Assessment of Therapeutic Options for Mild Obstructive Sleep Apnea Using Cardiopulmonary Coupling Measures

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Objective: To examine the efficacy of various therapeutic modalities for mild obstructive sleep apnea using cardiopulmonary coupling variables of sleep quality.

Methods: A 67-year-old Caucasian subject's sleep was recorded at home for 10 nights using a type 3 sleep recording device that measured ECG and body position, followed by generation of the cardiopulmonary sleep spectrogram. Three baseline nights, one night with a sleep jacket containing 3 tennis balls to restrict sleep in the supine position, 2 nights with oxygen only delivered via a nasal cannula at a flow rate of 2 L/minute, 2 nights with a mandible advancing appliance (MAA) only, and 2 nights using oxygen at 2 L/minute with the MAA were compared.

Results: Baseline sleep quality estimated using the ratio of high-frequency and low-frequency coupling (1.03) was below

the expected normal adult values ranging from 1.67-4.0. The sleep quality ratio was significantly higher (2.08) using the MAA alone compared to baseline, sleep position restriction (1.61), oxygen therapy (0.81), and the combination of MAA with oxygen (1.66).

Conclusion: Sleep quality measured objectively using cardiopulmonary coupling variables differentiated the efficacy of therapeutic options for mild obstructive sleep apnea. Such an approach may have practical utility.

Keywords: Cardiopulmonary coupling, sleep apnea, mild obstructive sleep apnea

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Mild obstructive sleep apnea is associated with cardiovascular stressors such as hypoxemia, sympathetic activation, acute pulmonary and systemic hypertension, and decreased stroke volume.¹ Patient symptoms often include daytime hypersomnolence, snoring, waking with a dry mouth, sexual dysfunction, and memory loss. Following diagnosis by polysomnography, patients receive treatment recommendations for continuous positive airway pressure (CPAP), mandible advancing appliance (MAA), sleep position restriction, or surgery as options. Treatment objectives include resolution of respiratory events with the goal of improving clinical symptoms by increasing sleep quality.

CPAP is considered the first-line treatment option. The use of an oral appliance is suggested by the American Academy of Sleep Medicine as an appropriate treatment for patients with primary snoring without features of OSA or upper airway resistance syndrome, and in cases of mild to moderate OSA who prefer MAA, do not respond to CPAP, or who fail behavioral interventions such as weight loss or body position restriction.² A follow-up full polysomnography or cardiorespiratory (type 3) sleep study with the MAA in place after final adjustment is recommended. Efficacy is based on the standard measures from respiratory flow/effort and oximetry that are summarized using the apnea hypopnea index and associated oxygen desaturations. However, these data provide no information on sleep quality or estimates of sleep time and sleep efficiency without simultaneous electroencephalogram (EEG) recording.

BRIEF SUMMARY

Current Knowledge/Study Rationale: This research was performed to: 1) assist the patient in determining which recommended therapy was the most effective intervention; and 2) demonstrate that alternative and cost effective evaluation methods can enable sleep clinicians in identifying treatment efficacy in the patient's home sleep environment.

Study Impact: The data suggests clinicians can obtain reliable objective information about sleep quality using a simple device when assessing the efficacy a therapeutic intervention for sleep breathing disorders. The emphasis of this study is on follow-up care and assessment of sleep quality which advances the field of sleep medicine by providing a method to improve disease management.

Surrogate sleep information can be acquired from the electrocardiogram (ECG) using cardiopulmonary coupling (CPC). CPC integrates mathematically heart rate variability (HRV) and respiration, which are strongly modulated by electrocortical activity.³ The result is a map of coupled autonomic/respiratory oscillations during sleep that provides information on sleep quality and sleep disordered breathing phenotypes independent of EEG analysis.⁴ Consolidated and stable NREM sleep is characterized by high-frequency coupling. Low-frequency coupling is enhanced in states of fragmented sleep. CPC variables could be sensitive to effects of sleep apnea treatment.

To examine treatment efficacy on sleep quality and to demonstrate the treatment tracking capability of the CPC method, we evaluated the effects on cardiopulmonary coupling of sleep

Figure 1—Timeline for M1 recordings with various treatments.

position restriction, oxygen therapy, MAA, and MAA with oxygen therapy in a female subject diagnosed with mild OSA.

METHODS

Case Description

A 67-year-old Caucasian female (140.0 lbs, 67.0 inches in height, BMI 21.9, neck size 13.5 inches) presented with an abnormal pulse oximetry study showing nocturnal desaturations and recently diagnosed atrial fibrillation and mitral valve prolapse. She complained of occasional insomnia and used over-the-counter sleep aids to facilitate sleep. Other complaints included snoring, waking with a dry mouth, memory impairment, shortness of breath with exertion, and tinnitus. She reported an anterior cervical disk replacement surgery 2 years earlier. The subject denied cataplexy, sleep paralysis, and falling asleep while driving. The physical examination was negative for a deviated septum or enlarged tonsils and adenoids. The medications used included metoprolol 12.5 mg, calcium 850 mg, and magnesium 400 mg. Subjective sleepiness assessed with the Epworth Sleepiness Scale resulted in a score of 5/24, consistent with an absence of excessive daytime sleepiness.

Polysomnography

Split-night polysomnography was performed at a community based sleep disorders center and scored by an American Board of Sleep Medicine certified specialist. The in-lab polysomnography data was not available for CPC analysis.

In-Lab Baseline

The baseline diagnostic analysis began at 23:03 and ended at 02:53 for a total recording time of 230 min. Total sleep time (TST) was 178.5 min, resulting in a sleep efficiency of 77.4%. Supine REM (7.6% of TST) was present. Apnea hypopnea index (AHI, desaturating hypopneas) was 10.8 events/h of sleep, and respiratory disturbance index (RDI) was 25.6/h. Body position showed a supine RDI of 23.9/h and a right-side RDI of 2.3/h. REM RDI was 40/h, and NREM RDI was 13.1/h. Oxygen desaturations occurred to a low of 75% with a mean of 92.9%. The PSG was negative for periodic limb movements and ECG abnormalities, although her history indicated otherwise.

In-Lab Treatment

CPAP was initiated with 5 cm H₂O and titrated to 9 cm H₂O while sleeping in the supine position. At 5 cm H₂O, the AHI

was 0 events/h with a RDI of 2.4/h and a lowest desaturation to 93% in NREM sleep. At 9 cm H₂O, the AHI was 2 events/h, the RDI was 8 events/h, and the lowest desaturation was 92% in both NREM and REM sleep.

Treatment recommendations included MAA and avoidance of sleep in the supine position, based on the subject's preference. CPAP was considered an alternative treatment option. The subject was fitted with an oral MAA, and the jaw was advanced to 65% of maximum by her dentist to resolve apnea events and improve sleep quality. Her cardiologist recommended the use of oxygen (2 L/min) at night because of event associated oxygen desaturation to 75% on polysomnography. Neither treatment was evaluated during sleep to determine if the patient's sleep quality had improved. The subject questioned the efficacy of each treatment.

Home Recording

The subject's sleep was recorded at home on 3 baseline nights, one night with a sleep jacket containing 3 tennis balls to restrict sleep in the supine position, 2 nights with oxygen only delivered via nasal cannula at a flow rate of 2 L/min, 2 nights with the MAA only, and 2 nights using both oxygen at 2 L/min with the MAA using a new Food and Drug Administration-approved type 3 home sleep monitoring device (M1; MyCardio, Thornton, CO.). (Figure 1) The subject slept supine in spite of restricted positioning with tennis balls. No sleep was recorded from the left side because of reported chronic left shoulder pain.

Cardiopulmonary Coupling Analysis

The M1 records the electrocardiogram (ECG), and uses the CPC algorithm to generate the sleep spectrogram. This data is then combined with actigraphy to estimate sleep and wake time. The CPC algorithm uses 2 separate physiological streams of data input (autonomic and respiration) and mathematically captures common ("coupled") activity that is strongly modulated by a third physiological stream (electrocortical activity).³ In addition to recording the heartbeat, the M1 also records actigraphy, body position, and snoring data during sleep.

Heart rate variability (HRV) is modulated by respiration, as evidenced by shorter RR intervals during inspiration and longer RR intervals during expiration. As tidal volume changes, there is an associated increase and decrease in the ECG R-wave amplitude. Both changes are captured by the CPC algorithm, integrated to derive a respiration signal (ECG-derived respiration or EDR) and coupled to normalized HRV data to create

Table 1—Comparison of CPC, sleep estimate, and snore variables between treatments

Variable	Treatment					Expected Adult value
	Baseline	Tennis balls	O ₂	MAA	MAA+O ₂	
HFC%	39.26 ± 3.04	51.04	35.02 ± 6.16	50.46 ± 5.90	50.52 ± 4.74	> 50%
LFC%	38.06 ± 1.96	31.77	43.16 ± 0.33	24.24 ± 3.58	31.13 ± 5.34	< 30%
VLFC%	21.24 ± 1.74	15.10	20.43 ± 5.12	24.14 ± 7.87	17.88 ± 1.27	< 20%
eLFC _{BB} %	18.21 ± 3.92	18.75	23.41 ± 5.57	8.35 ± 2.10	9.59 ± 4.90	< 15%
Snoring (% of sleep period)	0.32 ± 0.18	1.03	0.36 ± 0.40	0.22 ± 0.27	0.10 ± 0.01	
Snore events#	74.66 ± 54.16	183.00	68.00 ± 70.71	44.50 ± 54.44	23.00 ± 7.07	
Total Recording Time (min)	482.67 ± 30.56	436.00	496.00 ± 0.40	416.00 ± 0.00	521.00 ± 63.63	
Total Sleep Time (min)	386.37 ± 29.75	353.78	396.24 ± 20.83	341.76 ± 15.71	431.02 ± 50.31	
Total Wake Time (min)	57.19 ± 4.13	45.94	63.70 ± 3.40	35.07 ± 2.49	53.23 ± 2.01	
Sleep Efficiency (%)	79.94 ± 1.88	81.00	79.82 ± 0.36	82.07 ± 3.76	83.42 ± 0.58	
Supine BP (min)	314.32 ± 121.14	287.37	307.18 ± 56.37	244.72 ± 92.14	350.31 ± 61.73	
Supine BP as % of Sleep Period	80.62 ± 27.93	81.23	77.25 ± 10.16	72.30 ± 30.28	82.67 ± 23.97	
Right Side BP (min)	65.18 ± 106.90	51.44	87.51 ± 35.36	88.38 ± 119.02	73.86 ± 104.46	
Up BP (min)	6.78 ± 9.32	2.87	1.52 ± 0.21	8.65 ± 11.16	7.58 ± 2.87	

HFC, high-frequency coupling; LFC, low-frequency coupling; VLFC, very-low-frequency coupling; eLFC_{BB}, elevated low-frequency coupling broad band; BP, body position; MAA, mandible advancing appliance; O₂, oxygen. Snoring as a percent of sleep was obtained by using the total duration of snore events (minutes) detected from tissue conducted vibration divided by the estimated sleep time (minutes).

the sleep spectrogram. Combining HRV and EDR produces high, low, elevated-low, and very-low-frequency coupling. High-frequency coupling (HFC; 0.1-0.4 Hz) is the biomarker of stable and consolidated sleep, while low (LFC; 0.01-0.1 Hz), and elevated-low frequency coupling (e-LFC; a subset of LFC) are increased in states of fragmented sleep.^{3,4} Broad and narrow band e-LFC (e-LFC_{BB}, e-LFC_{NB}), reflect predominant obstructive upper airway and sustained strong chemoreflex effects on sleep respiration, respectively.⁴ Predominant obstructive upper airway events exhibit variable intrinsic oscillatory patterns (variable respiratory event cycle times) during PSG. Central and complex sleep apnea present with a highly predictable metronomic oscillatory pattern mediated by excessive chemoreflex effects on sleep-respiration.⁴ In this situation, the respiratory events have a nearly fixed cycle time. Very-low-frequency coupling (VLFC; 0.001-0.01 Hz) associates with wake or REM period.³

The result of this interplay creates a simple picture of sleep that provides information about sleep quality independent of conventional EEG-based measures. NREM duration, delta power, total sleep time, and REM duration demonstrate positive correlations to HFC, while LFC correlates positively with the arousal index and respiratory disturbance index.^{3,5} The sleep spectrogram approach is fundamentally different in that it eliminates the need for arbitrary scoring rules by directly measuring biological signals and provides a unique view into sleep physiology and pathology. It has the potential to readily show treatment efficacy responses. (**Figure 2**)

Statistical Analysis

Data analysis was performed using SPSS (version 11, Chicago, IL). Values are expressed as means ± standard deviation unless otherwise specified. The data from the night with tennis balls were obtained from a single night's recording.

RESULTS

Baseline versus Sleep Position Restriction with Tennis Balls

Visual comparison shows HFC was higher and LFC lower using tennis balls. The HFC/LFC ratio was higher with tennis balls compared to baseline (1.61 vs. 1.03 ± 0.14, respectively) but did not reach the therapeutic levels of MAA. Snoring as a percent of the sleep period and number of events was higher with tennis balls; this is likely due to the 287 min spent supine or partially supine, suggesting the sleep position restriction method was ineffective in treating her OSA. The biomarker of strong chemoreflex effects on sleep-respiration,⁶ e-LFC_{NB}, was not present on the baseline nights.

Baseline versus O₂

HFC/LFC values (1.03 ± 0.14 and 0.81 ± 0.14, respectively) did not meet expected normal adult values > 1.67 on either night.⁷ HFC was lower and LFC and e-LFC_{BB} higher on O₂ nights compared to baseline nights. VLFC was relatively similar under both conditions (**Table 1**).

Baseline versus MAA

The mean HFC/LFC ratio on the baseline nights was 1.03 ± 0.14 compared to 2.08 ± 0.06 on MAA nights. HFC was higher and LFC, VLFC, and e-LFC_{BB} lower on MAA nights.

Baseline versus MAA + O₂

The mean HFC/LFC ratio on baseline was 1.03 ± 0.14 compared to 1.66 ± 0.43 on MAA + O₂ nights. HFC was higher; and LFC, VLFC, and e-LFC_{BB} lower on MAA + O₂ nights.

MAA versus O₂

The HFC/LFC ratio was higher on MAA therapy nights (2.08 ± 0.06) compared to O₂ nights (0.81 ± 0.14). HFC was

Figure 2—Single night examples of CPC sleep spectrograms with treatment

Sleep stability and quality: The **top left** panel shows reduced high-frequency coupling (stable sleep) and increased low-frequency coupling (unstable sleep) on baseline night. The **top right** panel represents a trial of a nightshirt with tennis balls, during which stable sleep is increased. The **middle** panel shows significant decrease of stable sleep with oxygen only. The **bottom left** panel shows increased stable sleep and decreased unstable sleep with MAA. The **bottom right** panel has increased stable sleep compared to both baseline and oxygen only nights, but unstable sleep is elevated; suggesting oxygen therapy is influencing sleep quality. Act, actigraphy.

higher and LFC and e-LFC_{BB} lower on MAA nights. VLFC was higher on O₂ nights.

MAA + O₂ versus O₂

The HFC/LFC ratio was higher on MAA + O₂ nights (1.66 ± 0.43) compared to O₂ only nights (0.81 ± 0.14). HFC was higher; and LFC, VLFC, and e-LFC_{BB} lower on MAA + O₂ nights.

MAA versus MAA + O₂

The HFC/LFC ratio was higher on MAA nights (2.08 ± 0.06) compared to MAA + O₂ nights (1.66 ± 0.43). HFC was similar under both conditions. LFC and e-LFC_{BB} were higher and VLFC lower with MAA + O₂. (**Figure 3**)

DISCUSSION

The important findings in this case report include: (1) CPC variables differentiate between baseline and therapeutic interventions. (2) Tennis balls, O₂, MAA, and MAA + O₂ treatment efficacy could be evaluated using the M1 device with CPC.

The recommend first-line treatment of mild OSA is CPAP; however, this intervention is not always accepted by patients. Other options include sleep position restriction and MAA, but these are rarely followed up and assessed by objective measures in the home sleep environment. Traditional home data acquisition of respiratory effort and oximetry summarized by an apnea hypopnea index with desaturations can be cumbersome, requires manual scoring, and does not provide objective measures of sleep quality. The inbuilt monitoring capabilities of current positive pressure machines do not provide sleep quality measures. Furthermore, the impact of respiratory events not meeting current scoring rules is overlooked, since EEG data are usually not acquired for evaluation during home studies.

The baseline CPC values identified the presence of a sleep disorder, correctly phenotyped this case as predominantly obstructive sleep apnea,⁶ and validated the pre-treatment in-lab findings. The CPC report data was supported by the subject's comments. She noted that her sleep was most restorative on mornings following MAA use compared to any of the other interventions. CPC data from the MAA nights confirm expected normative adult values and showed that adding O₂ to MAA negatively affected sleep quality in this case. The subject reported nasal passage pain on awakening, runny nose, and found the use of the nasal cannula to be psychologically disturbing because she associated its use with medically infirm patients. The oxygen concentrator was stationed two rooms from the sleeping room to avoid noise, so it was not a likely cause of sleep disruption. Hypoxemia is a predictor of recurrent atrial fibrillation.⁸ Atrial fibrillations were not observed in either the PSG or home recordings. Oximetry measurements were not performed during home recordings.

Tennis balls did not prevent sleeping in the supine position but did improve sleep quality compared to baseline. The subject was recorded for 23 minutes less and spent 27 fewer minutes in the supine position and her sleep position could have been

Figure 3—Comparison of HFC/LFC ratio between baseline and therapy conditions

Sleep quality is based on the HFC/LFC ratio. Expected range of normal adult values for HFC/LFC is 1.67 to 4.0. MAA, mandibular advancing appliance; O₂, oxygen.

“partially” supine with tennis balls, which could account for some of the improvement.

In summary, the data demonstrate a simple method to evaluate sleep quality and treatment efficacy in the patient's home sleep environment. Further study of this simple approach in a larger population is required to establish clinical utility.

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DISCLOSURE STATEMENT

MyCardio, LLC has licensed the CPC software from Beth Israel Deaconess Medical Center and Dr. Thomas is one of the patent owners. Dr. Schramm is a consultant for MyCardio.