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Sleep Quality Change After Upper Airway Surgery in Obstructive Sleep Apnea: Electrocardiogram-Based Cardiopulmonary Coupling Analysis

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Objectives/Hypothesis: To test the effect of upper airway surgery on sleep quality in adults with obstructive sleep apnea (OSA) and the potential usefulness of electrocardiogram (ECG)-based cardiopulmonary coupling (CPC) analysis as metrics of sleep quality.

Study Design: Retrospective outcome research.

Methods: A total of 62 consecutive adult patients with OSA, consisting of 36 with successful and 26 with unsuccessful outcomes, were included in the study. Mean age was 37.7 ± 8.9 years, and body mass index (BMI, kg/m^2) was 26.9 ± 2.3. We compared clinical characteristics (age, BMI, and Epworth Sleepiness Scale [ESS]), sleep (sleep efficiency, stage non–rapid eye movement [N]1, N2, N3, rapid eye movement, and arousal index [ArI]), respiratory (apnea index [AI], apnea-hypopnea index [AHI], and minimum arterial oxygen saturation [SaO_2]), and CPC (high-frequency coupling [HFC], low frequency coupling [LFC], very–low-frequency coupling, and elevated low-frequency coupling [e-LFC]) parameters between the success and non-success groups before and after surgery. Surgical success was defined when the postoperative AHI was both <20 per hour and 50% of the preoperative value.

Results: Sleep quality measured by CPC analysis improved significantly (HFC, $P = .001$; LFC, $P = .002$; e-LFC, $P = .003$), along with parallel reduction in ESS, respiratory parameters (AHI, AI, minimum SaO_2), and sleep fragmentation (ArI) in the group with surgical success after upper airway surgery.

Conclusions: Successful upper airway surgery can improve objective sleep quality in adult patients with OSA. CPC metrics of sleep quality are potentially useful to monitor therapeutic responses during long-term postoperative follow-up, as the ECG-based analysis is available as a standalone option outside laboratory polysomnography.

Key Words: Cardiopulmonary coupling, sleep quality, polysomnography, obstructive sleep apnea, surgery.

Level of Evidence: 4

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INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent sleep disorder characterized by repeated or partial upper airway collapse during sleep.[1,2] OSA impairs daytime function and also increases the risk of future cardiovascular and metabolic disorder including hypertension, ischemic heart diseases, cardiac arrhythmias, and diabetes.[3–5] Two prominent effects of respiratory events during sleep are intermittent hypoxia and sleep fragmentation, which lead to oxidative injury, sympathetic overactivity, systemic inflammation, hypercoagulability, and pathologic hemodynamic profiles.[4] It has been recognized that surgical treatments for OSA not only improve subjective symptoms and disease-specific quality of life, but also reduce risk of automobile accidents, cardiovascular diseases, and mortality.[6–9]

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Beneficial effects of upper airway surgery are mediated by improvement in respiratory parameters, cardiovascular autonomic regulation, and sleep quality.[9–11]

The standard method for evaluating sleep quality is to assess sleep architecture by visual scoring of electroencephalography (EEG) that presents an arousal index or percentage of sleep stages. A possible limitation of EEG-based assessments is that sleep staging is constrained by the amplitude and morphology of EEG waves, which can show large individual variations and is not consistently correlated with perceived sleep quality.[12,13] Recently, the electrocardiogram (ECG)-based cardiopulmonary coupling (CPC) method has been introduced as a new metric for sleep quality.[14] CPC analysis is a method to measure the degree of coupling between heart rate variability (HRV) and variability of respiratory tidal volume. The latter is determined by measuring amplitude variations in the QRS complex on the ECG that occur due to shifts in the cardiac electrical axis relative to the ECG electrodes across a respiratory cycle, and due to changes in thoracic impedance as lungs inflate and deflate.

CPC analysis has several advantages over the conventional EEG-based method; it is readily repeatable (ECG recoding alone), automated, and scorer-independent. CPC presents the relative amount of stable and unstable sleep as an index of sleep quality as well as an estimate of sleep-disordered breathing.[14,15] High-frequency coupling (HFC) is the marker of stable sleep, and low-frequency coupling (LFC) that of unstable sleep. Such indices tightly correlate with cyclic alternating pattern and EEG slow wave spectral power, but not with conventional EEG sleep stages.[14,16,17] Elevated power in the low-frequency coupling region coincides with periods of scored apnea/hypopnea, which is designated as elevated low-frequency coupling (e-LFC) and is an indicator of sleep fragmentation and sleep-disordered breathing.[15]

We have previously demonstrated postoperative improvement of sleep quality using CPC analysis in pediatric OSA treated by adenotonsillectomy.[18] Impaired sleep quality in children with OSA is not readily captured by conventional EEG-based visual scoring and EEG spectral power analysis.[19–21] This study aimed to demonstrate the effect of upper airway surgery on sleep quality, using ECG-based CPC analysis, in adult OSA patients. For this goal, we documented pre- and postoperative CPC findings, and compared CPC profiles between the group with a successful and unsuccessful outcome.

MATERIALS AND METHODS

Subjects

Consecutive male adults (age $\geq$18 years) who underwent upper airway surgery for OSA from 2004 to 2011 at the Korea University Ansan Hospital were recruited. The inclusion criteria were: 1) subjects who were diagnosed with OSA according to *International Classification of Sleep Disorders: Diagnostic & Coding Manual* (2nd edition),[22] 2) subjects who were reluctant to use or intolerant of a continuous positive airway pressure device, 3) those who were treated with surgical therapy, 4) those who underwent pre- and postoperative polysomnography (PSG), and 5) those whose ECG data on both pre- and postoperative PSG were artifact free for more than 80% of the total sleep period. Postoperative follow-up PSG was performed 3 months after upper airway surgery. The exclusion criteria were: 1) insufficient total sleep time (<6 hours) or poor sleep efficiency (<80%) on either pre- or postoperative PSG; 2) use of neuroactive drugs (e.g., sedative, antidepressant medications); and 3) medical conditions that could possibly affect CPC profiles such as diabetes with significant complications, heart failure, and cardiac arrhythmia. Sixty-two consecutive male subjects (age 37.7 ± 8.9 years old; body mass index [BMI] 26.9 ± 2.3) were finally included in the study. The surgical outcome was successful in 36 and unsuccessful in 26 patients according to the criteria for surgical success given below. Subjective daytime sleepiness was measured with the Epworth Sleepiness Scale (ESS).[23] The study was reviewed and approved by the institutional review board at Korea University Ansan Hospital.

Polysomnography

Standard in-laboratory PSG (Alice 4; Respironics, Atlanta, GA) was performed to evaluate sleep structure (sleep efficiency [SE], stage non–rapid eye movement [N]1, N2, N3, and rapid eye movement [R], and arousal index [ArI]) and respiratory parameters (apnea index [AI], apnea-hypopnea index [AHI], and minimum arterial oxygen saturation). All PSG data were manually scored by a sleep technician and reviewed by a certified physician in accordance with the criteria of *the AASM Manual for the Scoring of Sleep and Associated Events*.[12] Apnea was defined as a decrease in airflow of $\geq$90% that lasts for at least 10 seconds, and hypopnea as a decrease in airflow of $\geq$30% associated with reduction in oxygen saturation of $\geq$4%. AI was defined as the number of apneas per hour of sleep, and AHI was defined as the number of apneas and hypopneas per hour. SE was defined as the proportion of total recording time scored as sleep (%). ArI was defined as the number of arousals per hour of sleep. OSA syndrome was diagnosed when AHI was $\geq$5 with OSA-related symptoms or AHI $\geq$15 regardless of symptoms.[22]

Upper Airway Surgery

All subjects underwent pharyngeal surgery (e.g., modified uvulopalatopharyngoplasty, uvulopalatal flap) with or without concomitant nasal surgery (e.g., septal surgery, turbinate surgery, endoscopic sinus surgery). Surgical success was defined as a reduction of at least 50% in the AHI to levels below 20.[24,25]

Cardiopulmonary Coupling Analysis

CPC analysis was carried out on the ECG data from the diagnostic and follow-up PSGs using the commercially available software, RemLogic 2.0 CPC analyzer (Embla Systems Inc., San Carlos, CA) as described elsewhere.[18] Five CPC parameters were of main interests: 1) HFC, (spectrogram peaks in the frequency range of 0.1 to 0.4 Hz), which indicates stable sleep; 2) LFC (spectrogram peaks in the frequency range of 0.01–0.1 Hz), which indicates unstable sleep; 3) very–low-frequency coupling (VLFC) (spectrogram peaks in the frequency range of 0–0.01 Hz), which indicates awake or parts of stage R; 4) other (spectrogram peaks other than HFC, LFC, and VLFC, typically <1%–2%); and 5) e-LFC (a subset of LFC with especially large low-frequency power), which correlates with sleep fragmentation and sleep apnea.[14,15]

Statistical Analysis

All outcomes are presented as the mean ± standard deviation for continuous variables and as proportion (percentage) for categorical variables. Comparisons of preoperative baseline data between successful and unsuccessful groups were performed with the Student t test for parametric comparisons and Mann-Whitney U test for nonparametric comparisons. Repeated measurement analysis of PSG (sleep and respiratory variables) and CPC parameters were conducted with analysis of covariance (ANCOVA), with successful/unsuccessful groups as the between-subject factor, and time between pre- and postoperative PSG as the within subject factor, and controlling for age as a covariate. Statistical analysis was performed using IBM SPSS version 20.0 statistical software (IBM SPSS Inc., Armonk, NY). The null hypothesis was rejected when the P value was $<.05$.

RESULTS

Preoperative Baseline Data

The surgically unsuccessful group was significantly older (Table I). Otherwise, there was no significant difference in baseline characteristics including BMI, subjective daytime sleepiness, sleep structure, respiratory parameters, and CPC profile.

Postoperative Change in Daytime Sleepiness and PSG Parameters

There was significant improvement in symptom (ESS) and some sleep parameters (stage N1, ArI) in the successful group after upper airway surgery, compared with the unsuccessful group (Table II). The postoperative changes in other parameters were not different between the two groups.

CPC Parameters

In the successful group, HFC significantly increased after surgery from 29.6% ± 19.1% to 46.8% ± 18.2%, with a significant reduction in LFC and e-LFC compared to the unsuccessful group (Table III). The results of repeated measures ANCOVA indicated the significant interaction between group (successful vs. unsuccessful) and time (interval between the pre- and postoperative PSG) factor for HFC ($P = .001$), LFC ($P = .002$), and e-LFC ($P = .003$) after controlling age. Changes in other CPC parameters such as VLFC were not different between the two groups.

TABLE I.
Comparison of Preoperative Data Between Surgically Successful and Unsuccessful Groups (N = 62).

	Successful (n = 36)	Unsuccessful (n = 26)	*P* Value
Baseline parameters			
Age, yr	35.9 ± 10.2	40.2 ± 6.0	.016
BMI, kg/m^2	27.0 ± 2.5	26.8 ± 2.2	.776
ESS score	11.5 ± 4.9	9.8 ± 2.4	.353
Sleep parameters			
SE, %	91.2 ± 4.4	89.7 ± 4.6	.212
Stage N1, %	26.3 ± 13.1	27.4 ± 15.2	.754
Stage N2, %	53.7 ± 11.9	54.1 ± 12.7	.914
Stage N3, %	2.2 ± 3.3	1.0 ± 1.8	.110
Stage R, %	17.7 ± 5.5	17.4 ± 4.7	.819
ArI, events/hr	43.1 ± 19.9	42.8 ± 19.7	.949
Respiratory parameters			
AI, events/hr	29.5 ± 21.9	19.6 ± 20.7	.077
AHI-total, events/hr	39.1 ± 24.4	27.8 ± 19.7	.055
AHI-R, events/hr	34.1 ± 25.4	28.1 ± 20.8	.333
AHI-N, events/hr	39.9 ± 25.5	27.8 ± 19.7	.053
Minimum SaO$_2$, %	77.0 ± 11.4	79.1 ± 10.3	.458
CPC parameters			
HFC, %	29.6 ± 19.1	29.5 ± 18.0	.988
LFC, %	58.2 ± 20.6	58.7 ± 20.5	.936
VLFC, %	11.3 ± 6.5	11.1 ± 6.0	.924
Other, %	0.9 ± 1.7	0.8 ± 1.1	.626
e-LFC, %	37.2 ± 21.8	40.2 ± 26.5	.628

Data are presented as mean ± standard deviation.

AHI = apnea-hypopnea index; AHI-N = apnea-hypopnea index during non–rapid eye movement sleep; AHI-R = apnea-hypopnea index during rapid eye movement sleep; AI = apnea index; ArI = arousal index; BMI = body mass index; CPC = cardiopulmonary coupling; e-LFC = elevated low-frequency coupling; ESS = Epworth Sleepiness Scale; HFC = high-frequency coupling; LFC = low-frequency coupling; N = non–rapid eye movement; SaO$_2$ = arterial oxygen saturation; R = rapid eye movement; SE = sleep efficiency; VLFC = very low-frequency coupling.

DISCUSSION

As hypothesized, ECG-derived CPC analysis can detect postoperative improvement of sleep quality in adult OSA patients. In the group successfully treated by upper airway surgery, the amount of HFC increased significantly along with a decrease in LFC. Those changes were parallel to the reduction of sleep-disordered breathing (AHI) and sleep fragmentation (ArI). In the unsuccessful group, CPC profiles did not change after surgery. The study results are concordant with earlier studies that demonstrated a noticeable shift from LFC to HFC in patients treated by continuous positive airway pressure or oral appliance.[14,26] These findings support the potential usefulness of CPC analysis to track sleep quality changes in adult OSA patients who undergo surgical therapy. This may be accomplished practically by a small wearable version of the software device, enabling postoperative tracking (www.sleepimage.com).

At present, the primary measure of surgical efficacy is to define the change in AHI after surgery. The current practice standard recommends that all patients should undergo follow-up evaluation including an objective measure of the presence and severity of sleep-disordered breathing.[27] Recommended objective measures of sleep-disordered breathing are full-night PSG and attended cardiorespiratory sleep study.[28] However, both methods are not always affordable for all the patients who undergo surgical treatment because of the relatively high cost and limited accessibility in clinical settings. Another unanswered issue is when to perform follow-up evaluation. Although postoperative follow-up evaluation is usually performed at postoperative 3 to 6 months, insufficient evidence exists to predict the duration that any immediate postoperative improvement is maintained.[24,27] Therefore, there is strong need for new tracking metrics for the postoperative follow-up, which

TABLE II.
Comparison of Clinical and Polysomnographic Parameters in Successful and Unsuccessful Groups Before and After Surgery (N = 62).

	Successful Group (n = 36)		Unsuccessful Group (n = 26)		
	Before	After	Before	After	*P* Value*
Clinical parameters					
BMI, kg/m^2	27.0 ± 2.5	26.9 ± 2.4	26.8 ± 2.2	26.6 ± 2.6	.914
ESS score	11.5 ± 4.9	5.9 ± 3.1	9.8 ± 2.4	9.3 ± 4.4	.005
Sleep parameters					
SE, %	91.2 ± 4.4	94.2 ± 4.0	89.7 ± 4.6	92.6 ± 4.3	.966
Stage N1, %	26.3 ± 13.1	17.7 ± 8.4	27.4 ± 15.2	27.0 ± 12.9	.020
Stage N2, %	53.7 ± 11.9	58.0 ± 7.5	54.1 ± 12.7	52.0 ± 10.9	.112
Stage N3, %	2.2 ± 3.3	3.2 ± 4.6	1.0 ± 1.8	1.1 ± 2.3	.389
Stage R, %	17.7 ± 5.5	21.1 ± 6.8	17.4 ± 4.7	19.8 ± 5.8	.370
ArI, events/hr	43.1 ± 19.9	18.7 ± 9.1	42.8 ± 19.7	39.8 ± 18.6	<.001
Respiratory parameters					
AI, events/hr of TST	29.5 ± 21.9	2.0 ± 2.3	19.6 ± 20.7	17.3 ± 21.9	<.001
AHI, events/hr of TST	39.1 ± 24.4	6.0 ± 6.3	27.8 ± 19.7	30.0 ± 20.8	<.001
AHI-R, events/hr	34.1 ± 25.4	11.9 ± 13.6	28.1 ± 20.8	25.8 ± 20.7	<.001
AHI-N, events/hr	39.9 ± 25.5	4.3 ± 5.4	27.8 ± 19.7	31.0 ± 21.5	<.001
Minimum SaO$_2$, %	77.0 ± 11.4	86.3 ± 6.5	79.1 ± 10.3	80.0 ± 6.9	.002

Data are presented as mean ± standard deviation.

**P* value using repeated measures analysis of covariance adjusted for age (covariate, age; between-subject factor, successful and nonsuccessful group; within-subject factor, time [time interval between pre- and postoperative polysomnography]).

AHI = apnea-hypopnea index; AHI-N = apnea-hypopnea index during non–rapid eye movement sleep; AHI-R = apnea-hypopnea index during rapid eye movement sleep; AI = apnea index; ArI = arousal index; BMI = body mass index; ESS = Epworth Sleepiness Scale; N = non–rapid eye movement; R = rapid eye movement; SaO$_2$ = arterial oxygen saturation; SE = sleep efficiency; TST = total sleep time.

is easily accessible and repeatable. In these aspects, CPC analysis could be a good alternative to standard full-night PSG.

The CPC analysis is cost-effective and easily accessible because it requires a simple physiologic ECG signal. Moreover, ECG signal has a high signal-to-noise ratio that endows reproducibility between tests at the individual level.[14,15] CPC analysis as a new metric for sleep quality has been validated by correlation analysis between CPC parameters and EEG-based metrics.[14,17] HFC as an indicator of stable sleep correlates well with noncyclic alternating pattern as well as EEG delta spectral power.[14,17]

The CPC technique measures coupled interactions between two physiologic streams. One is respiratory (ECG-derived respiration) and the other is autonomic (HRV), both of which are strongly modulated by sleep. Stable sleep reflects a dominance of sleep promoting mechanisms, which leads to dominance of breath-by-breath respiration coupled activity in autonomic physiology. Increased coupling between HRV and ECG-derived respiration is phenotyped as HFC on CPC analysis. During unstable sleep in OSA, sleep-disordered breathing disrupts coupling of multiple physiologic streams, and coupling between HRV and respiration shifts to a lower frequency, which is indicated as LFC on CPC analysis. Another strength of CPC analysis is that it allows clear switch-like separation of coupling states. As shown in Table I, nearly all of the sleep interval can be separated in to HFC, LFC, or VLFC. The coupling state could not

TABLE III.
Comparison of Cardiopulmonary Coupling Data in Successful and Unsuccessful Groups Before and After Surgery (N = 62).

	Successful Group (n = 36)		Unsuccessful Group (n = 26)		
	Before	After	Before	After	*P* Value*
HFC, %	29.6 ± 19.1	46.8 ± 18.2	29.5 ± 18.0	30.7 ± 18.2	.001
LFC, %	58.2 ± 20.6	37.7 ± 16.0	58.7 ± 20.5	53.8 ± 20.2	.002
VLFC, %	11.3 ± 6.5	14.5 ± 5.0	11.1 ± 6.0	14.3 ± 8.6	.786
Other, %	0.9 ± 1.7	1.1 ± 1.9	0.8 ± 1.1	1.2 ± 2.0	.278
e-LFC, %	37.2 ± 21.8	18.6 ± 14.2	40.2 ± 26.5	35.9 ± 22.7	.003

Data are presented as mean ± standard deviation.

**P* value using repeated measures analysis of covariance adjusted for age (covariate, age; between-subject factor, successful and nonsuccessful group; within-subject factor, time [time interval between pre- and postoperative polysomnography]).

e-LFC = elevated low-frequency coupling; HFC = high-frequency coupling; LFC = low-frequency coupling; VLFC = very–low-frequency coupling;

be determined in a very minor portion of the sleep period (<1%). Because CPC measures coupling and coherence between HRV and respiration, gating of HRV through respiration and vice versa allows clear separation of each state.

With CPC analysis we do not attempt to provide a specific threshold for good (or poor) sleep quality. CPC profiles have significant interindividual variations as shown in Table I and Table III. As in adults, interindividual difference is also high in children.[18] It may be assumed that CPC profiles reflect the individual trait-like character of sleep quality. Trait-like individual difference has been suggested in previous studies of EEG spectral analysis and sleep deprivation.[29,30] Interindividual difference does not necessarily exclude the usefulness of CPC technique in postoperative follow-up. At the individual level, CPC profiles are dependent on the presence of sleep-disrupting stimuli such as sleep-disordered breathing in OSA (Table III). The strength of the CPC technique is the practicality of repeated measures over time, and using clinical and spectrogram information in conjunction for clinical management.

Surgical treatment improves subjective symptoms or quality of life based on various questionnaires in OSA patients.[6,31] However, the effect of upper airway surgery on the objective outcomes such as AHI on PSG remains controversial. There are numerous confounding factors on the objective surgical outcomes including age, sex, BMI, anatomy, and the type of surgical procedure. Metrics other than AHI would be applicable before and after surgical treatment of OSA. As demonstrated here, ECG-based CPC analysis would be a potential candidate as an objective sleep quality measure. Another metric is to measure cardiovascular autonomic regulation. Sympathovagal imbalances or sympathetic surges related to sleep-disordered breathing contribute to the development of cardiovascular diseases in OSA.[32,33] HRV is a surrogate marker of sympathovagal balance. We previously demonstrated that successful upper airway surgery improves cardiovascular autonomic modulation measured by HRV.[10] Although both HRV and CPC analysis are based on ECG signal, CPC differs from conventional HRV assessments in that CPC measures coupling of HRV with respiration. Therefore, frequency bands of CPC analysis are distinct from the standard HRV bands, even though there is overlap of high frequency power on HRV and HFC.[14]

The present study has several limitations. First, the study was retrospective and not case-control in design. Second, there was a significant difference in age between the outcome groups. To minimize the effect of this difference, we adjusted age for the statistical analysis. Third, subjects of this study may not be representative of the general OSA population, especially in that women were not included. Fourth, the number of subjects included was relatively small. Future investigation on a large OSA population including women is necessary to identify the effect of upper airway surgery on objective sleep quality measured by the CPC technique.

CONCLUSION

We demonstrated that successful UA surgery can improve objective sleep quality in adult patients with OSA. CPC metrics of sleep quality are potentially useful to monitor therapeutic responses during long-term postoperative follow-up, as the ECG-based analysis is available as a standalone option outside laboratory polysomnography.

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