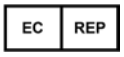
Introduction to SleepImage®

This document is only available in an electronic format, as a PDF document, on 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:

	**Manufacturer**	MyCardio LLC 3200 E Cherry Creek South Drive, Suite 540, Denver, CO 80209, USA support@sleepimage.com www.sleepimage.com
	**Instructions for Use Version Number**	Please read Instructions for Use carefully and periodically as it is updated from time to time. The current version (D-6.00285 Instructions for Use, Rev. 34) was issued on June 26, 2023. 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 support@sleepimage.com.
	**Medical Device**	This product is a Medical Device.
	**Prescription Use Only**	FDA-cleared K182618: 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 *+B315SLEEPIMAGESYSTEM0/$$72.205*
 2862	**CE Mark**	The CE mark is a declaration that the SleepImage System is in compliance with the EU Medical Device Regulation (EU 2017/745).

 European Representative
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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

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U.S. TM 98/056,452

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Contents

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), K182618. The SleepImage System provides simultaneous recording of heart rate, oxygen saturation, respiratory analysis, and sleep time using a photoplethysmography sensor (PPG) applied at the finger. The following signals (channels) are continuously sampled during sleep, not using Artificial Intelligence (AI): (1) peripheral arterial tone (measurement of pulsatile volume changes reflecting changes in sympathetic tone), (2) heart rate, (3) heart rate variability, (4) blood oxygenation (oximetry), (5) changes in breathing (respiration) and (6) movement (actigraphy). All channels of raw data are presented for the purpose of visualizing concurrent physiology and to review the autoscored events with ability for manual scoring/analysis as determined appropriate by the user. The signal quality of the recorded raw physiological data is documented and presented with the color-coded "Signal Quality" line.

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). The sleep disordered breathing (SDB) related output metrics include 3% and 4% desaturation events, including a total Apnea Hypopnea Index (AHI), an obstructive AHI (oAHI), a central AHI (cAHI), a Respiratory Disturbance Index (RDI), an Oxygen Desaturation Index (ODI), 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 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.

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). [2-5] Sleep is controlled in the midbrain and during sleep signals are sent to both the surface of the brain and changes in electroencephalographic (EEG) signals allow for estimating sleep stages from the surface of the brain by utilizing Polysomnography (PSG). Simultaneously to changes in brainwaves there are changes in the ANS-output that is therefore different during each sleep stage and allows for estimating of sleep stages (Figure 1).

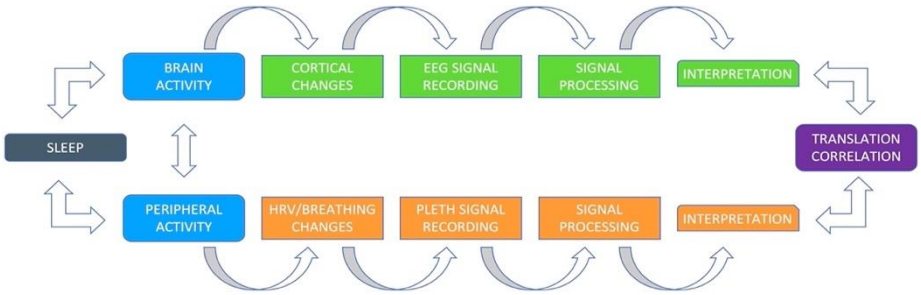


Figure 1. Changes in brain- and peripheral activity during sleep.

The SleepImage System is based on coupling heart rate variability (HRV) and tidal volume fluctuations in respiration during sleep, bio signals both highly influenced by the ANS (sympathetic and parasympathetic influence). Observing the synchronization between the cardiovascular- and respiratory systems (coupling) 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. [2, 3 4] SpO_2 data is used with CPC-analysis to calculate the SleepImage Apnea Hypopnea Index (AHI) and the SleepImage Respiratory Disturbance Index (RDI). 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, [6-9 10-18] (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). [19, 20]

The SleepImage System Features and Benefits are summarized as follows:

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

[1] To evaluate clinical symptoms of Insomnia or Sleep Apnea, [2] To track if treatment is improving objective sleep parameters

[3] 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*." [9]

Understanding the SleepImage Science

Everyone sleeps and sleep is an important modulator of various biological functions. The SleepImage is a tool that can enhance clinical practice across all medical specialties. 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 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. [21, 22] 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 is based on Cardiopulmonary Coupling (CPC) calculations and spectral analysis of continuously and evenly sampled data photoplethysmogram (PPG) sensors (Figure 2). The data collected contains information on heart (pulse) rate, heart rate variability (HRV) and tidal volume fluctuations in respiration (DR). The CPC calculations of sleep, used with the SpO_2 measurements to detect desaturation events, collectively create output parameters for diagnosis and management of sleep disordered breathing (obstructive and central sleep apnea) that can be manually scored in addition to the autoscoring.

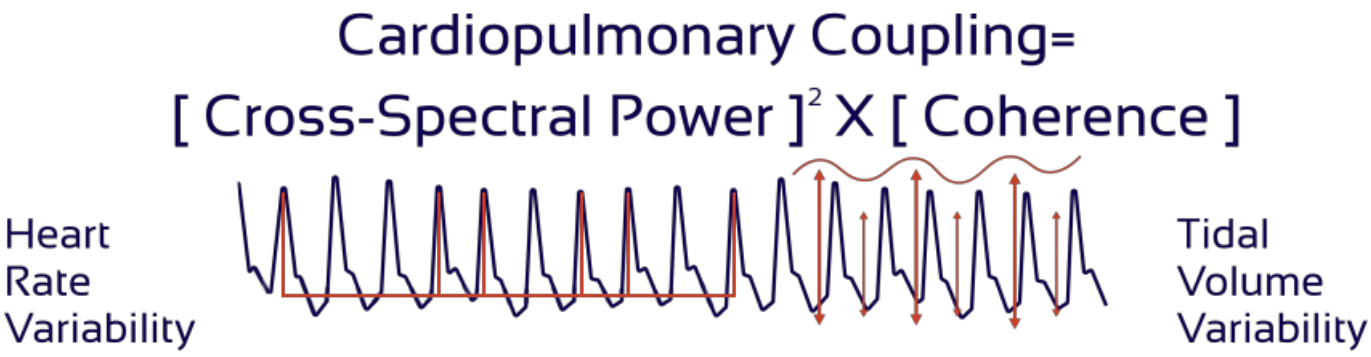


Figure 2. Cardiopulmonary Coupling.

The SleepImage System utilizes mathematical and frequency analysis to calculate synchronization between HRV and Tidal Volume Variability (TVV) to provide numerical and visualization of sleep states and sleep pathologies. There are two key factors when evaluating strength of the coupling between the two signals: (1) the oscillation amplitude at given frequency and (2) the synchronization between the two signals (phase relationship).[23] 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. [2-4]

The American Academy of Sleep Medicine (AASM) practice guidelines for scoring of sleep and associated events defines two methods to evaluate respiration, (1) an airflow channel and an effort channel, or alternatively (2) peripheral arterial tone[1] as a surrogate for "airflow/effort". These alternative methods are also commonly defined in insurance reimbursement policies for Home Sleep Apnea Testing (HSAT).

[1] Measurement of pulsatile volume changes reflecting changes in sympathetic tone.

The airflow channel is commonly recorded using a Nasal Pressure Transducer (measuring changes in pressure of nasal airflow) or an oronasal thermal flow sensor (measuring differences in temperature during inhalation and exhalation). The effort channel is commonly recorded using respiratory inductance plethysmography (RIP) belts measuring movement of the chest and/or abdominal wall during breathing to evaluate lung volume changes, presented as a derived digital signal that represents a breathing curve).

The peripheral arterial tone method utilizes a photoplethysmography (PPG) sensor to evaluates sleep through effects of the autonomic nervous system (ANS) on changes in peripheral arterial tone during sleep. More than one technique is available to present respiration from the peripheral arterial tone; SleepImage uses the method described in Figure 2 above.

When these three methods to evaluate respiration are compared from a sleep study using PSG that has all the sensors required to capture the data (an airflow sensor, a RIP belt and a PPG sensor), it is easy to see how the three methods compare in the respective raw signals and how each method provides clinical information that can be used for the same intended use, to evaluate respiratory events that can be manually reviewed and scored to define respiratory events.

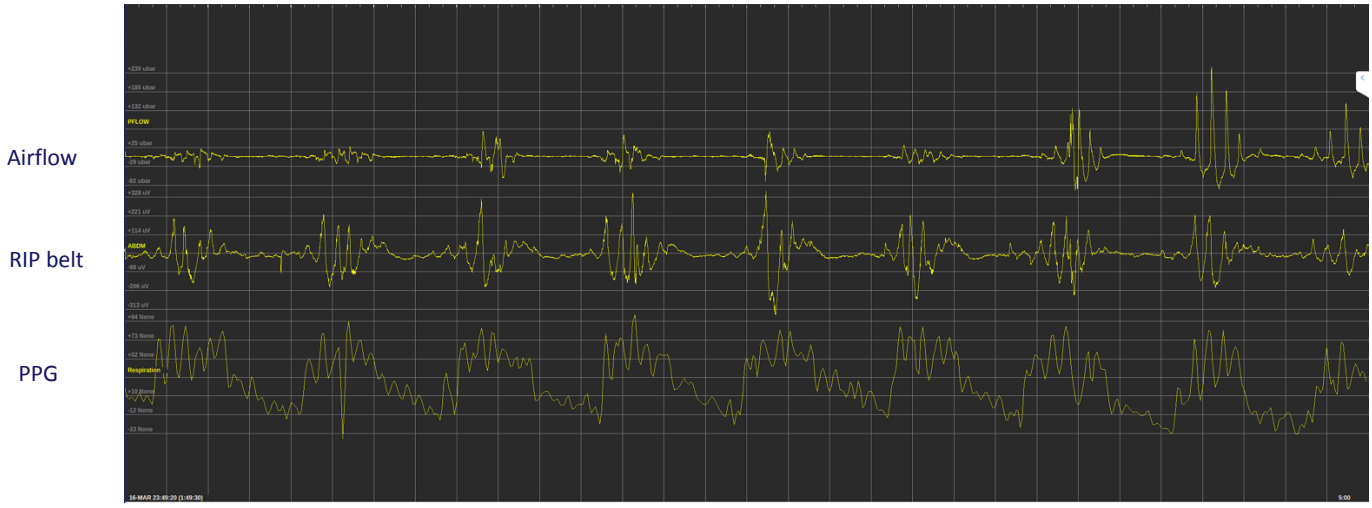


Figure 3. Respiratory Analysis.

The SleepImage spectrogram provides a clear visual of sleep health during the sleep period which 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 4).

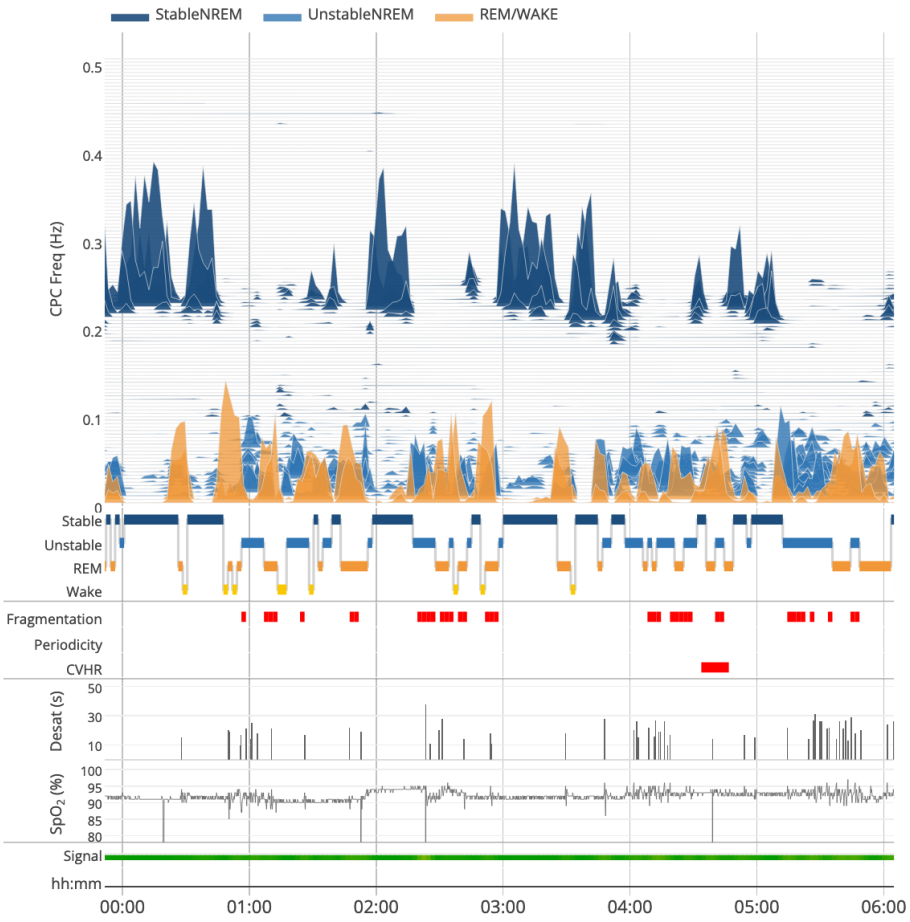


Figure 4. The sleep spectrogram reveals that NREM sleep has a distinct bimodal-type structure marked by distinct alternating and abruptly varying periods of strong high and low frequency cardiopulmonary coupling (HFC and LFC, respectively). These CPC states are separated widely in signal space with no 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 still 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 (Figure 1). The CPC-method integrates information from brain 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 CPC-synchronization dramatically changes with sleep stages, offering sleep-stage identification of NREM-sleep as Stable and Unstable and REM-Sleep. [3, 4, 16] 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. [3, 4]

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 automatically 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 frequency cardiopulmonary coupling as Stable sleep (High Frequency Coupling, HFC) and low-frequency cardiopulmonary coupling as Unstable sleep (Low Frequency Coupling, LFC). The 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 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). [2-4] 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. [16]

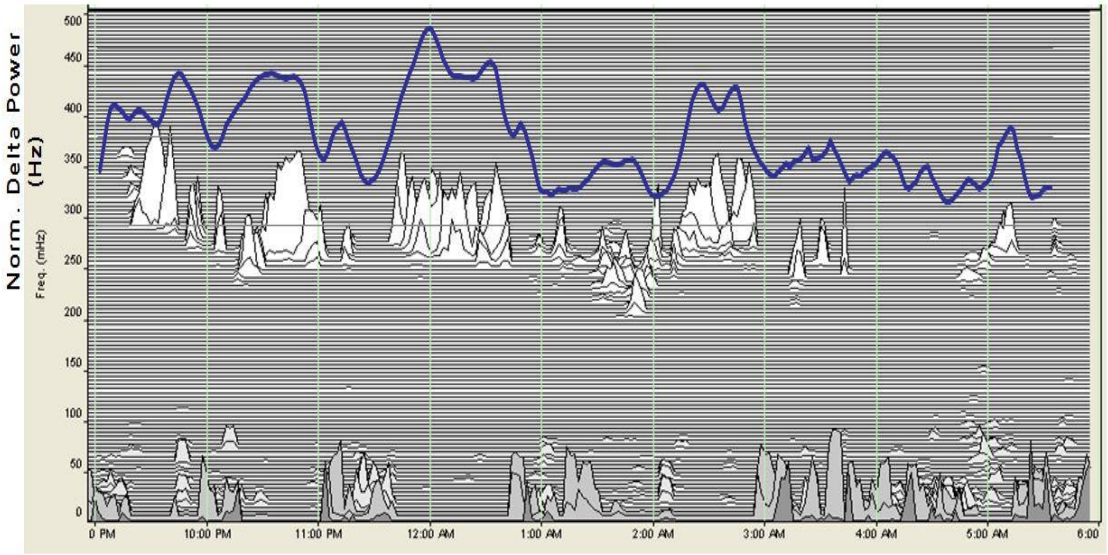


Figure 5. The figure above reveals the relationship between HFC and normalized delta power (blue line) during simultaneous data collection using CPC and PSG as discussed in the paper "Relationship between delta power and the electrocardiogram-derived CPC Spectrogram: possible implications for assessing 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 4, blue line), further supporting a link between cortical EEG electrical activity and brainstem-related cardiorespiratory functions. [3, 4] For diagnosis of SDB the

Sleep Image Apnea Hypopnea Index (sAHI) has a strong agreement with AHI calculated from PSG [20, 24] and the method is also able to differentiate between obstructive and central sleep apnea. [25, 26]

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 5.

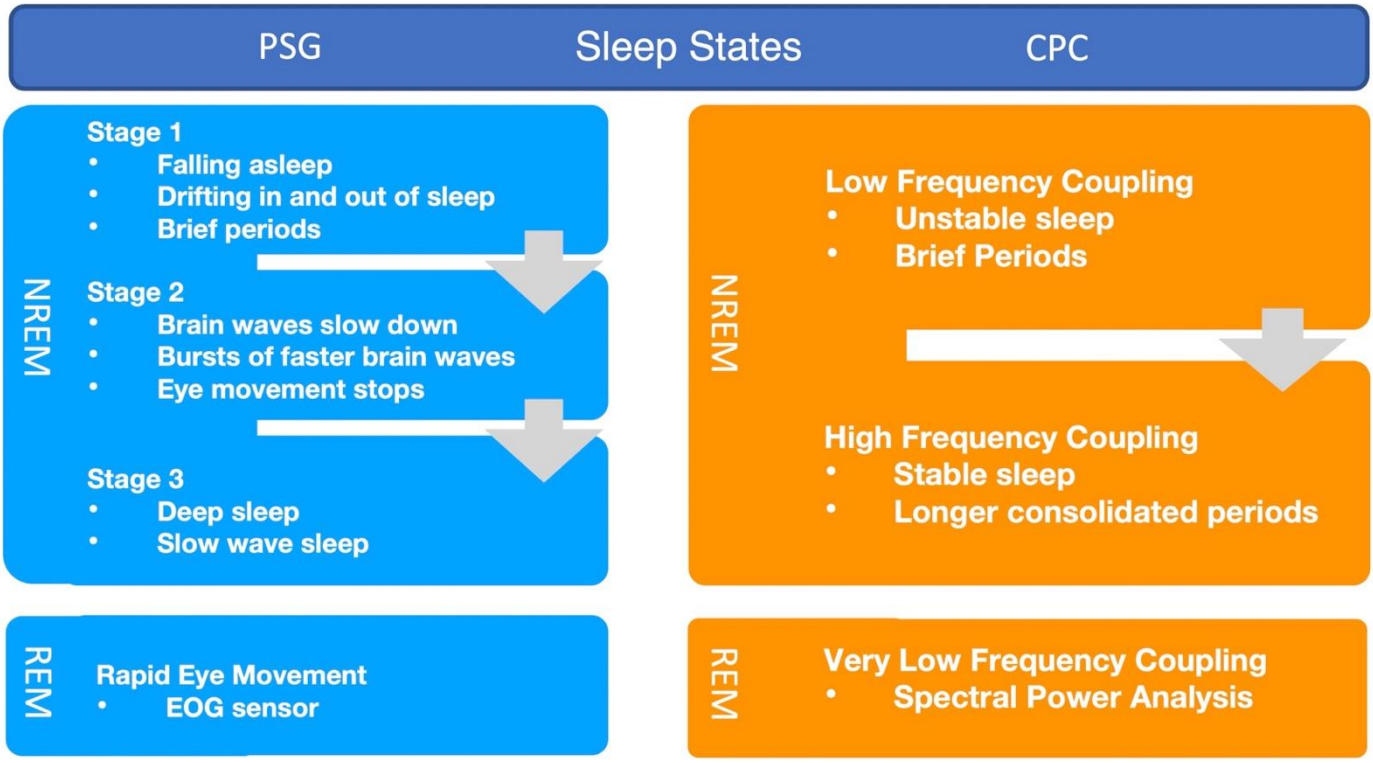


Figure 6. The relationship between conventional sleep scoring system and the Cardiopulmonary Coupling (CPC) scoring system.

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, [27-30] with repeated testing in patients' natural sleep environment over multiple nights and multiple time points to optimize disease management and patients' health. [7, 12, 18, 31]

Further description of the Cardiopulmonary Coupling can be found in the sleep medicine textbook, Principles and Practice of Sleep Medicine, (Kryger – Roth – Dement) Seventh Edition, Chapter 202. Cardiopulmonary Coupling. [2]

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. [2, 3, 7, 16, 18]

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_{NB}) and Fragmentation (elevated low frequency coupling broad band (e-LFC_{BB}). [2, 3, 7, 16, 18, 25]

Fragmentation (elevated low frequency coupling broad-band e-LFC_{BB}) 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). [2, 11, 24-26, 32]

Periodicity (elevated low frequency coupling narrow-band e-LFC_{NB}) 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). [12, 24, 25]

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. [7, 13, 18, 19, 32]

Apnea Hypopnea Index (AHI) 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_2-analysis, CPC-analysis and hypoxic events that are detected through the SpO_2 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. [20, 24]

Respiratory Disturbance Index (RDI) is intended to aid in the characterization of respiratory events during sleep in addition to AHI. While the sAHI includes events that meet the definitions of apneas and/or hypopneas for diagnosis of OSA, AHI does not include arousals that do not meet the criteria for desaturations. The RDI includes apnea- and hypopnea events and in addition arousals that are not related to desaturations but may disrupt sleep and cause sleep fragmentation (Respiratory effort-related arousals (RERA's)) and may therefore provide information for more comprehensive evaluation of respiratory disturbances during sleep. During a PSG-study, the RDI unlike AHI, also accounts EEG-arousals from sleep that do not meet the definitions of apneas or hypopneas. As the SleepImage system is not based on recording EEG brainwaves but rather cardiovascular and respiratory parameters, where presence of RERAs is detected from changes in the autonomic nervous system reflecting changes in the sympathetic tone based on changes in heart rate acceleration (HRa) and Fragmentation (eLFC_{BB}) without the requirement of a co-occurring oxygen desaturation 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. It is important to understand that the sRDI detects changes in sympathetic-tone, which should be treated as a non-invasive surrogate measure for EEG-arousal associated with non-desaturating hypopneas and RERA's scored during a PSG-study.

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. [24, 26] 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 ($sAHI_{STABLE}$, $sAHI_{UNSTABLE}$, and $sAHI_{REM}$) 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. [20, 24, 25]

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.[33] 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 Pediatricians (AAP), [34] 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), 55% 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: [33, 34]

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[1]
	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 during 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%. [35-37] 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. [27-29] 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. [38]

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 ±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.[29]

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_{BB})	<15	<8
Elevated Low Frequency Coupling, Narrow Band (e-LFC_{NB})	⩽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 in children are high but at the same time sleep is rarely addressed during routine pediatric visits. [39] During the preschool years (3-5 years of age) lymphoid tissue growth peaks, increasing the likelihood of symptoms of SDB to develop. [40] 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. [41, 42]

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. [43]

Considerable variability is in symptom presentation in children with OSA. 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. [42 44 45]

A recent study in healthy children suspected of OSA confirmed that 18% of children undergo adenotonsillectomy (AT) surgery without objective sleep evaluation and of the children that where 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. [46] 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%) [47, 48] as well as residual disease following surgery with less than a third of children with OSA achieving complete resolution with surgery. [49, 50] Additionally, surgery may potentially cause both serious short-term surgical complications and in the long-term significantly increased delayed respiratory, allergic, and infectious sequelae. [51-53]

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. [54] Although several screening questionnaires have been developed to identify children with OSA, they have not proven accurate and are rarely used. [39] 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.[55-58]

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. [59] It is furthermore important to implement therapy-tracking post intervention for objective evaluation with longitudinal care to improve clinical management as residual disease is common after AT-surgery in children. If left untreated, the disease may adversely affect the child's neurocognitive, behavioral, cardiovascular and cardiometabolic health over time and their future prospects. [45, 48]

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. [34, 42] These academic guidelines to establish objective evidence of OSA prior to surgical decisions are though frequently bypassed.[60] 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.[50,

Diagnosis of SDB requires clinical, subjective- and objective sleep data and OSA in children is defined as AHI > 1.0/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. [61]

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 [62] 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). [7, 18] 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. [7, 18, 63, 64]

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. [27-30] 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: [9]

1) Stable sleep tracks slow wave power and results of repeated testing could provide new insights into night-to-night sleep homeostatic mechanism. [2, 3, 31]

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. [31, 32, 65]

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. [27, 29, 30]

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 (StableNREM), LFC (UnstableNREM) and vLFC (REM/WAKE) for the time series. The vertical axis uses frequency range 0.004Hz to 0.5Hz and time in hours on the horizontal axis.

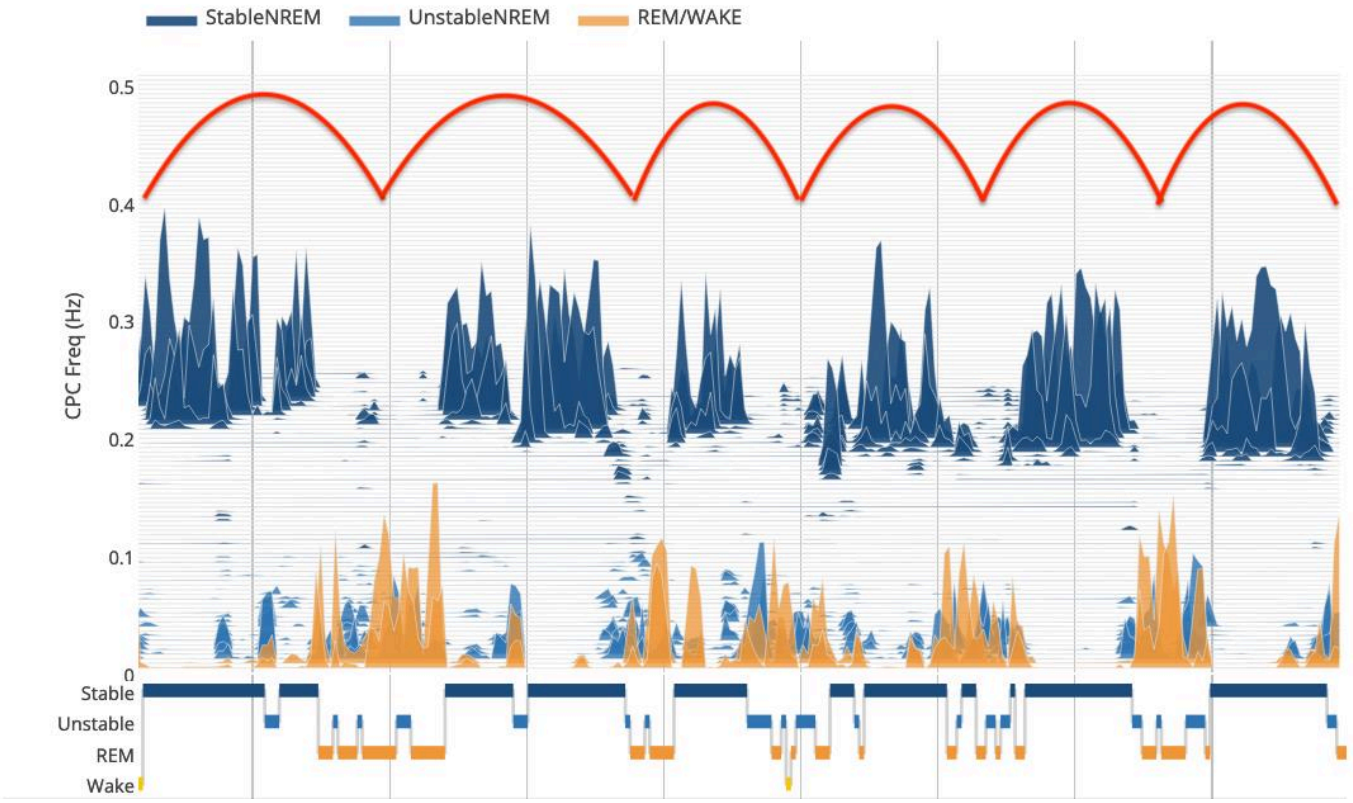


Figure 7. Oscillations between stable and unstable sleep are expected to modulate in 30-90-minute cycles that range from 4-8 Cycles in an adult 8-hour healthy night's sleep and correspond to the alternating periods of NREM and REM sleep. When sleep is disrupted (sleep apnea, insomnia, stress, pain and 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

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 $\geqslant$1, $\geqslant$5 and $\geqslant$10 respectively and for adult values for each category are $\geqslant$5, $\geqslant$15 and $\geqslant$30 respectively. Sleep Apnea Indicator (SAI) can indicate SA with good agreement when compared against AHI, despite being a 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_{BB}) indicating sleep fragmentation, arousals and obstructive apneas, and Periodicity (e-LFC_{NB}) 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_2 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
- Snoring
- Morning Headaches
- Difficulty Falling Or Maintaining Sleep
- Irregular (Paused Breathing During Sleep
- Bruxism / Teeth Grinding
- Waking Up Gasping Or Choking

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
- G47.32 High Altitude Periodic Breathing
- G47.10 Hypersomnia, Unspecified
- R06.3 Periodic Breathing
- R53.83 Other Fatigue
- G47.31 Primary Central Sleep Apnea
- G47.9 Sleep Disorder, Unspecified
- F51.01 Primary Insomnia
- R06.83 Snoring
- Other

Impressions and Recommendations

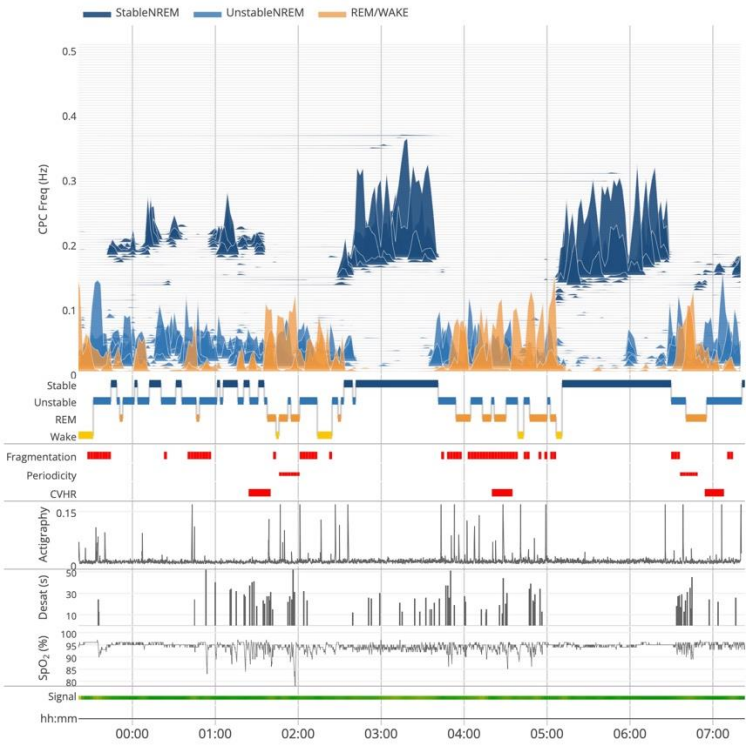
Character Count: 0 / 1040

Publish

Reviewing SleepImage Graphics for Associations & Patterns

P A T T E R N S

A S S O C I A T I



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_{BB}. Periodicity indicates metronomic activity that may be caused by central apnea or periodic breathing and are termed e-LFC_{NB}.
5. Desaturation and SpO_2: Review desaturation events and correlate in association with stable, unstable and REM sleep and look for concurrent CVHR. Areas of SpO_2 signal loss are often demonstrated by a large and sudden drop in SpO_2.
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 StableNREM, UnstableNREM and REM/Wake peaks (Clinician Users): The StableNREM, UnstableNREM, REM/WAKE 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$_{BB}$ is presented by broad gray peaks on the 3D Spectrogram.

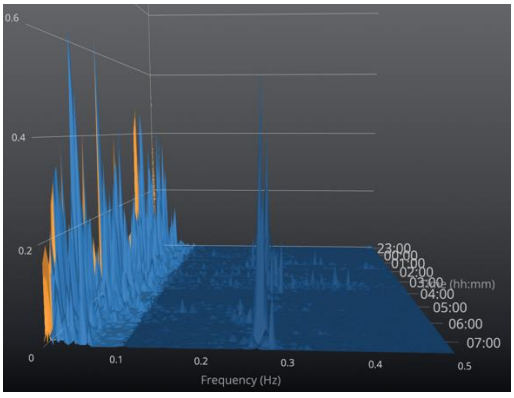


Figure 8. The 3D View Spectrogram - Obstructive Sleep Apnea shows a "broad" distribution of the peaks called Elevated Low Frequency Coupling broadband (e-LFC$_{BB}$).

3D Spectrogram - Central Sleep Apnea

Central Sleep Apnea or periodic breathing is represented by narrow red colored peaks as e-LFC$_{NB}$ 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.

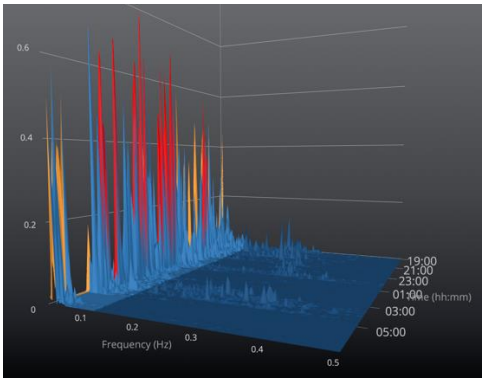


Figure 9. 3D Spectrogram - Central Sleep Apnea is presented as a line of narrow red peaks. The system colors these peaks red to make it easier for users to identify the periodicity.

CPC Publications

Books

1. CardioPulmonary Coupling. In. Penzel, T., Hornero, R. (eds) Advances in the Diagnosis and Treatment of Sleep Apnoea. Advances in Experimental medicine and Biology (185-204). Switzerland: Springer, Cham.

2. Cardiopulmonary Coupling Spectrograms. In: Kryger MH, Roth T, Dement WC (6th edition), Principles and practice of Sleep Medicine (1615-1623). Philadelphia, PA: Elsevier, Inc.

3. 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.

4. 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

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Glossary

AAP: American Academy of Pediatrics

AASM: American Academy of Sleep Medicine

ANS: Autonomic Nervous System

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_{BB}: 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_{NB}: 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_2: 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)