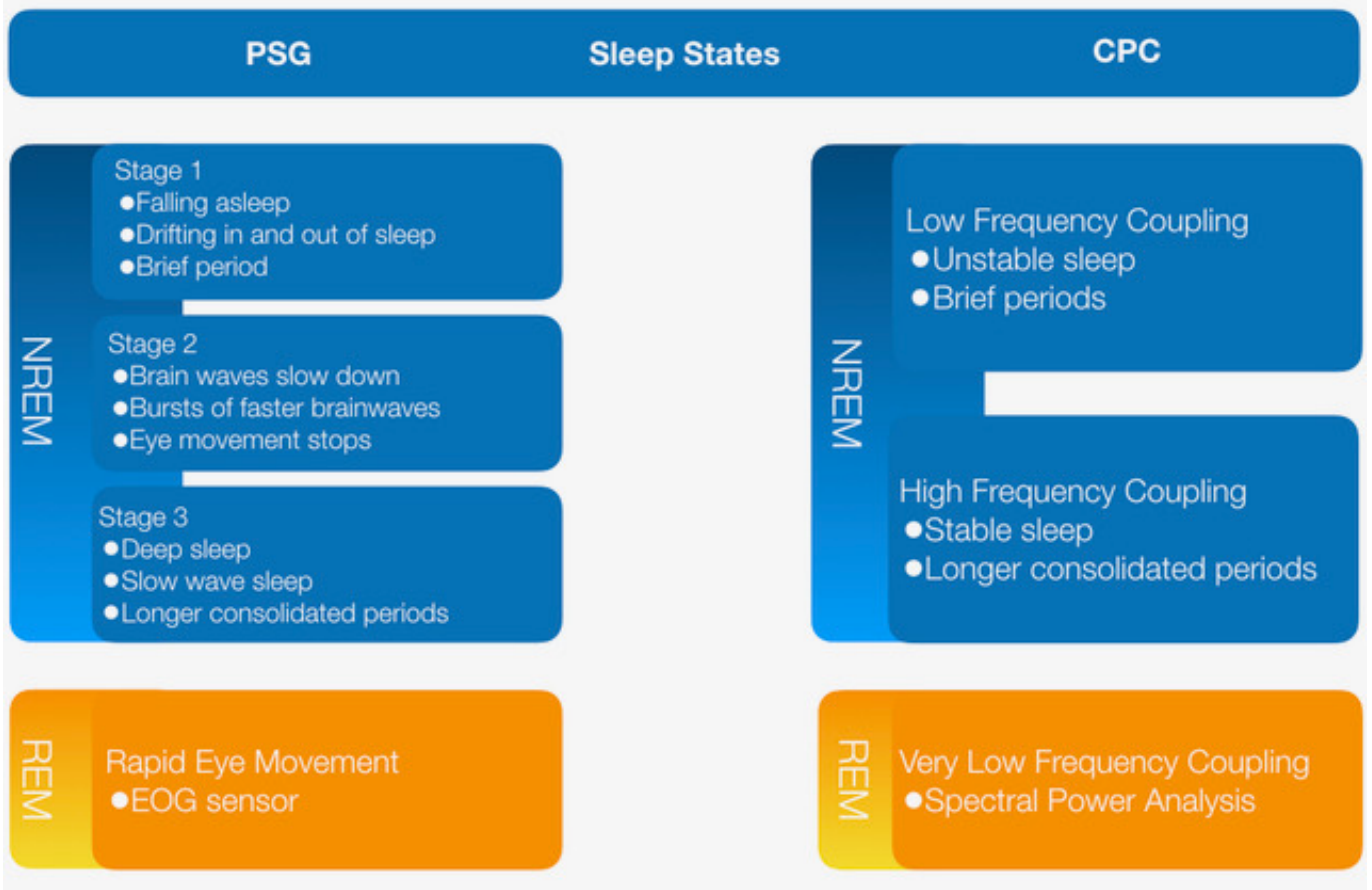


Figure 4. The relationship between conventional sleep scoring system and the Cardiopulmonary Coupling (CPC) scoring system.

Both the SleepImage and the PSG methods are quite capable instruments to evaluate sleep, though with some important differences. The Sleep Spectrogram and the software generated biomarkers of sleep quality, the CPC sleep pathology markers as well as sleep duration, efficiency, and latency, are simple to collect offering the possibility to collect multiple nights of data and observe intra-night variability providing a practical approach to assess sleep as a vital sign of health. The SleepImage method is particularly useful to track sleep health over time to identify relative changes in sleep quality, and in individuals with sleep disorders, for disease management, whether it is for insomnia or sleep disordered breathing, obstructive sleep apnea (OSA) and central sleep apnea (CSA). The simple interface offers the potential to implement personalized approach into sleep medicine by treating sleep disorders as other chronic diseases,<sup>26-29</sup> with repeated testing in patients’ natural sleep environment over multiple nights and multiple time points to optimize disease management and patients’ health.<sup>7, 12, 18, 30</sup>

Further description of the Cardiopulmonary Coupling can be found in the sleep medicine textbook, Principles and Practice of Sleep Medicine, (Kryger – Roth – Dement) Sixth Edition, Chapter 166. Cardiopulmonary Coupling Sleep Spectrogram.<sup>2</sup>

## SleepImage Output Parameters

**Stable sleep** (High-frequency coupling; 0.1-0.5Hz) is a biomarker of stable NREM sleep, which is characterized by stable breathing, high vagal tone, a non-cyclic alternating pattern (n-CAP) on the electroencephalogram (EEG), high relative delta power, blood pressure dipping, and stable arousal threshold. This state may be considered as “effective” NREM sleep. Effective sleep enables the desirable functions of sleep, across multiple dimensions (e.g., neuronal network health, metabolic, immune etc.), such that spending periods in this state enables recovery and restoration processes.<sup>2, 3, 7, 16, 18</sup>

**Unstable sleep** (Low-frequency coupling; 0.01-0.1Hz) is a biomarker of unstable NREM, with exactly opposite features when compared to stable sleep: low-frequency tidal volume fluctuations, cyclic variation in heart rate, a cyclic alternating pattern (CAP), electroencephalogram (EEG) low relative delta power, non-dipping of blood pressure and variable arousal thresholds. This state may be considered “ineffective” NREM sleep. Ineffective sleep fails to accomplish the desirable functions of healthy sleep. A subset of low-frequency coupling is termed Elevated Low-Frequency Coupling (e-LFC) and has two subsets; an indicator of Periodicity (elevated low frequency narrow band; e-LFC<sub>NB</sub>) and Fragmentation (elevated low frequency coupling broad band (e-LFC<sub>BB</sub>)).<sup>2, 3, 7, 16, 18, 24</sup>

**Fragmentation** (elevated low frequency coupling broad-band e-LFC<sub>BB</sub>) is a subset of low-frequency coupling during NREM sleep which is an indicator of sleep pathology (e.g., pain) or disordered breathing patterns like Obstructive Sleep Apnea (OSA) and Upper Airway Resistance Syndrome (UARS).<sup>2, 11, 23-25, 31</sup>

**Periodicity** (elevated low frequency coupling narrow-band e-LFC<sub>NB</sub>) is a subset of low-frequency coupling, consisting of periodic-type breathing patterns that may occur during NREM and/or REM and indicates sustained periods of Central Sleep Apnea (CSA) and periodic breathing, or “physiologic” periodicity due to Periodic Leg Movements (PLM’s).<sup>12, 23, 24</sup>

**Sleep Quality Index (SQI)** is a summary index of the CPC biomarkers of sleep quality, sleep stability, fragmentation, and periodicity, and provides a meaningful unit of measure of sleep health. The SQI is displayed on a scale of 0-100 with expected values for both children and adults. The SQI is useful to track sleep health over time, whether to identify the need for further clinical investigation or to track therapy. The SQI is easily communicated and relatable to the patient or other lay persons, while at the same time being a comprehensive measure of sleep health based on clinical validation.<sup>7, 13, 18, 19, 31</sup>

**Apnea Hypopnea Index (sAHI)** is an automated measure of Apnea/Hypopnea events and is FDA-cleared to aid diagnosis of Sleep Disordered Breathing (SDB) in both children and adults following AASM categorization (mild, moderate, severe) as summarized in table 1. The sAHI is calculated by combining SpO<sub>2</sub>-analysis, CPC-analysis and hypoxic events that are detected through the SpO<sub>2</sub> signal where a qualifying event is characterized by a minimum of ten (10) seconds in duration and is displayed based on: (1) both 3% and 4% oxygen desaturation (2) as “Total”, “Obstructive” and “Central” events, (3) the sAHI, like the Apnea Hypopnea Index (AHI), reports the number of paused breathing events during the sleep period calculated according to the rules set by the Academy of Sleep Medicine (AASM) guidelines for event scoring.<sup>20, 23</sup>

**Respiratory Disturbance Index (sRDI)** is intended to aid in the characterization of respiratory events during sleep. While the sAHI includes events that meet the definitions of apneas or hypopneas, the sRDI additionally includes respiratory-effort related arousals (RERAs). Presence of RERAs is detected from autonomic arousals and Fragmentation without the requirement of a co-occurring oxygen saturation of 3% or more. The sRDI, when put into the context of patient symptoms for SDB, may thus provide the clinician with additional relevant information to aid clinical evaluation of SDB and to track treatment benefit.

**Sleep Apnea Indicator (SAI)** is based on detecting cardiac reaction associated with prolonged cycles of oxygen desaturation, based on Cyclic Variation of Heart Rate (CVHR) during unstable breathing (tidal volume fluctuations in breathing). During each

apnea event, blood oxygen decreases and is accompanied by a physiological reaction of bradycardia and, when breathing resumes, a relative tachycardia; hypoxemia is thus reflected in the SleepImage output as SAI.<sup>23, 25</sup> CVHR can be detected during stable sleep that often may reflect events that are typically scored as mild hypopneas but may also be triggered by other pathologies such as periodic limb movements (PLMS) or restless leg syndrome (RLS). For clinical evaluation it is important to consider both SAI that is likely to reflect apnea events that disturb sleep to lower the SQI, and CVHR that is likely to reflect milder apneas and hypopneas that may or may not disturb sleep to lower the SQI.

Table 1: Categorization of Sleep Apnea by American Academy of Sleep Medicine (AASM) for adults and children (events/hr.)				
	No Sleep Apnea	Mild Sleep Apnea	Moderate Sleep Apnea	Severe Sleep Apnea
Adults	AHI/REI < 5.0	AHI/REI ≥5.0 to < 15.0	AHI/REI ≥15.0 to < 30.0	AHI/REI ≥30.0
Children	AHI < 1.0	AHI ≥1.0 to < 5.0	AHI ≥5.0 to < 10.0	AHI ≥10.0

When reviewing the sAHI and sRDI scores, it is recommended to consider SDB events concurrent with CPC sleep states (sAHI<sub>STABLE</sub>, sAHI<sub>UNSTABLE</sub>, and sAHI<sub>REM</sub>) when evaluating and determining disease category and severity. It is furthermore recommended to take into consideration the pathology biomarkers of Fragmentation (associated with obstruction) and Periodicity (associated with periodic breathing) when interpreting the study output for diagnosis.<sup>20, 23, 24</sup>

The performance of the SleepImage Apnea Hypopnea Index (sAHI) was validated by comparing the fully automated software generated sAHI to manually derived AHI from in-laboratory PSG-sleep studies currently considered as the “reference standard”. The data were collected in prospective clinical trials that included both children and adults. Additionally, in adults the sAHI was compared to respiratory event index (REI) from prospective clinical trials collected with Home Sleep Apnea Tests (HSAT). All comparisons are based on disease severity categorization of sleep apnea based on definition by the American Academy of Sleep Medicine (AASM), Table 1.

The comparison of sAHI to AHI was further based on published guidelines from the American Academy of Sleep Medicine (AASM), Obstructive Sleep Apnea Devices for Out-Of-Center (OOC) Testing: Technology Evaluation.<sup>32</sup> This guidance was prepared to “*help clinicians decide which out-of-center (OOC) testing devices are appropriate for diagnosing obstructive sleep apnea (OSA)*” and is based on emphasizing Sensitivity and Positive Likelihood Ratio. Guidelines from the American Academy of Pediatrics (AAP),<sup>33</sup> calls for information on sensitivities, specificities and predictive values to be available for physicians to familiarize themselves with before use in clinical evaluation and diagnosis of pediatric obstructive sleep apnea (POSA), this information is presented in Table 2.

Children (n=1,334) in the cohort; 39% of the children had no disease (n=518), 45% had mild sleep apnea (n=601), 9% moderate sleep apnea (n=123) and 7% had severe sleep apnea (n=92).

Adults (PSG, n=189; HSAT, n=572) in the cohort; 12% had no sleep apnea (n=102), 30% had mild sleep apnea (n=251), 37% moderate sleep apnea (n=313) and 21% severe sleep apnea (n=173).

Performance-testing, comparing the two indices sAHI (CPC-output) and AHI (PSG-output), demonstrated strong correlation as well as significant agreement in both defining events/hour and to identify SDB categories (no-disease, mild sleep apnea, moderate sleep apnea, severe sleep apnea). The results are summarized in table 3.

The difference between Likelihood Ratios and Predictive Values, can be explained as follows:<sup>32, 33</sup>

Likelihood Ratios (LR) are used to assess the value of performing a diagnostic test and is performed to determine whether a test result usefully changes the probability that a disease state exists. AASM guideline defines acceptable results as sensitivity of at

least 82.5% and LR+ of at least 5 at an in-lab AHI of 5, demonstrating a 95% post-test probability of the disease based on 80% pre-test probability of the disease.

**Predictive Values (PV)** reflect the diagnostic power of the test and depend on sensitivity, specificity and disease prevalence, as well as the reporting probability of the patient being positive/negative based on a positive/negative test result. AAP does not have a guideline for what values are sufficient to generate passing results to diagnose a disease.

Table 2. Results of comparing automated sAHI (CPC) and manually scored AHI (PSG) output.				
sAHI vs AHI		Mild	Moderate	Severe
Agreement	Adults	96.3%	90.5%	98.9%
	CI95%	[.936, .990]	[.863, .947]	[.975, 1.000]
	Children	89.1%	95.2%	98.1%
	CI95%	[.875, .908]	[.941, .964]	[.974, .989]
Sensitivity	Adults	98.7%	92.6%	95.1%
	CI95%	[.970, 1.000]	[.869, .983]	[.835, .994]
	Children	90.7%	89.3%	91.3%
	CI95%	[.887, .927]	[.852, .934]	[.855, .971]
Specificity	Adults	84.8%	88.9%	100%
	CI95%	[.726, .971]	[.830, .948]	[.975, 1.000]
	Children	86.7%	96.3%	98.6%
	CI95%	[.834, .895]	[.951, .974]	[.978, .992]
Positive Likelihood Ratio	Adults	6.52	8.33	280 <sup>1</sup>
	Children	6.81	24.37	66.71
Negative Likelihood Ratio	Adults	0.015	0.083	0.060
	Children	0.107	0.111	0.088
Positive Predictive Values	Adults	96.9%	86.2%	100%
	Children	91.5%	82.4%	83.2%
Negative Predictive Values	Adults	93.3%	94.1%	98.7%
	Children	85.5%	97.9%	99.4%
1 Division by zero. PLR estimated using substitution formula				

The sAHI, sRDI and SAI are indices intended to aid clinical evaluation, diagnosis, and management of sleep apnea in children and adults. The sAHI is an event counter of paused breathing events per hour of sleep using the same scale and reporting metrics as AHI derived from in-laboratory PSG-studies. The sRDI adds autonomic arousal detection to the sAHI which is reported on the same scale as the AHI from PSG-studies. The SAI is based on cardiovascular reaction to paused breathing (CVHR) during unstable sleep with a scale of 0 – 100. As the sAHI/sRDI are based on different scaling-rules than SAI, they are not expected to have the same numerical output.

The SAI can though be compared categorically to the AHI from PSG-studies, although it is based on different physiological signals and the unit of measure to quantify sleep apnea is different. SAI can be perceived as a severity biomarker for CPC-derived parameters of SDB, while the AHI is literally a prevalence measure counting events per hour of sleep. Classification of SDB utilizing the SAI is based on the same premise as the AHI, the common biomarker used to quantify severity of SDB, as Mild, Moderate and Severe. Table 3 summarizes a comparison of SAI to AHI from Polysomnography (PSG) studies at each of the severity thresholds for mild, moderate, and severe sleep apnea in children and adults.



Table 3. Results of comparing automated SleepImage Apnea Indicator (SAI/CVHR) and manually scored AHI (PSG) output.					
SAI/CVHR vs AHI			Mild	Moderate	Severe
Agreement	Adults	SAI	79%	79%	87%
		CVHR	83%	81%	89%
	Children	SAI	88%	87%	96%
		CVHR	88%	85%	94%

Sleep Apnea is associated with significantly increased risk of cardiovascular morbidity and mortality. In patients with cardiac autonomic dysfunction, that presents as decreased heart rate variability (HRV) and ultimately can lead to a fixed heart rate due to progressive dysfunction of the cardiac sympathetic nervous system. In this subgroup of patients, the SAI is an ineffective tool to detect apneas, as they do not exhibit the oscillatory heart rate dynamics, but the CPC e-LFC biomarkers (Fragmentation and Periodicity) and the sAHI/sRDI are useful biomarkers to aid in the diagnosis of SDB in this patient population. In patients with chronic Atrial Fibrillation, complex patterns cannot be identified and the chaos of the ANS results in less meaningful CPC output, thus warranting caution in interpretation.

## SleepImage in Sleep (Disorder) Management

SleepImage is a simple to use and low-cost method that offers the opportunity of multi-night testing during the process of evaluating if there may be a sleep disorder, to evaluate night-to-night variability in sleep and to track changes in sleep over time, as part of sleep health management. Before prescribing a study using a PPG sensor (also known as pulse oximeters), ensure that the sensor size fits the patient properly.

The Sleep Quality Index (SQI) is a summary index of the SleepImage output, indicating sleep health in individuals of all ages. Healthy aging is accompanied by a reduction in HRV and respiratory variability, causing an expected gradual reduction of SQI values to be a normal part of healthy aging. While SQI values are comparable between individuals, the greatest value is to track sleep quality for each individual over time.

Night-to-night variability in sleep is recognized and this variance should be expected to increase in patients with sleep disorders (sleep pathology) and/or the presence of comorbidity. Differences should also be expected over time due to environmental conditions, lifestyle changes and behavior or other factors that can affect sleep and cause night-to-night variability in sleep. It is well documented in the peer-reviewed clinical publications that sleep apnea severity can vary considerably from night to night as has been reported in SDB-patients undergoing PSG-studies on consecutive nights or one month apart, where changes in AHI were observed to be in the range of 18%-65%.<sup>34-36</sup> When sleep disorders are suspected, it is important to treat them as other chronic conditions that can present different levels of symptoms over time. Measuring sleep in patients' normal sleep environment over multiple nights and on multiple occasions to capture the dynamics of sleep physiology and pathology is important.<sup>26-28</sup> Capturing and mitigating the night-to-night variability respects the chronic nature of sleep disorders that should improve the diagnostic process, the management of the disease and patient outcomes.<sup>37</sup>

None of the values for the SleepImage biomarkers should be considered absolute threshold values; they are expected to be generally similar when using the same sensor type. Although there are no signal specific contraindications, certain conditions such as cardiovascular disease and arterial stiffness can reflect signal specific differences that can cause variability where it is normal to expect  $\pm 10\%$  differences that can be greater for certain patients based on disease conditions. For clinical use, it is recommended to consistently use the same sensor type in the patient's natural sleep environment.<sup>29</sup>

## Expected Values - Sleep Quality and Sleep Pathology

Expected Values	Adults	Children
Sleep Quality Index (SQI)	>55	>70
Sleep Apnea Indicator (SAI) Mild / Moderate / Severe threshold markers	≥5 / ≥15 / ≥30	≥1 / ≥5 / ≥10
Apnea Hypopnea Index (sAHI) Mild / Moderate / Severe threshold markers	≥5 / ≥15 / ≥30	≥1 / ≥5 / ≥10
Respiratory Disturbance Index (sRDI) Mild / Moderate / Severe threshold markers	≥5 / ≥15 / ≥30	≥1 / ≥5 / ≥10
Elevated Low Frequency Coupling, Broad Band (e-LFC <sub>BB</sub> )	<15	<8
Elevated Low Frequency Coupling, Narrow Band (e-LFC <sub>NB</sub> )	≤2	0

Table 4. Expected values for CPC biomarkers are not absolute thresholds and need to be considered in context of patients' sleep complaints, comorbidity and patient history.

## Children

Prevalence of sleep disorders are high in children but at the same time sleep is rarely addressed during routine pediatric visits.<sup>38</sup> During the preschool years (3-5 years of age) lymphoid tissue growth peaks, increasing the likelihood of symptoms of SDB to develop.<sup>39</sup> Clinical guidelines regarding diagnosis of sleep disordered breathing (SDB) in children, emphasize that attempts to specify severity of SDB and make treatment decisions solely based on the Respiratory Event Index (REI) or Apnea Hypopnea Index (AHI) and minimum oxygen saturation may lead to misclassification as children often present with changes in sleep architecture and fragmented sleep. Multi-night testing will assist clinicians to evaluate SDB in children.<sup>40, 41</sup>

The most common form of SDB in children is obstructive sleep disordered breathing (oSDB), characterized by abnormal respiratory and ventilation patterns during sleep. SDB is highly prevalent condition in children, with disease severity ranging from primary habitual snoring (6%-25%) to obstructive sleep apnea (OSA), diagnosed when apnea-hypopnea index (AHI) ≥1.0 on nocturnal polysomnography (PSG). Tonsillar-hypertrophy and obesity are the most common risk factors for OSA in children and tonsillectomy is recommended as first-in-line therapy for children with tonsillar-hypertrophy and OSA.<sup>42</sup>

Considerable variability is in symptom presentation in children. This makes OSA difficult to diagnose and demands increased awareness of SDB in children among clinicians. Excessive daytime sleepiness is not a frequently reported symptom in children with OSA, but often present with hyperactivity, difficulty concentrating, attention- behavioral- and mood-problems, enuresis, persistent mouth breathing with dry mouth and morning headaches.<sup>41 43 44</sup>

A recent study in healthy children suspected of OSA confirmed that 18% of children undergo surgery without objective sleep evaluation and of the children that were evaluated with PSG-sleep-study based on parent's concern and preference for their child to have objective evaluation of their sleep before surgery, found that only about 45% of the children had OSA and might benefit from surgery.<sup>45</sup> Performing a surgery on a child without a need, may cause both unnecessary distress for the child and affect their future health prospects as well as incurring unnecessary cost for both parents and payers. To further complicate disease management of OSA in children, spontaneous polysomnographic improvements are well known and documented (46%)<sup>46, 47</sup> as well as residual disease following surgery with less than a third of children with OSA achieving complete resolution with surgery.<sup>48, 49</sup> Additionally, surgery may potentially cause both serious short-term surgical complications and in the long-term significantly increased delayed respiratory, allergic, and infectious sequelae.<sup>50-52</sup>

Studies looking at sleep management in pediatric care have observed a mismatch between prevalence of parents reported symptoms of sleep problems, including snoring, SDB and insomnia and documented diagnoses by the physician. In a study screening for snoring in primary care, only 38% of the children that screened positive for snoring were referred for further evaluation.<sup>53</sup> Although several screening questionnaires have been developed to identify children with OSA, they have not proven accurate and are rarely used.<sup>38</sup> Parent/caregiver reports of symptoms correlate poorly with PSG findings, and subjective clinical evaluation of tonsillar-size is not a reliable indicator of need for surgery or surgical success.<sup>54-57</sup>

Because of age related airway growth, children in particular stand to benefit from repeated objective and clinical symptom evaluation over time. This symptom variability of OSA in children as well as the complexity of the disease, mandates a careful data-driven clinical decision-making process prior to therapy, including surgery.<sup>58</sup> It is furthermore important to implement therapy-tracking post intervention for objective evaluation with longitudinal care to improve clinical management. If left untreated, the disease may adversely affect the child's neurocognitive, behavioral, cardiovascular and cardiometabolic health over time and their future prospects.<sup>44, 47</sup>

Both the American Academy of Pediatrics (AAP) and the American Academy of Sleep Medicine (AASM) recommend a PSG-study to objectively assess and diagnose OSA in children prior to surgery, as questionnaires alone do not provide a good diagnostic prediction of OSA in children.<sup>33, 41</sup> These academic guidelines to establish objective evidence of OSA prior to surgical decisions are though frequently bypassed.<sup>59</sup> This may be caused by limited access to pediatric sleep laboratories, high cost of testing with increased parent out-of-pocket expenses, or reported inconvenience for both the child and their caregivers.<sup>49,</sup>

Diagnosis of SDB requires clinical, subjective- and objective sleep data and SDB in children is defined as  $AHI > 1$ /per hour of sleep. However, the AHI must be considered in the context of the child's health, symptoms, and daytime functional impairment to most accurately assess SDB significance, severity, and impact. The fact that majority of treatment-related changes in outcomes of OSA in children are not causally attributable to polysomnographic resolution or changes in severity calls for additional sleep metrics that can be tracked over time.<sup>60</sup>

SleepImage is FDA-cleared for diagnosis of OSA in children based on the sAHI, it is low-cost, simple to use and not intrusive for the child. This offers the potential to measure multiple nights of sleep in the child's natural sleeping environment to capture the dynamics of SDB in children, which may be a more appropriate method than making a therapy decision from presentation of subjective symptoms, clinical evaluation, and objective measure at one specific point in time.

## Adults

The same approach for sleep management in adults is important and PSG and HSAT generally do not offer the opportunity for repeated testing prior to disease diagnosis or to track efficacy of therapy. Currently the ratio of undiagnosed SDB is estimated to be around 85% of the patient population or more than 936 million people<sup>61</sup> are estimated to have the disease. Long-term compliance on positive airway pressure (PAP) therapy is considered generally low and is problematic, as effectiveness of therapy is greatly dependent on consistent use. The lack of compliance may be caused by patients' own subjective evaluation of not finding the benefit from therapy to outweigh the burden of the therapy or be caused by negative effects of PAP-therapy on sleep quality (SQI).<sup>7, 18</sup> Sleep quality evaluation at baseline as well as repeated testing for therapy efficacy is therefore highly desirable for both patients and their clinicians to improve clinical management of sleep disorders.<sup>7, 18, 62, 63</sup>

Only with this kind of repeated objective testing, will the opportunity for more comprehensive phenotypic profiling in both clinical management of sleep disorders as well as in design and conduction of research studies be fully utilized. Sleep disorder management needs to be practiced comparably to how other chronic conditions like diabetes or hypertension are managed.<sup>26-</sup><sup>29</sup> A change in clinical protocols to this extent could have a meaningful and measurable positive impact on patient outcomes and on quality of research to provide insight into sleep in both health and disease. Improvements in management of sleep disorders will only be achievable with access to accurate and actionable clinical sleep-tests that are evidence based, simple, low-cost, scalable, and can be self-administered in the patients' own natural sleep environment.

The SleepImage system offers a FDA-cleared, fully automated and rigorously validated output, that is simple to use both for patients and clinicians for unique insight into sleep health and sleep regulation:<sup>9</sup>

- 1) Stable sleep tracks slow wave power and results of repeated testing could provide new insights into night-to-night sleep homeostatic mechanism.<sup>2, 3, 30</sup>
- 2) Substantial overlap in symptom presentation of insomnia and OSA is documented. This advances the need for methods that capture data and provide output that can be used for clinical evaluation of both insomnia and OSA before making



diagnostic decisions and initiation of therapy. Validated sleep tests for patients with sleep complaints who currently are considered ineligible for PSG or HSAT testing fill a void in clinical management of sleep disorders.<sup>30, 31, 64</sup>

- 3) The possibility to record sleep for more than one night in the patient's natural sleep environment should offer opportunity for improved clinical management of sleep disorders. Change in clinical protocols to objectively test all patients with sleep complaints for more than one night before any therapy is initiated could have a meaningful and measurable positive impact on patient's health and quality of life, disease management and public health.<sup>26, 28, 29</sup>

## Understanding the SleepImage Spectrogram

SleepImage graphically displays the coupling of heart (pulse) rate variability (HRV/PRV) and respiration activity (EDR/PDR) in the Sleep Spectrogram. On the front-view Spectrogram, time (hh:mm) is displayed on the horizontal axis, and frequency (Hz) is on the vertical axis. When both data streams (HRV/EDR or PRV/PDR) are in phase (coupled/synchronized), peaks are generated on the graph to form a visual representation of the frequencies collected during the recording.

## Full View Spectrogram

The full view Spectrogram displays the peaks and oscillation pattern of HFC, LFC and vLFC for the time series. The vertical axis uses frequency range 0.004Hz to 0.5Hz and time in hours on the horizontal axis.

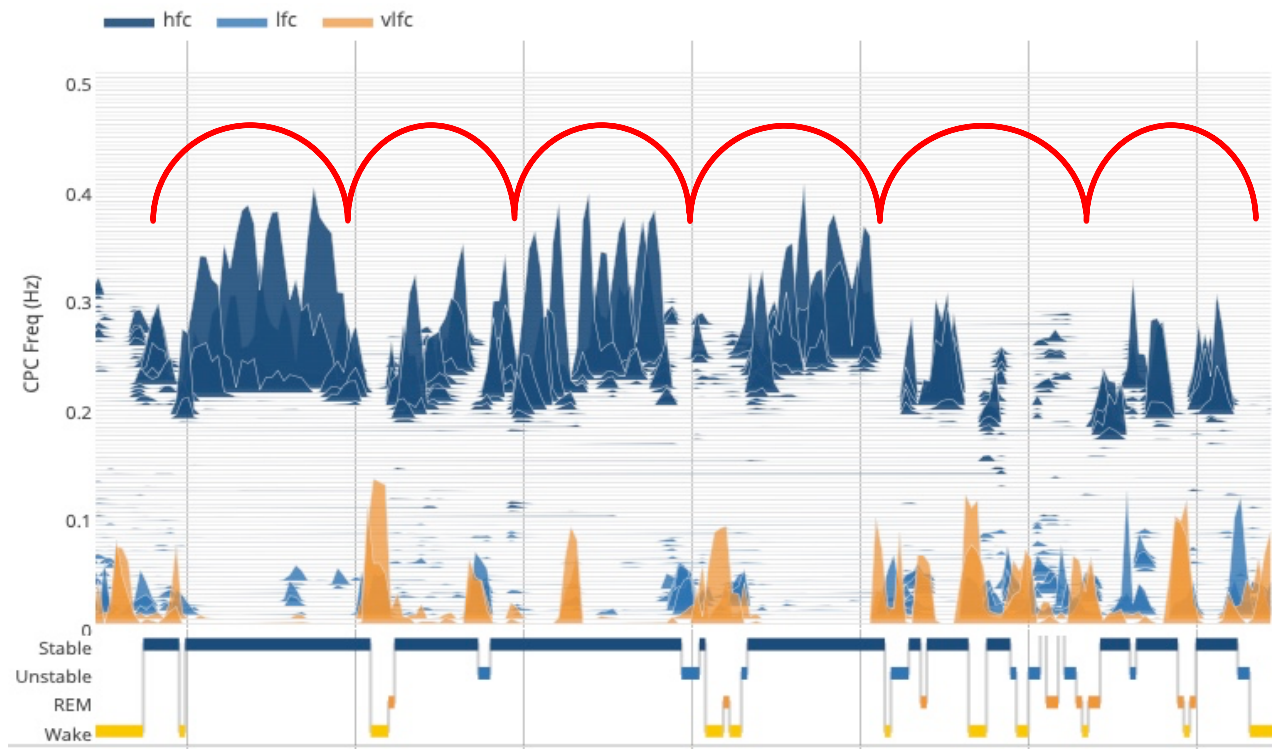


Figure 5. Oscillations between stable and unstable sleep are expected to modulate in 30-90-minute cycles that range from 4-8 Cycles in an adult 8-hour healthy night's sleep and correspond to the alternating periods of NREM and REM sleep. When sleep is disrupted (sleep apnea, insomnia, stress, pain and a variety of other factors), the healthy sleep rhythm is disrupted.

HFC peak amplitude is in relation to the amount of coupling or synchronization between the curves generated by the coupling activity. Greater coupling results in higher amplitude peaks. Low amplitude peaks result from less overlap between the curves generated by heart (pulse) rate variability and respiratory rate activity. A lack of coupling between these two input data streams will result in zero value and no peak generation.

## Stable Sleep or High Frequency Coupling - HFC

Stable sleep (High frequency coupling) is displayed on the Spectrogram as dark blue peaks in the frequency range of 0.1 - 0.5Hz. Most Stable sleep occurs during part of NREM stage-2 and all of NREM stage-3, correlating with the EEG morphology called noncyclic alternating pattern (n-CAP) and delta waves. Stable sleep is a biomarker of integrated stable NREM sleep and is associated with periods of stable breathing, high vagal tone, generally a non-cyclic alternating pattern on the electroencephalogram, high relative delta power, physiologic blood pressure dipping, and stable arousal threshold.

## Unstable Sleep or Low Frequency Coupling - LFC

Unstable (Low frequency coupling) is displayed on the Spectrogram as light blue peaks in the frequency range of 0.01 - 0.1Hz. Unstable sleep is a biomarker of integrated unstable NREM sleep, with opposite features to Stable sleep and occurs during NREM stage-1 and part of NREM stage-2 sleep. Unstable sleep is associated with EEG activities called cyclic alternating pattern (CAP), periods of fluctuating breathing patterns (tidal volume fluctuations), cyclic variations in heart rate (CVHR), blood pressure non-dipping and variable arousal thresholds. Fragmented REM sleep has low-frequency coupling characteristics.

## Wake & REM sleep or Very Low Frequency Coupling - vLFC

Very low frequency coupling (vLFC) is displayed on the Spectrogram as orange peaks in the frequency range of 0.004 - 0.01Hz and represent REM sleep & wake.

During the course of the sleep period, spontaneous shifts occur between stable and unstable sleep. Oscillations between stable and unstable sleep are expected to modulate in 60-90 minute-cycles ranging from 4-8 cycles for an adult's 8-hour healthy sleep and correspond to the alternating periods of NREM and REM sleep (Figure 5). Disease states negatively impact this pattern. Healthy, stable sleep is dominated by high vagal tone, and results in characteristic heart rate variability where the heart rate slows down and speeds up in synchrony with regular respiration. This is normal rhythm and is associated with stable NREM sleep (HFC).

# The SleepImage Report & Graphics

## The SleepImage Report

### Sleep Quality

SQI 66 Expected >55	EFFICIENCY 86% Expected >85%
------------------------	---------------------------------

### Sleep Opportunity

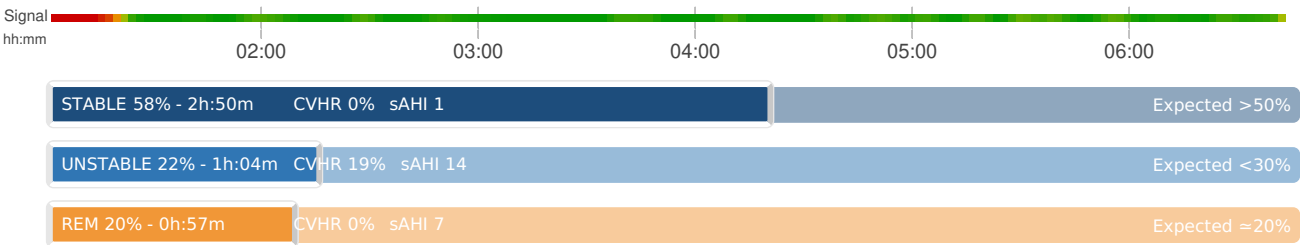
LATENCY 0h:21m Expected <30 min	DURATION 5h:20m Expected 7-9 hours
------------------------------------	---------------------------------------

### Sleep Apnea

sRDI 9 Mild	sAHI 5 Mild
----------------	----------------

### Sleep Pathology

FRAGMENTATION 16% Expected <15%	PERIODICITY 0% Expected ≤2%
------------------------------------	--------------------------------



TST	4h:52m
WASO	0h:27m
WAKE TRANSITIONS	#8
SAI	4

SpO <sub>2</sub> <90%	0m:17s - 0%
SpO <sub>2</sub> <88%	0h:0m - 0%
SpO <sub>2</sub> <80%	0h:0m - 0%
MIN-MAX-MEAN SpO <sub>2</sub>	88% - 99% - 96%

	Desaturations	
	3%	4%
sAHI <sub>TOTAL</sub>	5	2
sAHI <sub>OBSTRUCTIVE</sub>	5	2
sAHI <sub>CENTRAL</sub>	0	0
sRDI	9	8
ODI	3	1

	Min Max Mean		
	Min	Max	Mean
APNEA DURATION (sec)	10	26	16
HEART RATE (BPM)	47	103	63

#### Test Summary:

#### Patient: 51 year old Male

Average Signal Quality is **94** %.  
Sleep Quality is **above** expected value.  
Sleep Efficiency is **above** expected value.  
Sleep Duration is **not within** expected value.

Sleep Apnea Indicator is **below** expected value.  
Apnea Hypopnea Index is **Mild** .  
Sleep Fragmentation is **above** expected value.  
Periodicity is **below** expected value.

## Reviewing SleepImage Report Output

1. **Check Signal Quality.** Only predominantly green signal quality should be considered for clinical decision-making. Yellow and Red signal should be evaluated for signal abnormalities (signal noise) or signal loss.
2. **Evaluate Sleep Quality.** SQI indicates sleep health, with expected values as SQI >55 (adults) or >70 (children). SQI is a summary of sleep stability, fragmentation, and periodicity on a scale from 0 – 100. Sleep Efficiency is the ratio of Total Sleep Time divided by Sleep Opportunity and should be >85%.
3. **Evaluate Sleep Opportunity** which is defined by time in bed allocated to sleep, including Sleep Onset Latency (SOL) and Sleep Duration (SD). SD includes Total Sleep Time (TST), Wake After Sleep Onset (WASO). Expected SL is generally defined as <30min. SD is defined by age groups. Although Insomnia cannot be diagnosed from a single night of sleep and needs to be combined with subjective evaluation, including daytime symptoms, SL and Sleep Efficiency (SE) are the most used metrics to evaluate symptoms of Insomnia. For accurate SE during the sleep period, exclude the wake period after the last sleep period by recalculating the sleep recoding.
4. **Evaluate Sleep Apnea.** The SleepImage Apnea Hypopnea Index (sAHI) and the SleepImage Respiratory Disturbance Index (sRDI) are intended to aid in evaluating sleep apnea (SA) and in the characterization of respiratory events during sleep. The indices are categorized as 'Mild'; 'Moderate' and 'Severe' with values for Children for each category  $\geq 1$ ,  $\geq 5$  and  $\geq 10$  respectively and for adult values for each category are  $\geq 5$ ,  $\geq 15$  and  $\geq 30$  respectively. Sleep Apnea Indicator (SAI) can indicate SA with good agreement when compared against AHI, despite being based on cardiovascular reaction rather than desaturations to detect and quantify SA. Threshold values for SAI are the same as for sAHI/sRDI for children and adults, respectively.
5. **Review Sleep Pathology.** The Sleep Pathology biomarkers are Fragmentation (e-LFC<sub>BB</sub>) indicating sleep fragmentation, arousals and obstructive apneas, and Periodicity (e-LFC<sub>NB</sub>) indicating central apneas.
6. **Review Sleep Stability.** Stable Sleep is the most important indicator of restorative sleep that has good agreement with Slow Wave (Delta) Sleep from PSG-sleep recordings. Stable sleep is expected to be >50% in adults and >65% in children.
7. **Review Transition.** Sleep Stability is affected by transitions to Wake and should be evaluated.
8. **Review CVHR.** Evaluating CVHR events in relation to sleep stability may help clinical evaluation of apnea severity beyond the prevalence that is reported by the sAHI and/or sRDI that adds RERAs to the sAHI metrics. CVHR during Stable Sleep is excluded from calculations of the Sleep Apnea Indicator (SAI), but may indicate events typically scored as mild hypopnea events in PSG sleep studies and/or can be caused by periodic leg movements.
9. **Apnea Hypopnea Index (sAHI) & Respiratory Disturbance Index (sRDI).** Observe the sleep stages (Stable-, Unstable- and REM sleep) to evaluate where sAHI is dominant and observe relationship with CVHR and how fragmentation has caused autonomic arousals as indicated with the sRDI. sAHI & sRDI are displayed based on 3% and 4% desaturations and separated to obstructive and central events in the sAHI Summary Table. Observe the relationship of SQI and sAHI/sRDI. Evaluate how severely sleep apnea is affecting sleep quality, the maximum, minimum and mean duration of apnea events and how the events affect heart rate (BPM).
10. **Review Oxygen Summary.** The percentage of oxygen saturation <90%, <88%, <80% are indicators of hypoxemia severity during sleep, in addition to the Min, Max, and Mean SpO<sub>2</sub> during the sleep period.
11. **Summary,** the SleepImage Report automatically summarizes the key metrics from the SleepImage analysis to aid the Clinician in summarizing the Clinical Evaluation and recommendations for further testing, further evaluation (referral of patient to another clinician) or therapy.
12. **Clinicians Notes.** Allows treating clinicians to document signs and symptoms of sleep disorders, patient's medications, and medical history and to document sleep disorder diagnosis. **As additional information is gathered from multi-night testing, the Clinician can edit his/her Notes to reflect changes, commonly used to document treatment tracking.**

# Clinician Notes

Add Clinician Notes :

Metric

US Customary

Height :

Weight :

BMI :

Medicare : 

Yes

No

Clear

Epworth Sleepiness Scale :

Sleep Complaints :  
Select all that apply

Excessive Daytime Sleepiness

Irregular (Paused Breathing During Sleep

Snoring

Bruxism / Teeth Grinding

Morning Headaches

Waking Up Gasping Or Choking

Difficulty Falling Or Maintaining Sleep

Medical History

Character Count: 0 / 1040

Medications Used :

1.

2.

3.

Add More

Treatment Device Used :

1.

2.

3.

Add More

Diagnosis :

Select all that apply

G47.33 Obstructive Sleep Apnea

G47.31 Primary Central Sleep Apnea

G47.32 High Altitude Periodic Breathing

G47.9 Sleep Disorder, Unspecified

G47.10 Hypersomnia, Unspecified

F51.01 Primary Insomnia

R06.3 Periodic Breathing

R06.83 Snoring

R53.83 Other Fatigue

Other

Impressions and Recommendations

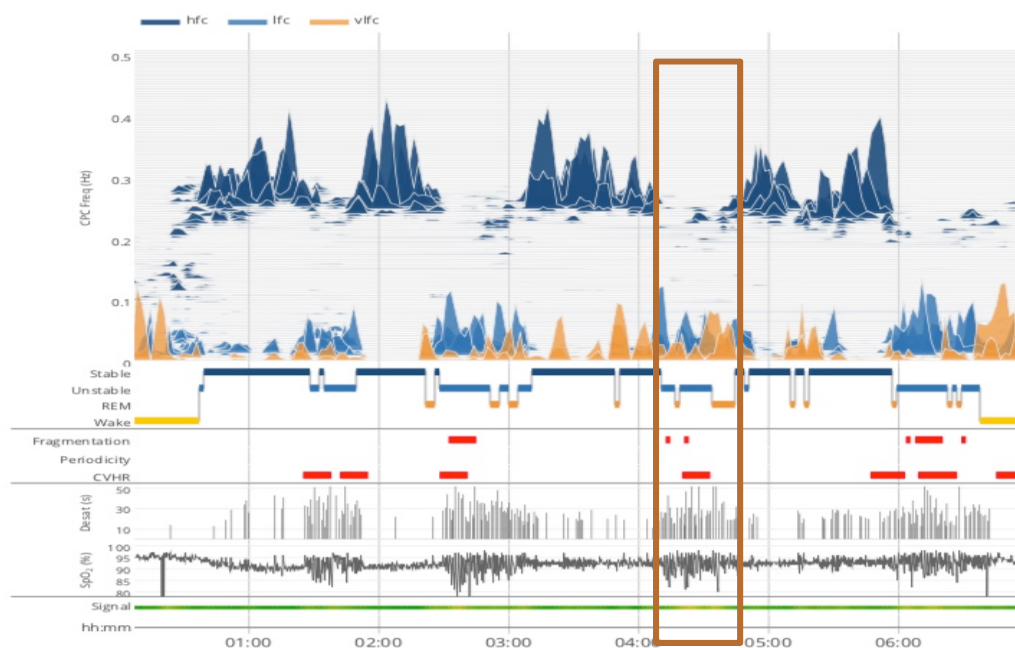
Character Count: 0 / 1040

Publish

21

## Reviewing SleepImage Graphics for Associations & Patterns

### P A T T E R N S



### A S S O C I A T I O N S

1. **Signal Quality:** Evaluate the signal quality during the recording period. Red may indicate signal loss and therefore the SleepImage algorithms may not produce clinically relevant data during these periods. If long periods of signal loss are present it is recommended to repeat the sleep study.
2. **Spectrogram:** Review for HFC (stable sleep), LFC (unstable sleep) and vLFC (wake and REM sleep) distribution during the recording period, CVHR (cyclic variation of heart rate, during unstable sleep presented as SAI) and sAHI/sRDI.
3. **Hypnogram:** Observe the frequency of transitions between Stable Sleep, Unstable Sleep, REM Sleep and Wake. A high number of transitions indicate more fragmented sleep. Healthy sleep is indicated by higher prevalence of Stable Sleep during the first third of the sleep period, with increased REM sleep towards the last third of the sleep period.
4. **Sleep Disordered Breathing (sAHI, sRDI):** While evaluating SDB, also consider fragmentation and periodicity. Fragmentation indicates events that may be caused by obstructive apnea are termed e-LFC<sub>BB</sub>. Periodicity indicates metronomic activity that may be caused by central apnea or periodic breathing and are termed e-LFC<sub>NB</sub>.
5. **Desaturation and SpO<sub>2</sub>:** Review desaturation events and correlate in association with stable, unstable and REM sleep and look for concurrent CVHR. Areas of SpO<sub>2</sub>-signal loss are often demonstrated by a large and sudden drop in SpO<sub>2</sub>.
6. **CVHR:** Evaluate CVHR in association with the Spectrogram, and oxygen saturation. CVHR is a marker of changes in heart rate happening during and at the cessation of an apnea event.
7. **Actigraphy:** Associate level of Actigraphy with concurrent events, assess any patterns across the recording period.
8. **Adjust the study period (Clinician Users):** Drag the green and red markers on the orange line above the spectrogram to the desired beginning and end of the study and click the Recalculate button.
9. Examine the raw data traces in the interactive graph that coincide with the timeline of the recording, concurrent events can be observed in increments or 10 sec., 30 sec., 1 min., 2 min. and 4 min.
10. **Toggle HFC, LFC and vLFC peaks (Clinician Users):** The hfc, lfc, vlfc buttons above the spectrogram can turn stable, unstable and REM/Wake peaks on and off to isolate coupling types for analysis of each sleep state.

## Distinguishing Sleep Disordered Breathing Types

Sleep Disordered Breathing (SDB) comprises a wide spectrum of sleep-related breathing abnormalities, from snoring to severe sleep apnea. There are two major categories of SDB:

1. **Obstructive Sleep Apnea (OSA)** is the most common type of sleep apnea and is related to increased upper airway resistance and closure of the airway during sleep. Patients who suffer from OSA periodically struggle to breathe and are unable to inhale effectively because of a blocked airway that causes oxygen levels to drop and fragments sleep causing arousals (RERAs) and/or awakenings.

2. **Central Sleep Apnea (CSA)** is caused by the brain temporarily not sending signals to the muscles that control breathing. This condition often occurs in people who have certain medical problems and when not associated with another disease it is called idiopathic central sleep apnea. A condition, Cheyne-Stokes respiration, subtype of CSA presents similarly on the SleepImage-Spectrogram.

### 3D Spectrogram - Obstructive Sleep Apnea

OSA causes sleep fragmentation. In addition to the sAHI quantifying obstructive events and the sRDI categorizing RERAs, the presence of a broad band of peaks indicates that the upper airway is the primary pathophysiological contributor to the patient's sleep apnea. E-LFC<sub>BB</sub> is presented by broad gray peaks on the 3D Spectrogram.

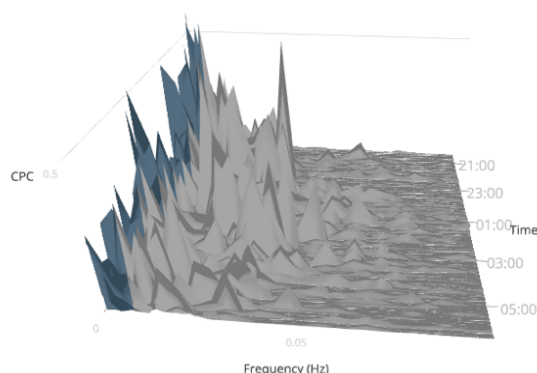


Figure 6. The 3D View Spectrogram - Obstructive Sleep Apnea shows a “broad” distribution of the peaks called Elevated Low Frequency Coupling broadband (e-LFC<sub>BB</sub>).

### 3D Spectrogram - Central Sleep Apnea

Central Sleep Apnea or periodic breathing is represented by narrow red colored peaks as e-LFC<sub>NB</sub> on the 3D Spectrogram view and identifies patterns of breathing or movement having a “narrow band” LFC profile as a visual identifier in addition to the sAHI quantifying central events.

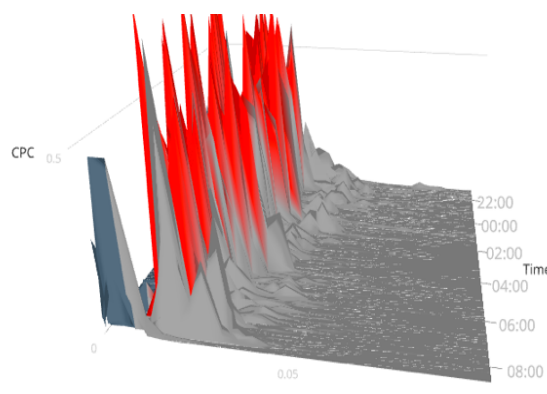


Figure 7. 3D Spectrogram - Central Sleep Apnea is presented as a line of narrow peaks. The system colors these peaks red to make it easier for users to identify the periodicity.

### 3D Spectrogram - Mixed Sleep Apnea

A combination of both obstructive and central components showing narrow band e-LFC (e-LFC<sub>NB</sub>) and broad band e-LFC (e-LFC<sub>BB</sub>) as a visual identifier in addition to the sAHI quantifying separation of obstructive and central events.

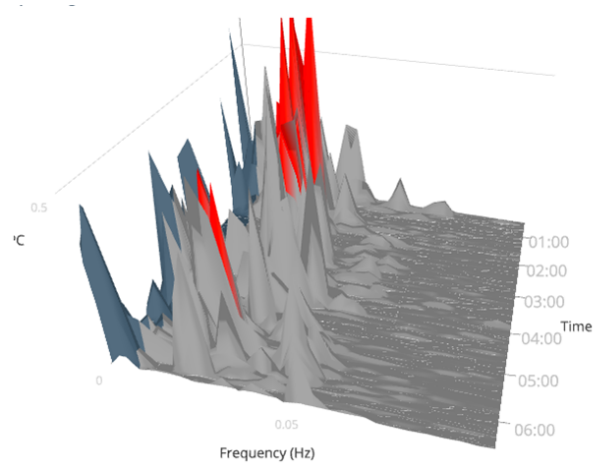


Figure 8. 3D Spectrogram – Mixed Sleep Apnea is a combination of both obstructive and central components.



## CPC Publications

### Books

1. Cardiopulmonary Coupling Spectrograms. In: Kryger MH, Roth T, Dement WC (6th edition), Principles and practice of Sleep Medicine (1615-1623). Philadelphia, PA: Elsevier, Inc.
2. Scoring of Sleep-Related Breathing Events. In: Sudhansu Chokroverty. Sleep Disorders Medicine. Basic Science, Technical Considerations and Clinical Aspects (431-447). New York, NY: Springer Inc.
3. Sleep Stage Classification Based on Heart Rate Variability and Cardiopulmonary Coupling. In: Cyberspace Data and Intelligence, and Cyber-Living, Syndrome, and Health. CyberDI, CyberLife. Communications in Computer and Information Science 2019; Springer CCIS volume 1138.

### Published papers

#### Technique

1. Ashry A, Hilmisson H, Ni Y, Thomas R. Automated Apnea Hypopnea Index from Oximetry and Spectral Analysis of Cardiopulmonary Coupling. Annals of the American Thoracic Society 2021; [e-publication ahead of print]. DOI: 10.1513/AnnalsATS.202005-510OC.
2. Seo M, Yoo J, Hwang S, Lee S. Diagnosis of Obstructive Sleep Apnea in Adults Using the Cardiopulmonary Coupling-Derived Software-Generated Apnea-Hypopnea Index. Clinical and Experimental Otorhinolaryngology 2021; [E-pub ahead of print] DOI: 10.21053/ceo.2020.07984
3. Hilmisson H, Berman S, Magnusdottir S. Sleep Apnea Diagnosis using Software generated Apnea Hypopnea Index Derived from data Recorded with a Single Photoplethysmogram Sensor (PPG): Results from the Childhood Adenotonsillectomy Study (CHAT) based on Cardiopulmonary Coupling analysis. Sleep Breath 2020. DOI: 10.1007/s11325-020-02049-6
4. Thomas R, Wood C, Bianchi M. Cardiopulmonary Coupling spectrogram as an ambulatory clinical biomarker of sleep stability and quality in health, sleep apnea and insomnia. Sleep 2018; 41(2):1-11. DOI:10.1093/sleep/zsx196.
5. Penzel T, Kantelhardt JW, Bartsch RP, et al. Modulations of Heart Rate, ECG, and Cardio-Respiratory Coupling Observed in Polysomnography. Frontiers in Physiology. 2016; 7:460. doi:10.3389/fphys.2016.00460
6. Hilmisson H, Lange N, Duntley S. Sleep apnea detection: accuracy of using automated ECG analysis compared to manually scored polysomnography (apnea hypopnea index). Sleep Breath 2018; 23(1): 125-133. DOI: 10.1007/s11325-018-1672-0
7. Magnusdottir S, Hilmisson H. Ambulatory screening tool for sleep apnea: analyzing a single-lead electrocardiogram (ECG). Sleep Breath 2017; 22(2): 421-429. DOI: 10.1007/s11325-017-1566-6
8. Thomas RJ, Mietus JE, Peng CK, et al. Relationship between delta power and the electrocardiogram-derived cardiopulmonary spectrogram. Possible implications for assessing the effectiveness of sleep. Sleep Med 2014; 15(1): 125-31 DOI: 10.1016/j.sleep.2013.10.002
9. Y Ma, S Sun A new approach to sleep study: does heart tell us a lot? Sleep Med 2013; e188-e189. DOI: 10.1016/j.sleep.2013.11.446
10. Thomas RJ, Mietus JE. Mapping Sleep Using Coupled Biological Oscillations. IEEE Eng Med Biol Soc 2011;1479-82. DOI: 10.1109/IEMBS.2011.6090361
11. Thomas RJ, Mietus J, Peng C, et al. Differentiating Obstructive from Central and Complex Sleep Apnea Using an Automated Electrocardiogram-Based Method, Sleep 2007; 30 (12): 1756 - 1769. DOI: 10.1093/sleep/30.12.1756
12. Thomas RJ, Mietus JE, Peng CK, et al. An Electrocardiogram-Based Technique to Assess Cardiopulmonary Coupling During Sleep, Sleep 2005; 28 (9): 1151-1161, DOI: 10.1093/sleep/30.12.1756
13. Mietus JE, Peng CK, Ivanov PC, Goldberger AL. Detection of obstructive sleep apnea from cardiac interbeat interval time series. Comput Cardiol, 2000; 753-758

#### Relationship between CPC and PSG

1. Thomas RJ, Mietus JE, Peng CK, et al. Relationship between delta power and the electrocardiogram-derived cardiopulmonary spectrogram. Possible implications for assessing the effectiveness of sleep. Sleep Med 2014; 15(1): 125-31 DOI: 10.1016/j.sleep.2013.10.002
2. Thomas RT, Shin C, Bianchi M, Kushida C, Yun CH: Distinct polysomnographic and ECG-spectrographic phenotypes embedded within obstructive sleep apnea. Sleep Science Practice 2017; 1:11 DOI: 10.1186/s41606-017-0012-9
3. Park YK, Choi SJ, Joo EY. Electrophysiological Difference in Obstructive Sleep Apnea with and without REM sleep Behavior Disorder: Cardiopulmonary Coupling Analysis. J Sleep Disord Ther 2017; 6: 261. DOI: 10.4172/2167-0277.1000261.
4. Park JU, Urtnasan E, Joo EY, Lee KY. Classification of REM sleep behavior disorder based on convolutional neural network using cardiopulmonary coupling

spectrogram. *Sleep Med* 2017; 40(1): e253. DOI: 10.1016/j.sleep.2017.11.740

5. Thomas RJ, Bianchi MT, Yun CH, Wood C, Shin C. Multicomponent analysis of sleep using electrocortical, respiratory, autonomic and hemodynamic signals reveals distinct features of stable and unstable NREM and REM sleep. *Front Physiol* 2020. DOI: 10.3389/fphys.2020.592978

## Sleep Quality

1. Magnúsdóttir S, Thomas R, Hilmisson H. Can improvements in sleep quality positively affect serum adiponectin-levels in patients with obstructive sleep apnea. *Sleep Medicine* 2021; E-pub ahead of print. DOI: 10.1016/j.sleep.2021.05.032
2. Magnúsdóttir S, Hilmisson H, Thomas R. Cardiopulmonary coupling-derived sleep quality is associated with improvements in blood pressure in patients with obstructive sleep apnea at high-cardiovascular risk. *J Hypertension* 2020; 38:000-000. DOI: 0000000000002553.
3. Hilmisson H, Magnúsdóttir S. Beyond the Apnea Hypopnea Index (AHI): Importance of Sleep Quality in Management of Obstructive Sleep Apnea and Related Morbidity and Mortality in Patients with Cardiovascular Disease. *Sleep medicine* 2019; 64: S155. DOI: 10.1019/j.sleep.2019.11.424
4. Hilmisson H, Lange N, Magnúsdóttir S. Objective Sleep Quality and Metabolic Risk in Healthy Weight Children Results from the randomized Childhood Adenotonsillectomy Trial (CHAT). *Sleep Breath* 2019; 23(4): 1197-1208. DOI: 10.1007/s11325-019-01802-w
5. Thomas R, Mietus J, Peng C, et al. Relationship between delta power and the electrocardiogram-derived cardiopulmonary spectrogram. Possible implications for assessing the effectiveness of sleep. *Sleep Med* 2014; 15(1): 125-31 DOI: 10.1016/j.sleep.2013.10.002
6. Magnúsdóttir S, Hilmisson H, Sveinsdóttir E. Sleep Disorder Screening: Integration of Subjective and Objective Measures. *SM J Sleep Disord* 2017; 3(2): 1014 <https://smjournals.com/sleep-disorders/download.php?file=fulltext/smj-sd-v3-1014.pdf>
7. Kwon AM, Baik I, Thomas RJ et al. The association between leukocyte telomere lengths and sleep instability based on cardiopulmonary coupling analysis. *Sleep Breath* 2015; 19(3): 963-8. DOI:10.1007/s11325-014-1110-x
8. Magnúsdóttir S. Role of Objectively Measuring Sleep in Drug Research. *International Journal of Drug Research and Technology* May 2018; 8(2). <http://www.ijdr.com/drug-research-and-technology/article/view/163>
9. S. Mariani S, Congiu P, Milioli G, Gioi, et al. ECG-based cardiopulmonary coupling for sleep stability assessment in patients with amyotrophic lateral sclerosis. *Mov Disord* 2016; 31 (2). <http://www.mdabstracts.org/abstract/ecg-based-cardiopulmonary-coupling-for-sleep-stability-assessment-in-patients-with-amyotrophic-lateral-sclerosis/>
10. Visco D, Niesley M, Hughes A, Lewis M. Incidence of Sleep Disturbance and Evaluation of Sleep Quality in Patients Diagnosed with Cancer. *Clin Res Pulmonol* 2015; 3(1): 1030. <https://pdfs.semanticscholar.org/87b4/ebeffdaa3fbccacbb494ed40b9a131adae4d.pdf>
11. Chien PL, SU HF, Hsieh PC et al. Sleep Quality among Female Hospital Staff Nurses. *Sleep Disord* 2013; Article ID 283490 DOI: 10.1155/2013/283490
12. Yin JH, Ho YC, Lin HS et al. On-Call Duty Effects on Sleep-State Physiological Stability in Male Medical Interns. *PLoS One* 2013;8(6): e65072 DOI: 10.1371/journal.pone.0065072

## Sleep Disordered Breathing

1. Ashry A, Hilmisson H, Ni Y, Thomas R. Automated Apnea Hypopnea Index from Oximetry and spectral Analysis of Cardiopulmonary Coupling. *Annals of the American Thoracic Society* 2021; [e-publication ahead of print]. DOI: 10.1513/AnnalsATS.202005-510OC.
2. Seo M, Yoo J, Hwang S, Lee S. Diagnosis of Obstructive Sleep Apnea in Adults Using the Cardiopulmonary Coupling-Derived Software-Generated Apnea-Hypopnea Index. *Clinical and Experimental Otorhinolaryngology* 2021; [E-pub ahead of print] DOI: 10.21053/ceo.2020.07984
3. Seo M, Hwang S, Nam K, Lee S. Significance of sleep stability using cardiopulmonary coupling in sleep disorder breathing. *Laryngoscope* 2019. DOI: <https://doi.org/10.1002/lary.28379>
4. Wu G, Wang D, Roswell L, et al. The Effect of Acute Exposure to Morphine on Breathing Variability and Cardio-Pulmonary Coupling in Men with Obstructive Sleep Apnea – an RCT Study. *J Sleep Res* 2019; 00: e12930. DOI: 10.1111/jsr.12930
5. Ma Y, Sun S., Zhang M. et al. Electrocardiogram-based sleep analysis for sleep apnea screening and diagnosis. *Sleep Breath* (2019). <https://doi.org/10.1007/s11325-019-01874-8>
6. Na J, Kang D, Kim, et al. Sleep-disordered breathing assessed by Holter-monitoring is associated to worsened one-year clinical outcomes in ischemic stroke patients: a cardiopulmonary coupling analysis. *Sleep Medicine* 2019; 64(1): S271. DOI: 10.1016/j.sleep.2019.11756
7. Al Ashry HS, Thomas RJ, Hilmisson H. A Combination Index of Low Frequency Cardio-Pulmonary -Coupling and Oxygen Desaturation has a Strong Correlation with the Apnea Hypopnea Index. *Sleep* 2019; 42(1). A188. DOI: 10.1093/sleep/zsz067.466
8. Thornton A, Maijer R, Christie D, Peach H. Personalizing Treatment for OSA: A Pilot Study Comparing Two Mobile Health Technologies. *Sleep* 2019; 42(Supp\_1): Page A407. DOI: 10.1093/sleep/zsz067.1009
9. Song P, Park YK, Choi SJ, Joo EY. Electrophysiological difference in obstructive sleep apnea with or without REM sleep behavior disorder: cardiopulmonary

coupling analysis. *Sleep Med* 2017; 40(1): 311-214. DOI: 10.1016/j.sleep.2017.11.917

10. Hilmisson H, Lange N, Duntley S. Sleep apnea detection: accuracy of using automated ECG analysis compared to manually scored polysomnography (apnea hypopnea index). *Sleep Breath* 2018; 23(1): 125-133. DOI: 10.1007/s11325-018-1672-0
11. Magnúsdóttir S. The Ophthalmologist's Role in identifying Obstructive Sleep Apnea (OSA). *Ophthalmol Ophthalmic Surg* 2018; 2 (1): 113 <https://scientificliterature.org/Ophthalmology/Ophthalmology-18-113.pdf>
12. Tseng P-H, Lee P-L, Hsu W-C, Ma Y, Lee Y-C, Chiu H-M, et al. (2017) A Higher Proportion of Metabolic Syndrome in Chinese Subjects with Sleep-Disordered Breathing: A Case-Control Study Based on Electrocardiogram-Derived Sleep Analysis. *PLoS ONE* 12(1): e0169394. DOI: 10.1371/journal.pone.0169394
13. Magnúsdóttir S, Hilmisson H. Ambulatory screening tool for sleep apnea: analyzing a single-lead electrocardiogram (ECG). *Sleep Breath* 2017; 22(2): 421-429. DOI: 10.1007/s11325-017-1566-6
14. Harrington J, Schramm PC, Davies CR et al. An electrocardiogram-based analysis evaluating sleep quality in patients with obstructive sleep apnea. *Sleep Breath* 2013; 17(3): 1071-78 DOI: 10.1007/s11325-013-0804-9
15. Ramar K, Desrués B, Ramar P, Morgenthaler T. Analysis of cardiopulmonary coupling to assess adaptive servo-ventilation success in complex sleep apnea management. *Sleep Breath* 2013; 17(2): 861-6 DOI: 10.1007/s11325-012-0780-5
16. Schramm PJ, Thomas RJ. Assessment of therapeutic options for mild obstructive sleep apnea using cardiopulmonary coupling measures. *J Clin Sleep Med* 2012;8(3): 315-20 DOI: 10.5664/jcsm.1924
17. Ibrahim LH, Jacono FJ, Patel SR, et al. Heritability of abnormalities in cardiopulmonary coupling in sleep apnea: use of an electrocardiogram-based technique. *Heritability of Abnormalities in Cardiopulmonary Coupling in Sleep Apnea: Use of an Electrocardiogram-based Technique*, *Sleep* 2010;33 (5): 643-646, DOI: 10.1093/sleep/33.5.643
18. Robert J. Thomas, M.D. Strong Chemoreflex Modulation of Sleep-Breathing: Some Answers but Even More Questions. Commentary on Javaheri S, et al. The prevalence and natural history of complex sleep apnea. *J Clin Sleep Med* 2009; 5(3):205-211. <https://www.ncbi.nlm.nih.gov/pmc/articles>
19. Thomas R, Mietus J, Peng C, et al. Differentiating Obstructive from Central and Complex Sleep Apnea Using an Automated Electrocardiogram-Based Method. *Sleep* 2007;30 (12): 1756 – 1769. DOI: 10.1093/sleep/30.12.1756

## Sleep Disordered Breathing - Therapy

1. Magnúsdóttir S, Thomas R, Hilmisson H. Can improvements in sleep quality positively affect serum adiponectin-levels in patients with obstructive sleep apnea. *Sleep Medicine* 2021; E-pub ahead of print. DOI: 10.1016/j.sleep.2021.05.032
2. Magnúsdóttir S, Hilmisson H, Thomas R. Cardiopulmonary coupling-derived sleep quality is associated with improvements in blood pressure in patients with obstructive sleep apnea at high-cardiovascular risk. *J Hypertension* 2020; 38:000-000. DOI: 0000000000002553.
3. Hilmisson H, Magnúsdóttir S. Beyond the Apnea Hypopnea Index (AHI): Importance of Sleep Quality in Management of Obstructive Sleep Apnea and Related Morbidity and Mortality in Patients with Cardiovascular Disease. *Sleep Medicine* 2019; 64: S155. DOI: 10.1019/j.sleep.2019.11.424
4. Thornton A, Maijer R, Evert C. Multidisciplinary Care for Obstructive Sleep Apnea in the Age of “Personalized” Sleep Medicine. *Sleep Medicine* 2019; 64: S383-S384. DOI: 10.1016/k/sleep/2019.11.1069
5. Thomas R, Wood C, Bianchi M. Cardiopulmonary coupling spectrogram as an ambulatory clinical biomarker of sleep stability and quality in health, sleep apnea and insomnia. *Sleep* 2018; 41(2): DOI: 10.1093/sleep/zsx196.
6. Magnúsdóttir S. Obstructive Sleep Apnea and Chronic Pulmonary Diseases. *J Respir Med* 2017; 1: 2-7. <https://www.omicsonline.org/open-access/obstructive-sleep-apnea-and-chronic-pulmonary-diseases.pdf>
7. Lee W, Hong S, Kim H, et al. A Comparison of Different Success Definitions in Non-Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea Using Cardiopulmonary Coupling. *Jour Clin Sleep Med* 2016; 12(1): 35-41 DOI: 10.5664/jcsm.5388
8. Cho J, Kim H. The effect of continuous positive airway pressure on cardiopulmonary coupling. *Sleep Breath* 2017; 21(2): 341-345. DOI: 10.1007/s11325-016-1419-8
9. Thomas R, Bianchi M. Urgent need to improve PAP management: the devil is in two (fixable) details. *J Clin Sleep Med*. 2017;13(5):657–664. DOI: 10.5664/jcsm.6574
10. Penzel T, Kantelhardt J, Bartsch R, et al. Modulations of Heart Rate, ECG, and Cardio-Respiratory Coupling Observed in Polysomnography. *Frontiers in Physiology*. 2016; 7:460. doi:10.3389/fphys.2016.00460
11. Choi J, Thomas R, Suh S, et al. Sleep quality changes after upper airway surgery in obstructive sleep apnea. *Electrocardiogram-based cardiopulmonary coupling analysis*. *Laryngoscope* 2015; 125(7): 1737-42. DOI: 10.1002/lary.25101
12. Lee H, Lee K, Jung K, Joo E. Analysis of sleep quality after uvulopalatopharyngoplasty in patients with obstructive sleep apnea based on cardiopulmonary coupling analysis. *Sleep Med* 2015; 16 (1): S217. DOI: 10.1016/j.sleep.2015.02.1457

13. Song P, Lee H, Lee E, Hone S. Sleep Med 2015. Effects of mandibular advancement devices for the treatment of sleep apnea syndrome based on cardiopulmonary coupling analysis. Sleep Med 2015; 16(1): S367. DOI: 10.1016/j.sleep.2015.02.506
14. Park J, Erdenebayar U, Jeong P, Lee K. Automatic classification of sleep-disordered breathing using cardiopulmonary coupling analysis. Sleep Med 2015; 16(1): S232. DOI: 10.1016/j.sleep.2015.02.1495
15. Lee W, Ahn J, We J, et al. Cardiopulmonary coupling analysis: changes before and after treatment with mandibular advancement device. Sleep Breath 2014; 18(4): 891-96. DOI: 10.1007/s11325-014-0961-5

## Cardiovascular and Cardiometabolic

1. Magnusdottir S, Thomas R, Hilmisson H. Can improvements in sleep quality positively affect serum adiponectin-levels in patients with obstructive sleep apnea. Sleep Medicine 2021; E-pub ahead of print. DOI: 10.1016/j.sleep.2021.05.032
2. Kim W, Na J, Thomas R, et al. Impact of Catheter Ablation on Sleep Quality and Relationship Between Sleep Stability and Recurrence of Paroxysmal Atrial Fibrillation After Successful Ablation: 24-Hour Holter-Based Cardiopulmonary Coupling Analysis. J Am Heart Assoc 2020; e017016. DOI: 10.1161/JAHA.120.017016
3. Magnusdottir S, Hilmisson H, Thomas R. Cardiopulmonary coupling-derived sleep quality is associated with improvements in blood pressure in patients with obstructive sleep apnea at high-cardiovascular risk. J Hypertension 2020; 38:000-000. DOI: 0000000000002553.
4. Kang D, Kim C, Park Y. Impact of Sleep-Disordered Breathing on Functional Outcomes in Ischemic Stroke; A Cardiopulmonary Coupling Analysis. Stroke 2020; 51:00-00. DOI: 10.1161/STROKEAHA.119.028730
5. Majer R, Thornton A, Lauffenburger J, Marino J, Tsai M, Stellingwerff T, Peach H. Associations between Subjective and Objective Measures of Sleep Dysfunction and Hemoglobin A1c in Professional Athletes. Sleep Med 2019; 64: S239-240. DOI: 10.1016/j.sleep.2019.11.670
6. Hilmisson H. Assessing Risk of Fatality in Chronic Heart Failure Patients, using Nocturnal Periodicity Biomarker of Cardiopulmonary Coupling. Sleep Medicine 2019; 64: S154-155. DOI: 10.1016/k/sleep/2019.11.423
7. Kang D, Kim C, Park Y, Jang W, Kim W, Choi J, Choi C, Na J. Impact of sleep-disordered breathing on short-term functional outcomes in ischemic stroke patients: a cardiopulmonary coupling analysis using Holter-monitoring, European Heart Journal 2019; 40 (1). DOI: 10.1093/eurheartj/ehz745.05690569
8. Kang D, Kim C, Park Y, Jang W, Kim W, Choi J, Choi C, Na J. Sleep-disordered breathing assessed by Holter-monitoring is associated to worsened one-year clinical outcomes in ischemic stroke patients: a cardiopulmonary coupling analysis. European Heart Journal 2019; 40 (1) DOI: 10.1093/eurheartj/ehz746.0684
9. Kim W, Na J, Jang W, Park E, Choi J, Choi C, Kim J, Kim E, Rha S, Park C, Swo H, Lim H. Sleep Quality Change After RFCA In Paroxysmal Atrial Fibrillation & Relation of Sleep Stability To the Recurrence: 24 – hour Holter – based Cardiopulmonary Coupling Analysis. Sleep 2018; 41(Suppl\_1): A327. DOI: 10.1093/sleep/zsy061.879
10. Pogach, MS, Punjabi NM, Thomas N, et al. Electrocardiogram-based sleep spectrogram measures of sleep stability and glucose disposal in sleep disordered breathing. Sleep 2012; 35(1): 139-48. DOI: 10.5665/sleep.1604
11. Kim W, Na J. Sleep quality Change After Catheter Ablation in Paroxysmal Atrial Fibrillation and Relation of Sleep Stability to the Recurrence – 24 Hour Holter Based Cardiopulmonary Coupling Analysis. Circulation 2017; 136: A19496 [https://www.ahajournals.org/doi/abs/10.1161/circ.136.suppl\\_1.19496](https://www.ahajournals.org/doi/abs/10.1161/circ.136.suppl_1.19496)
12. Thomas RJ, Weiss MD, Mietus JE, et al. Prevalent hypertension and stroke in the Sleep Heart Health Study: association with an ECG-derived spectrographic marker of cardiopulmonary coupling. Sleep 2009; 32(7): 897-904.
13. Yeh GY, Mietus JE, Peng CK et al. Enhancement of sleep stability with Tai Chi exercise in chronic heart failure: preliminary findings using an ECG-based spectrogram method. Sleep Med 2008; 9(5): 527-36. DOI: 10.1016/j.sleep.2007.06.003

## Pediatric

1. Seo M, Han M, Jeong Y, et al. Variation in Sleep Stability with Differences in Severity of Sleep-Disordered Breathing in Children. Laryngoscope 2020. DOI: 10.1002/lary.28769
2. Hilmisson H, Berman S, Magnusdottir S. Sleep Apnea Diagnosis using Software generated Apnea Hypopnea Index Derived from data Recorded with a Single Photoplethysmogram Sensor (PPG): Results from the Childhood Adenotonsillectomy Study (CHAT) based on Cardiopulmonary Coupling analysis. Sleep Breath 2020. DOI: 10.1007/s11325-020-02049-6
3. Hilmisson H, Lange N, Magnusdottir S. Objective Sleep Quality and Metabolic Risk in Healthy Weight Children Results from the randomized Childhood Adenotonsillectomy Trial (CHAT). Sleep Breath 2019; 23(4): 1197-1208. DOI: 10.1007/s11325-019-01802-w
4. Cysarz D, Linhard M, Seifert G, Edelhauser F. Sleep Instabilities Assessed by Cardiopulmonary Coupling Analysis Increase During Childhood and Adolescence. Front Physiol 2018; 9: 460. DOI: 10.3389/fphys.2018.00468
5. Zhai F, Chen J. The comparison of polysomnography, sleep apnea screening test and cardiopulmonary coupling in the diagnosis of pediatric obstructive sleep apnea syndrome. Sleep medicine 2017; 40(1): e361. DOI: 10.1016/j.sleep.2017.11.1065

6. Y. Ma, J. Yeh, S. Sun, J. Qiao, C. Peng. Detecting pediatric sleep apnea: consistency on cardiopulmonary coupling and oximetry measurement. *Sleep Med* 2013; 14(1): e189. DOI: 10.1016/j.sleep.2013.11.447
7. Lee SH, Choi JH, Park IH, et al. Measuring sleep quality after adenotonsillectomy in pediatric sleep apnea. *Laryngoscope* 2012; 122(9): 2115-21. DOI:10.1002/lary.23356
8. Guo D, Peng CK, Wu HL, et al. ECG-derived cardiopulmonary analysis of pediatric sleep-disorder breathing. *Sleep Med* 2011; 12 (4): 384-9 DOI: 10.1016/j.sleep.2010.09.011

## Insomnia/Mental Health

1. Sun Q, Xing L, Wang C, Liang W. Cardiopulmonary coupling analysis predicts early treatment response in depressed patients: A pilot study. *Psychiatry Res* 2019; 276. DOI: 10.1016/j.psychres.2019.04.002
2. Hilmisson H, Sveinsdottir E, Lange N, Magnusdottir S. Insomnia symptoms in primary care: A prospective study focusing on prevalence of undiagnosed co-morbid sleep disordered breathing. *Eur J Intern Med* 2019; 63: 19-26. DOI: 10.1016/j.ejim.2019.01.011
3. Ma Y, Yeung A, Yang A, Peng C, Clain A, Alpert J, Fava M, Yeung A. The Effects of Tai Chi on Sleep quality in Chinese American Patients with Major Depressive Disorder. *Behav Sleep Med* 2018; 16(4): 398-411. DOI: 10.1080/145002002.2016.1228643
4. Thornton A, Majjer R, Schramm P. Snoring and Insomnia – Neurocognitive consequences in Professional Athletes. *Sleep Medicine* 2017; 40 (Suppl\_1). DOI: 10.1016/j.sleep.2017.11.960
5. Schramm PJ, Zobel I, Monch K, et.al. Sleep quality changes in chronically depressed patients treated with Mindfulness-based Cognitive Therapy or the Cognitive Behavioral Analysis system of Psychotherapy: a pilot study. *Sleep Med* 2016; 17:57-63 DOI: 10.1016/j.sleep.2015.09.022
6. Park H, Joo E, Hong S. Electrophysiological Characteristics of Obstructive Sleep Apnea Syndrome with Insomnia: Polysomnography and Cardiopulmonary Coupling Analysis *J Sleep Med* 2015;12(2):53-58. DOI: 10.13078/jsm.15010
7. Na G, Choi S, Joo E, Hong S. Objective Sleep Quality in Subjects with Restless Legs Syndrome versus with Psychophysiological Insomnia: Polysomnography and Cardiopulmonary Coupling Analysis. *J Sleep Med* 2015; 12(1): 13-17. DOI: 10.13078/jsm.15003
8. Sylvia LG, Salcedo S, Bianchi M. A Novel Home Sleep Monitoring Device and Brief Intervention for Bipolar Disorder: Feasibility, Tolerability, and Preliminary Effectiveness. *Cogn Ther and Res* 2014; 38(1): 55-61. DOI: 10.1007/s10608-013-9575-7
9. Schramm PJ, Polland RE, Rao U et al. Bupropion response on sleep quality in patients with depression: implications for increased cardiovascular disease risk. *Eur Neuropsychopharmacol* 2014; 24(2): 207-14. DOI: 10.1016/j.euroneuro.2013.09.007
10. Schramm PJ, Thomas R, Feige B, et.al. Quantitative measurement of sleep quality using cardiopulmonary coupling analysis: a retrospective comparison of individuals with and without primary insomnia. *Sleep Breath* 2013; 17(2):713-21. DOI: 10.1007/s11325-012-0747-6
11. Yang AC, Yang CH, Hong CJ et al. Sleep state instabilities in major depressive disorder: Detection and quantification with electrocardiogram-based cardiopulmonary coupling analysis. *Psychophysiology* 2011; 48(2): 285-91. DOI: 10.1111/j.1469-8986.2010.01060.x

## Pain

1. Thomas RJ, Mietus JE, Peng CK, et al. Impaired sleep quality in fibromyalgia: Detection and quantification with ECG-based cardiopulmonary coupling spectrograms. *Sleep Med* 2010; 11(5): 497-8. DOI: 10.1016/j.sleep.2009.09.003
2. Chen L, Liu C, Ye Z, Wang B, He S. Assessment of sleep quality using cardiopulmonary coupling analysis in patients with Parkinson's disease. *Brain Behavior* 2018 May; 8(5): e00970. DOI:10.1002/brb3.970
3. Jackson ML; Bruck D. Sleep abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a review. *J Clin Sleep Med* 2012;8(6):719-728. DOI: 10.5664/jcsm.2276

## Other

1. De Chazal P, Sutherland K, Cistulli P. Advanced polysomnographic analysis for OSA: A pathway to personalized management? *Respirology* 2020;25: 251-258. DOI: 10.1111/resp.13564
2. Bianchi, M. Sleep devices: wearables and nearables, informational and interventional, consumer and clinical. *Metabolism* 2018; 84: 99-108. DOI: 10.1016/j.metabol.2017.10.008
3. Heckman EJ, Salazar R, Hardy S, Manders E, Liu Y, Au R, et al. Wearable sleep epidemiology in the Framingham heart study. *Sleep* 2017; 40 (suppl\_1): A289, <https://doi.org/10.1093/sleepj/zsx050.779>
4. Verbraecken J. Applications of evolving technologies in sleep medicine. *Breathe* 2013; 9: 442-455. DOI: 10.1183/20734735.012213
5. Bianchi MT, Thomas RJ. Technical advances in the characterization of the complexity of sleep and sleep disorders. *Proc Neuropsychopharmacol Biol Psychiatry*. 2013; 1(45): 277-86. DOI: 10.1016/j.pnpbp.2012.09.017
6. Liu D, Yang X, Wang G et al. HHT based cardiopulmonary coupling analysis for sleep apnea detection. *Sleep Med* 2012 13(5): 503-9 DOI: 10.1016/j.sleep.2011.10.035

## References

1. FDA US. Software as a Medical Device (SaMD). May 31, 2021. Accessed May 31, 2021. <https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd>
2. Thomas R. Cardiopulmonary coupling sleep spectrograms. In: Kryger M RT, Dement W, ed. *Principles and practices of sleep medicine*. Elsevier, Inc; 2016:chap 166.
3. Thomas RJ, Mietus JE, Peng CK, et al. Relationship between delta power and the electrocardiogram-derived cardiopulmonary spectrogram: possible implications for assessing the effectiveness of sleep. *Sleep Med*. Jan 2014;15(1):125-31. doi:10.1016/j.sleep.2013.10.002
4. Bartsch RP, Schumann AY, Kantelhardt JW, Penzel T, Ivanov P. Phase transitions in physiologic coupling. *Proc Natl Acad Sci U S A*. Jun 26 2012;109(26):10181-6. doi:10.1073/pnas.1204568109
5. Penzel T, Kantelhardt JW, Bartsch RP, et al. Modulations of Heart Rate, ECG, and Cardio-Respiratory Coupling Observed in Polysomnography. *Front Physiol*. 2016;7:460. doi:10.3389/fphys.2016.00460
6. Hilmisson H, Magnusdottir S. Beyond the Apnea Hypopnea Index (AHI): Importance of Sleep Quality in Management of Obstructive Sleep Apnea and Related morbidity and Mortality in Patients with Cardiovascular Disease. *Sleep Medicine*. 2019;64(1):S155. doi:10.1016/j.sleep.2019.11.424
7. Magnusdottir S, Hilmisson H, Thomas RJ. Cardiopulmonary coupling-derived sleep quality is associated with improvements in blood pressure in patients with obstructive sleep apnea at high-cardiovascular risk. *J Hypertens*. Nov 2020;38(11):2287-2294. doi:10.1097/HJH.0000000000002553
8. Hilmisson H, Lange N, Magnusdottir S. Objective sleep quality and metabolic risk in healthy weight children results from the randomized Childhood Adenotonsillectomy Trial (CHAT). *Sleep Breath*. Dec 2019;23(4):1197-1208. doi:10.1007/s11325-019-01802-w
9. FDA US. SleepImage System (K182618) Indications for Use. May 31, 2021. Accessed May 31, 2021. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf18/K182618.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf18/K182618.pdf)
10. Pogach MS, Punjabi NM, Thomas N, Thomas RJ. Electrocardiogram-based sleep spectrogram measures of sleep stability and glucose disposal in sleep disordered breathing. *Sleep*. Jan 1 2012;35(1):139-48. doi:10.5665/sleep.1604
11. 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. *Sleep*. Jul 2009;32(7):897-904.
12. Hilmisson H. Assessing Risk of Fatality in Chronic Heart Failure Patients, using Nocturnal Periodicity Biomarker of Cardiopulmonary Coupling. *Sleep Medicine*. 2019;64(S154-155)doi:10.1016/j.sleep.2019.11.423
13. Maijer R, Thornton A, Lauffenburger J, Marion J, Tsai M, Stellingwerff T, Peach H. Associations between subjective and objective measures of sleep quality and hemoglobin a1c in professional athletes. *Sleep Medicine*. 2019;64(1):S239-S240. doi:10.1016/j.sleep.2019.11.670
14. Schramm PJ, Zobel I, Monch K, Schramm E, Michalak J. Sleep quality changes in chronically depressed patients treated with Mindfulness-based Cognitive Therapy or the Cognitive Behavioral Analysis System of Psychotherapy: a pilot study. *Sleep Med*. Jan 2016;17:57-63. doi:10.1016/j.sleep.2015.09.022
15. Schramm PJ, Poland RE, Rao U. Bupropion response on sleep quality in patients with depression: implications for increased cardiovascular disease risk. *Eur Neuropsychopharmacol*. Feb 2014;24(2):207-14. doi:10.1016/j.euroneuro.2013.09.007
16. Wood C, Bianchi MT, Yun CH, Shin C, Thomas RJ. Multicomponent Analysis of Sleep Using Electrocardiogram, Respiratory, Autonomic and Hemodynamic Signals Reveals Distinct Features of Stable and Unstable NREM and REM Sleep. *Front Physiol*. 2020;11:592978. doi:10.3389/fphys.2020.592978
17. Thomas RJ, Mietus JE, Peng CK, Goldberger AL, Crofford LJ, Chervin RD. Impaired sleep quality in fibromyalgia: Detection and quantification with ECG-based cardiopulmonary coupling spectrograms. *Sleep Med*. May 2010;11(5):497-8. doi:10.1016/j.sleep.2009.09.003
18. Magnusdottir S, Thomas R, Hilmisson H. Can improvements in sleep quality affect serum adiponectin-levels in patients with obstructive sleep apnea? *Sleep Medicine*. 2021;doi:10.1016/j.sleep.2021.05.032



19. Hilmisson H, Berman S, Magnusdottir S. Sleep apnea diagnosis in children using software-generated apnea-hypopnea index (AHI) derived from data recorded with a single photoplethysmogram sensor (PPG) : Results from the Childhood Adenotonsillectomy Study (CHAT) based on cardiopulmonary coupling analysis. *Sleep Breath.* Dec 2020;24(4):1739-1749. doi:10.1007/s11325-020-02049-6
20. Al Ashry HS, Hilmisson H, Ni Y, Thomas RJ. Automated Apnea Hypopnea Index from Oximetry and Spectral Analysis of Cardiopulmonary Coupling. *Ann Am Thorac Soc.* Jan 20 2021;doi:10.1513/AnnalsATS.202005-510OC
21. Rasch B, Born J. About sleep's role in memory. *Physiol Rev.* Apr 2013;93(2):681-766. doi:10.1152/physrev.00032.2012
22. Schmidt MH. The energy allocation function of sleep: a unifying theory of sleep, torpor, and continuous wakefulness. *Neurosci Biobehav Rev.* Nov 2014;47:122-53. doi:10.1016/j.neubiorev.2014.08.001
23. Hilmisson H, Lange N, Duntley SP. Sleep apnea detection: accuracy of using automated ECG analysis compared to manually scored polysomnography (apnea hypopnea index). *Sleep Breath.* Mar 2019;23(1):125-133. doi:10.1007/s11325-018-1672-0
24. Thomas RM, J.; Peng C.; Gilmartin, G.; Daly, R.; Goldberger, A.; Gottlieb, D. Differentiating Obstructive from Central and Complex Sleep Apnea Using an Automated Electrocardiogram-Based Method. *Sleep.* 2007;30(12):1756-1769. doi:10.1093/sleep/30.12.1756
25. Magnusdottir S, Hilmisson H. Ambulatory screening tool for sleep apnea: analyzing a single-lead electrocardiogram signal (ECG). *Sleep Breath.* May 2018;22(2):421-429. doi:10.1007/s11325-017-1566-6
26. Penzel T. Prospective Cohort Studies of Major Disorders Can Facilitate Phenotyping for Sleep Apnea. *Am J Respir Crit Care Med.* Jan 21 2021;doi:10.1164/rccm.202012-4414ED
27. Mazzotti DR, Lim DC, Sutherland K, et al. Opportunities for utilizing polysomnography signals to characterize obstructive sleep apnea subtypes and severity. *Physiol Meas.* Sep 13 2018;39(9):09TR01. doi:10.1088/1361-6579/aad5fe
28. Pack AI. Application of Personalized, Predictive, Preventative, and Participatory (P4) Medicine to Obstructive Sleep Apnea. A Roadmap for Improving Care? *Ann Am Thorac Soc.* Sep 2016;13(9):1456-67. doi:10.1513/AnnalsATS.201604-235PS
29. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med.* Feb 26 2015;372(9):793-5. doi:10.1056/NEJMp1500523
30. Thomas RJW, C.; Bianchi, M. Cardiopulmonary Coupling spectrogram as an ambulatory clinical biomarker of sleep stability and quality in health, sleep apnea and insomnia. *Sleep.* 2018;41(2):1-11. doi:10.1093/sleep/zsx196
31. Hilmisson H, Sveinsdottir E, Lange N, Magnusdottir S. Insomnia symptoms in primary care: A prospective study focusing on prevalence of undiagnosed co-morbid sleep disordered breathing. *Eur J Intern Med.* May 2019;63:19-26. doi:10.1016/j.ejim.2019.01.011
32. Collop NA, Tracy SL, Kapur V, et al. Obstructive sleep apnea devices for out-of-center (OOC) testing: technology evaluation. *J Clin Sleep Med.* Oct 15 2011;7(5):531-48. doi:10.5664/JCSM.1328
33. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* Sep 2012;130(3):576-84. doi:10.1542/peds.2012-1671
34. Thomas RJ, Chen S, Eden UT, Prerau MJ. Quantifying statistical uncertainty in metrics of sleep disordered breathing. *Sleep Med.* Jan 2020;65:161-169. doi:10.1016/j.sleep.2019.06.003
35. White LH, Lyons OD, Yadollahi A, Ryan CM, Bradley TD. Night-to-night variability in obstructive sleep apnea severity: relationship to overnight rostral fluid shift. *J Clin Sleep Med.* Jan 15 2015;11(2):149-56. doi:10.5664/jcsm.4462
36. Punjabi NM, Patil S, Crainiceanu C, Aurora RN. Variability and Misclassification of Sleep Apnea Severity Based on Multi-Night Testing. *Chest.* Jul 2020;158(1):365-373. doi:10.1016/j.chest.2020.01.039
37. Levendowski DJ, Zack N, Rao S, et al. Assessment of the test-retest reliability of laboratory polysomnography. *Sleep Breath.* May 2009;13(2):163-7. doi:10.1007/s11325-008-0214-6
38. Honaker SM, Meltzer LJ. Sleep in pediatric primary care: A review of the literature. *Sleep Med Rev.* Feb 2016;25:31-9. doi:10.1016/j.smrv.2015.01.004

39. Dayyat E, Kheirandish-Gozal L, Sans Capdevila O, Maarafeya MMA, Gozal D. Obstructive sleep apnea in children: relative contributions of body mass index and adenotonsillar hypertrophy. *Chest*. Jul 2009;136(1):137-144. doi:10.1378/chest.08-2568
40. Paruthi S. Evaluation of suspected obstructive sleep apnea in children. UpToDate. May 31, 2021. Updated Februar 18 2021. Accessed May 31, 2021. <https://www.uptodate.com/contents/evaluation-of-suspected-obstructive-sleep-apnea-in-children>
41. Lloyd R, Kirsch DB, Carden KA, Malhotra RK, Rosen IM, Ramar K. Letter to the Editor Regarding the Updated American Academy of Otolaryngology-Head and Neck Surgery Foundation Clinical Practice Guideline on Tonsillectomy in Children. *J Clin Sleep Med*. Feb 15 2019;15(2):363-365. doi:10.5664/jcsm.7650
42. Patel HH, Straight CE, Lehman EB, Tanner M, Carr MM. Indications for tonsillectomy: a 10 year retrospective review. *Int J Pediatr Otorhinolaryngol*. Dec 2014;78(12):2151-5. doi:10.1016/j.ijporl.2014.09.030
43. Goldstein NA, Post JC, Rosenfeld RM, Campbell TF. Impact of tonsillectomy and adenoidectomy on child behavior. *Arch Otolaryngol Head Neck Surg*. Apr 2000;126(4):494-8. doi:10.1001/archotol.126.4.494
44. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. *Proc Am Thorac Soc*. Feb 15 2008;5(2):242-52. doi:10.1513/pats.200708-135MG
45. Abraham EJ, Bains A, Rubin BR, Cohen MB, Levi JR. Predictors of a Normal Sleep Study in Healthy Children with Sleep Disordered Breathing Symptoms. *Ann Otol Rhinol Laryngol*. Feb 5 2021;3489421990156. doi:10.1177/0003489421990156
46. Marcus CL, Moore RH, Rosen CL, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med*. Jun 20 2013;368(25):2366-76. doi:10.1056/NEJMoa1215881
47. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *Am J Respir Crit Care Med*. Sep 1 2010;182(5):676-83. doi:10.1164/rccm.200912-1930OC
48. Suri JC, Sen MK, Venkatachalam VP, et al. Outcome of adenotonsillectomy for children with sleep apnea. *Sleep Med*. Oct 2015;16(10):1181-6. doi:10.1016/j.sleep.2015.02.539
49. Mitchell RB, Kelly J. Outcome of adenotonsillectomy for obstructive sleep apnea in obese and normal-weight children. *Otolaryngol Head Neck Surg*. Jul 2007;137(1):43-8. doi:10.1016/j.otohns.2007.03.028
50. Cote CJ, Posner KL, Domino KB. Death or neurologic injury after tonsillectomy in children with a focus on obstructive sleep apnea: houston, we have a problem! *Anesth Analg*. Jun 2014;118(6):1276-83. doi:10.1213/ANE.0b013e318294fc47
51. Goldman JL, Baugh RF, Davies L, et al. Mortality and major morbidity after tonsillectomy: etiologic factors and strategies for prevention. *Laryngoscope*. Oct 2013;123(10):2544-53. doi:10.1002/lary.23926
52. Byars SG, Stearns SC, Boomsma JJ. Association of Long-Term Risk of Respiratory, Allergic, and Infectious Diseases With Removal of Adenoids and Tonsils in Childhood. *JAMA Otolaryngol Head Neck Surg*. Jul 1 2018;144(7):594-603. doi:10.1001/jamaoto.2018.0614
53. Erichsen D, Godoy C, Granse F, Axelsson J, Rubin D, Gozal D. Screening for sleep disorders in pediatric primary care: are we there yet? *Clin Pediatr (Phila)*. Dec 2012;51(12):1125-9. doi:10.1177/0009922812464548
54. Chervin RD, Weatherly RA, Garetz SL, et al. Pediatric sleep questionnaire: prediction of sleep apnea and outcomes. *Arch Otolaryngol Head Neck Surg*. Mar 2007;133(3):216-22. doi:10.1001/archotol.133.3.216
55. Borgstrom A, Nerfeldt P, Friberg D. Questionnaire OSA-18 has poor validity compared to polysomnography in pediatric obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol*. Nov 2013;77(11):1864-8. doi:10.1016/j.ijporl.2013.08.030
56. Villa MP, Pietropaoli N, Supino MC, et al. Diagnosis of Pediatric Obstructive Sleep Apnea Syndrome in Settings With Limited Resources. *JAMA Otolaryngol Head Neck Surg*. Nov 2015;141(11):990-6. doi:10.1001/jamaoto.2015.2354
57. Pierce B, Brietzke S. Association of Preoperative, Subjective Pediatric Tonsil Size With Tonsillectomy Outcomes: A Systematic Review. *JAMA Otolaryngol Head Neck Surg*. Sep 1 2019;145(9):854-859. doi:10.1001/jamaoto.2019.1842
58. Machado Junior AJ, Crespo AN. Pediatric obstructive sleep apnea: beyond adenotonsillectomy. *Sleep Med*. Feb 2020;66:282-283. doi:10.1016/j.sleep.2019.09.011
59. Friedman NR, Perkins JN, McNair B, Mitchell RB. Current practice patterns for sleep-disordered breathing in children. *Laryngoscope*. Apr 2013;123(4):1055-8. doi:10.1002/lary.23709



60.        Isaiah A, Pereira KD, Das G. Polysomnography and Treatment-Related Outcomes of Childhood Sleep Apnea. *Pediatrics*. Oct 2019;144(4)doi:10.1542/peds.2019-1097
61.        Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. Aug 2019;7(8):687-698. doi:10.1016/S2213-2600(19)30198-5
62.        Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev*. Dec 2011;15(6):343-56. doi:10.1016/j.smr.2011.01.003
63.        Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea With Positive Airway Pressure: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. *J Clin Sleep Med*. Feb 15 2019;15(2):301-334. doi:10.5664/jcsm.7638
64.        Krakow B, McIver ND, Ulibarri VA, Krakow J, Schrader RM. Prospective Randomized Controlled Trial on the Efficacy of Continuous Positive Airway Pressure and Adaptive Servo-Ventilation in the Treatment of Chronic Complex Insomnia. *EClinicalMedicine*. Aug 2019;13:57-73. doi:10.1016/j.eclinm.2019.06.011

## Glossary

AAP: American Academy of Pediatrics

AASM: American Academy of Sleep Medicine

CAP: Cyclic Alternating Pattern

CPAP: Continuous Positive Airway Pressure

CPC: Cardiopulmonary Coupling - the synchronization of heart (pulse) rate variability and breathing activity

CSA: Central Sleep Apnea

CVHR: Cyclic Variation of Heart Rate. Heart rate pattern that happens during and at cessation of apnea events.

DSAT: Desaturation Events

e-LFC<sub>BB</sub>: Elevated Low Frequency Coupling, Broad Band - an indicator of sleep fragmentation (e.g. pain) or airway disordered breathing patterns (e.g. Obstructive Sleep Apnea, Upper Airway Resistance. (see [Understanding the SleepImage Spectrogram](#))

e-LFC<sub>NB</sub>: Elevated Low Frequency Coupling, Narrow Band - an indicator of periodic-type breathing patterns e.g. Central Sleep Apnea (see [Understanding the SleepImage Spectrogram](#))

ECG (EKG): Electrocardiogram - recording the electrical activity of the heart over a period of time

EDR: Electrocardiogram Derived Respiration

EEG: Electroencephalogram - recording electrical activity of the brain along the scalp

HFC: High Frequency Coupling – an indicator of stable sleep (see [Understanding the SleepImage Spectrogram](#))

HRV: Heart Rate Variability

LFC: Low Frequency Coupling – an indicator of unstable sleep (see [Understanding the SleepImage Spectrogram](#))

N-CAP: Non-Cyclic Alternating Pattern

NREM: Non-Rapid Eye Movement

OSA: Obstructive Sleep Apnea

PDR: Plethysmograph Derived Respiration

PRV: Pulse Rate Variability

PSG: Polysomnography – an in-laboratory sleep study where each 30 sec window (epoch) is manually scored.

REM: Rapid Eye Movement

SA: Sleep Apnea

SAI: Sleep Apnea Indicator. Displays “one number” for apnea events through the recording period by automatically detecting known changes that occur in the cardiovascular system during periods of sleep disordered breathing.

sAHI: SleepImage Apnea Hypopnea Index

SaMD: Software as a Medical Device

SDB: Sleep Disordered Breathing - refers to a wide range of sleep-related breathing abnormalities

SpO<sub>2</sub>: Oxygen Saturation

sRDI: SleepImage Respiratory Disturbance Index

SQI: Sleep Quality Index. Presents “one number” encompassing overall sleep health based on CPC metrics.

Spectrogram: Visual representation of the spectrum of the frequencies of Cardiopulmonary Coupling.

UARS: Upper Airway Resistance Syndrome

vLFC: Very Low Frequency Coupling – Wake/REM Sleep (see more in [Understanding the SleepImage Spectrogram](#))