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Cardiopulmonary coupling 분석을 이용한 폐쇄성수면무호흡증에서 수면의 질에 관한 연구

Study on sleep quality of obstructive sleep apnea using cardiopulmonary coupling analysis.

2014 년 1 월

서울대학교 대학원

임상의과학과 석사과정

이 우 현

A thesis of the Master’s degree

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Study on sleep quality of obstructive sleep apnea using cardiopulmonary coupling analysis.

by
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A thesis submitted to the Department of Otorhinolaryngology in partial fulfillment of the requirements for the Degree of Master of Science in Medicine (Otorhinolarygology) at Seoul National University College of Medicine

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ABSTRACT

Study on sleep quality of obstructive sleep apnea using cardiopulmonary coupling analysis.

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Background: The aim of this study is (Chapter 1) to evaluate the changes of sleep quality in patients using a mandibular advancement device (MAD) for obstructive sleep apnea (OSA) based upon cardiopulmonary coupling (CPC) and (Chapter 2) to define the success of non-CPAP therapy using CPC analysis in OSA.

Materials and methods: (Chapter 1) A total of 52 patients (mean, 53.7 ± 9.6 years; range, 33–74 years) were included in this study. All subjects were diagnosed with OSA after in-laboratory full-night polysomnography (PSG) and reevaluated after 3 month use of a MAD. We compared CPC parameters at baseline with those after 3 month use of a MAD.

(Chapter 2) A total of 98 OSA patients (mean 51.6 ± 9.5 years; range 33–74 years) with OSA who treated with sleep surgery or MAD were retrospectively included in this study

Results: (Chapter 1) All respiratory indices improved with the use of MAD. However, there were no differences in the sleep architectures except N3 sleep (3.7 ± 4.3 to 6.9 ± 6.4 %, $p < 0.001$). The CPC parameters showed a significant improvement with the use of MAD. Low frequency coupling (59.5 ± 16.1 to 47.7 ± 14.8 %, $p < 0.001$) and elevated low frequency coupling (44.6 ± 18.4 to 32.6 ± 15.7 %, $p < 0.001$) significantly decreased. High frequency coupling (28.6 ± 16.0 to 36.5 ± 15.7 %, $p = 0.004$) and very low frequency coupling (11.7 ± 7.2 to 15.3 ± 6.6 %, $p = 0.028$) significantly increased.

(Chapter 2) The improvement of sleep quality was significant in the success group which was defined as more than 50% reduction of AHI after treatment. Using this criterion, the best cutoff value for success was at LFC_{dec} = 10.1% with a sensitivity of 66.2 % and a specificity of 66.7 %.

Conclusions: (Chapter 1) The CPC parameters showed that the sleep quality was improved by MAD therapy. The CPC analysis may detect a subtle improvement of sleep quality even though patients are unaware of it. (Chapter 2) The criteria of more than 50% reduction of AHI was an optimal criterion to determined successful non CPAP treatment in terms of sleep quality. Using this criterion, the $LFC_{dec} \geq 10.1\%$ cutoff represented clinical value in identifying successful non CPAP therapy.

Key words: Obstructive sleep apnea, Mandibular advancement device, Cardiopulmonary coupling, Treatment success, Sleep quality

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LIST OF ABBREVIATIONS

OSA: obstructive sleep apnea

ECG: electrocardiography

CPC: cardiopulmonary coupling

MAD: mandibular advancement device

ESS: Epworth sleepiness scale

PSQI: Pittsburgh sleep quality index

HFC: high frequency coupling

LFC: low frequency coupling

e-LFC: elevated low frequency coupling

VLFC: very low frequency coupling

AHI: apnea-hypopnea index

REM: rapid eye movement

CPAP: continuous positive airway pressure

HRV: heart rate variability

EDR: electrocardiogram derived respiration

CAP: cyclic alternating pattern

HFC_{inc}: HFC increment

LFC_{dec}: LFC decrement

ROC: receiver operating characteristic

TST: total sleep time

PLM: Periodic leg movement

WASO: wake after sleep onset

AI: apnea index

HI: hypopnea index

ODI: oxygen desaturation index

MR: Mandibular repositioner

UPPP: uvulopalatopharyngoplasty

GA: genioglossus advancement

HS: hyoid suspension

TBS: Tongue base suspension

HM: hypoid myotomy

SSI: subjective symptom improvement

CHAPTER 1

Cardiopulmonary Coupling Analysis of Sleep Quality in Treatment with a Mandibular Advancement Device for Obstructive Sleep Apnea

INTRODUCTION

It seems to clinicians that there are some discrepancies between a subjective improvement of sleep quality and improvements of objective findings in polysomnography with any kind of treatment for obstructive sleep apnea (OSA). Therefore, sleep quality cannot be assessed only by patients' subjective judgment. Though various polysomnographic parameters may be associated with sleep quality, [1-3] another method to assess the quality of sleep with electrocardiography (ECG) has been proposed. [4-6] Among them, an analysis of heart rate variability has been the most commonly used method to evaluate the activity of the autonomic nervous system in OSA. The analysis of heart rate variability is a useful, sensitive, and noninvasive method for measuring the balance between the sympathetic and the parasympathetic activity during sleep. [7] However, the analysis of heart rate variability alone has some limitations in assessing sleep physiology. Certain disease conditions and drugs are associated with a marked reduction in the variability. Moreover, it also varies considerably between individuals and is affected by age and physical conditioning. [8]

Recently, ECG-based cardiopulmonary coupling (CPC) analysis was developed to evaluate the sleep quality as well as sleep disordered breathing in OSA. [8] In the CPC analysis, ECG-derived respiration is also analyzed as a surrogate respiration signal in addition to the heart rate variability. [9] The ECG-derived respiration is extracted from a surface single-lead ECG and calculated from relative positions of the ECG electrode on the chest surface to the heart because transthoracic impedance varies according to the cycle of inspiration and expiration. Thus, the lead axis varies at different points during the respiratory cycle and a precise measurement of the mean cardiac electrical axis shows variations that are correlated with respiration. [8] The information related to the simultaneous heart rate and respiratory dynamics is readily extractable from a continuous single-lead ECG.

A mandibular advancement device (MAD) is one of main treatment modalities for OSA. [10]

The changes of sleep quality have been evaluated using CPC analysis for other treatment modalities, including continuous positive airway pressure [8,11] and adenotonsillectomy. [12] However, there has been no study based on CPC analysis in treatment with MAD until now. The aim of this study was to evaluate the alterations of sleep quality based upon CPC measures in patients with OSA after application of MAD.

MATERIALS & METHODS

Subjects

We retrospectively screened 79 patients who underwent in-laboratory full-night polysomnographies twice before and 3 months after application of a MAD between January, 2011 and September, 2012. Exclusion criteria were as follows: significant arrhythmias including atrial fibrillation, low quality data (artifact more than 20% of total sleep time), less than 4 hours of total sleep time, less than 80% of sleep efficiency. Finally, a total of 52 patients with OSA were included in this study. All patients were treated only with a MAD. To estimate the sleep quality, we calculated the CPC parameters from each polysomnography. Daytime sleepiness was evaluated with Epworth sleepiness scale (ESS) and subjective sleep quality was assessed with Pittsburgh sleep quality index (PSQI).

Cardiopulmonary coupling analysis

The CPC was measured on the exported single-lead ECG data using a polysomnography software RemLogic 2.0 CPC analyzer (Embla Systems, San Carlos, CA, USA). Thomas and his colleagues described technical details regarding how to process the data in a previous study. [8] Details of the method have been published and are also available in the online Appendix (www.journalsleep.org). The CPC analyzer, in accordance with the published algorithms, determined the amount and frequency of coupling between ECG-derived respiration and heart rate variability, including high frequency coupling (HFC; 0.1 - 0.4 Hz), low frequency coupling (LFC; 0.01 - 0.1 Hz), elevated low frequency coupling (e-LFC; a subset of LFC) and very low frequency coupling (VLFC; 0.001 - 0.01 Hz).

Statistical Analysis

Data analysis was performed using SPSS (version 18, Chicago, IL). All the values are

expressed as means ± standard deviation unless otherwise specified. We used paired t test to compare the differences of parameters before and after application of a MAD. The Pearson correlation analysis was employed to evaluate the relationship between two continuous variables. A p-value < 0.05 was considered significant.

RESULTS

Demographic and polysomnographic characteristics

Of the 52 patients, there were 47 males (90.4 %) and 5 females (9.6 %) with a mean age of 53.7 ± 9.6 (range, 33-74) years. The mean body mass index was 25.2 ± 2.3 kg/m^2.

The mean total sleep time was 396.1 ± 52.3 minutes with the mean apnea-hypopnea index (AHI) of 33.6 ± 17.0 /hour. The results of polysomnography before and after MAD therapy are summarized in **Table 1**.

Among the sleep parameters, the total sleep time and wake time after sleep onset were not changed by MAD treatment. Respiratory arousal and periodic leg movement, which represent

	Baseline	With MAD	*p* value
Sleep parameters			
TST, min	396.1 ± 52.3	394.3 ± 46.1	0.832
WASO, min	56.5 ± 36.1	50.5 ± 33.9	0.255
Respiratory arousal, /hour	26.2 ±17.9	8.9 ± 10.6	< 0.001
PLM, /hour	4.4 ± 9.7	9.1 ± 18.8	0.013
Sleep stage, % of TST			
N1	13.7 ± 7.3	10.1 ± 10.6	0.018
N2	52.0 ± 11.2	52.1 ± 10.4	0.935
N3	3.7 ± 4.3	6.9 ± 6.4	< 0.001
REM	18.3 ± 7.2	19.7 ± 5.6	0.175
Respiratory index			
AHI, /hour	33.6 ± 17.0	13.1 ± 12.6	< 0.001
AI, /hour	19.7 ± 17.2	5.1 ± 9.1	< 0.001
Average apnea duration, sec	26.8 ± 7.0	21.3 ± 10.0	< 0.001
HI, /hour	13.9 ± 7.4	8.0 ± 6.3	< 0.001
ODI, /hour	25.6 ± 17.4	8.8 ± 9.4	< 0.001
Minimal Oxygen sat, %	80.7 ± 6.1	84.0 ± 5.8	< 0.001
Average Oxygen sat, %	95.2 ± 1.4	95.5 ± 1.2	0.110

Table 1. In-laboratory full-night polysomnographic parameters without and with a mandibular advancement device (MAD) in patients with obstructive sleep apnea.

the degree of sleep fragmentation, were significantly decreased by MAD application (p < 0.001 and P = 0.013, respectively). The proportion of sleep stages did not change except N3 sleep (3.7 ± 4.3 to 6.9 ± 6.4 %, p < 0.001). Most of the respiratory indices (apnea-hypopnea index, AHI; apnea index, AI; average apnea duration; hypopnea index, HI; oxygen desaturation index, ODI; and minimal oxygen saturation) were significantly improved by MAD treatment.

Parameters of cardiopulmonary coupling

The parameters of CPC analysis were significantly changed by MAD therapy (**Figure 1**). The HFC and VLFC were significantly increased (p = 0.004 and 0.028, respectively), while LFC and e-LFC were significantly decreased (p < 0.001 in both) (**Table 2**).

CPC parameters	Baseline	With MAD	*p* value
HFC, %	28.6 ± 16.0	36.5 ± 15.7	0.004
LFC, %	59.5 ± 16.1	47.7 ± 14.8	< 0.001
VLFC, %	11.7 ± 7.2	15.3 ± 6.6	0.028
Other, %	0.3 ± 0.4	0.5 ± 0.8	0.066
e-LFC, %	44.6 ± 18.4	32.6 ± 15.7	< 0.001

Table 2. Changes in parameters of cardiopulmonary coupling (CPC) after use of a mandibular advancement device (MAD) in patients with obstructive sleep apnea.

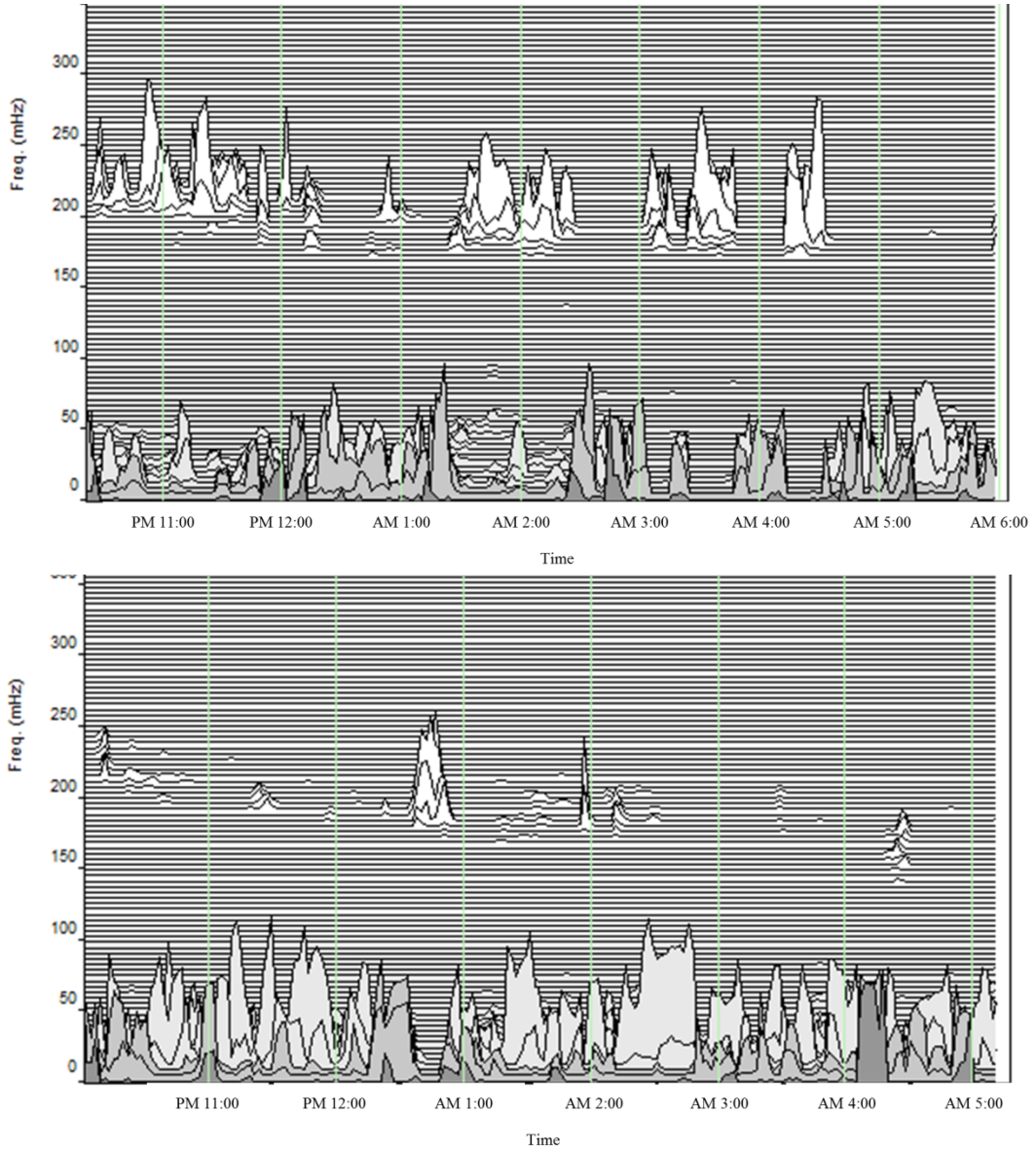

Figure 1. A representative cardiopulmonary coupling analysis spectrograph across 7 – 8 hours of sleep in a 56-year-old man with obstructive sleep apnea. His apnea hypopnea index was decreased from 57.6 to 19.2/ h with a mandibular advancement device (MAD). While, there was a preponderance of low frequency coupling without a MAD (above), there was a marked increase in high frequency coupling and a decrease in low frequency coupling with a MAD (below).

Relationship between changes of AHI and CPC parameters

The change in HFC after MAD therapy was negatively correlated with the change in AHI (r = -0.572, p < 0.001). On the other hand, the changes in LFC and e-LFC after MAD application were positively correlated with the change in AHI. (r = 0.604 and 0.497, p < 0.001, respectively). However, the change in VLFC showed no significant correlation with the change in AHI (**Table 3**).

	AHI change	HFC change	LFC change	VLFC change	e-LFC change
AHI change	1				
HFC change	-0.572**	1			
LFC change	0.604**	-0.821**	1		
VLFC change	-0.111	-0.192	-0.400**	1	
e-LFC change	0.497**	-0.734**	0.866**	-0.306*	1

Table 3. Correlations between changes in apnea-hypopnea index (AHI) and cardiopulmonary coupling (CPC) parameters after use of a mandibular advancement device. (**; < 0.001, *; < 0.05)

	ESS change	p value	PSQI change	p value
HFC change	-0.196	0.219	-0.124	0.439
LFC change	0.178	0.265	0.032	0.844
VLFC change	-0.010	0.948	0.119	0.460
e-LFC change	0.173	0.281	-0.050	0.755

Table 4. Correlations between changes cardiopulmonary coupling parameters (CPC) and changes of questionnaire scores after use of a mandibular advancement device.

Changes in daytime sleepiness and subjective sleep quality

The mean ESS score was 10.2 ± 4.6 at baseline and it was significantly decreased to 8.5 ±

4.0 by MAD therapy (p = 0.009). Also, the mean PSQI score was significantly decreased (5.9 ± 2.9 to 4.6 ± 2.3, p = 0.001). However, the changes in the ESS and PSQI did not show any significant correlation with the changes in the CPC parameters (**Table 4**).

DISCUSSION

Good quality sleep might be defined as sleep with more physiologic sleep architecture and a normal pattern of sleep-related breathing from the standpoint of medical professionals. However in an actual clinical setting, we encounter patients who feel good in spite of their abnormal sleep architecture and sleep-related breathing disorder. Thus, it is so far unclear how to quantitatively evaluate the sleep quality. The CPC has been developed as alternative method to evaluate the sleep quality since Thomas and his colleagues reported a closer relationship between cyclic alternating pattern scoring system and CPC scoring system. [8] Among the CPC parameters, the HFC is associated with breath-to-breath stability of tidal volumes and physiologic respiratory sinus arrhythmia, so it is a biomarker of stable and consolidated sleep. On the other hand, the LFC is related to breath-to-breath fluctuation of tidal volumes and cyclic variations in a heart rate, reflecting unstable and fragmented sleep. [11] The VLFC is associated with wake or rapid eye movement (REM) period and e-LFC is associated with probable apneas or hypopneas. [8,11] Healthy subjects show a predominance of HFC, while those with untreated OSA show a predominance of LFC. Though HFC and LFC have an only weak correlation with the standard sleep staging system, LFC is associated with cyclic alternating pattern (unstable sleep) and HFC is associated with non-cyclic alternating pattern (stable sleep) in the cyclic alternating pattern scoring system. [13] Thus, the CPC analysis can be used for evaluation of treatment efficacy including sleep quality [12,14] as well as OSA screening [15,16] because it reflects sleep instability.

Our study showed significant improvements in the respiratory indices with MAD application. The proportion of sleep stage N3 was increased by use of the MAD, which was also shown in successful continuous positive airway pressure therapies. [17,18] The CPC parameters were also significantly changed with MAD application. We found a switch from LFC dominance

to HFC dominance which means improvement of the sleep quality. [8] Though there are studies on CPC analysis in patients treated with continuous positive airway pressure [11,14] or adenotonsillectomy, [12] there has been no study in patients treated with a MAD. To our knowledge, this is the first study that showed sleep quality improvement with MAD application in terms of CPC.

Among the CPC parameters, VLFC and e-LFC also showed significant changes with MAD application. The VLFC, which is associated with REM period, showed a significant increase though a duration of REM sleep only showed an increasing tendency without a statistical significance. It is conceivable that the change in VLFC might represent an improvement of REM sleep quality better than the change of REM sleep proportion. This is a new finding in our MAD study because the previous CPC studies did not show significant changes in VLFC. [12,19]

The changes in HFC, LFC and e-LFC showed significant correlations with the change in AHI. Given this result, the changes of these parameters may be potential surrogates which can simply evaluate a treatment outcome in patients with OSA in that the parameters of CPC can be calculated from a single-lead ECG. Interestingly, even though VLFC were improved after a MAD was applied, their changes were not correlated with the change in AHI. This might imply that the change of sleep quality is not necessarily interpreted in terms of AHI.

The sleep quality which was subjectively measured with questionnaires was also improved by using a MAD. However, the change in subjective sleep quality caused by MAD therapy had no correlation with the changes in CPC parameters. This finding suggests that CPC analysis might detect a subtle improvement of sleep quality even though patients are unaware of it and might be considered more valuable in the evaluation of sleep quality than questionnaires.

This study also has several limitations. Firstly, our study included a limited number of patients. However, the improvement with MAD use was consistent in most of the patients. A

subsequent large population-based research is required to consolidate the clinical implications of CPC parameters in MAD therapy for OSA. Secondly, the clinical implications of CPC parameters are still lacking in terms of co-morbidities. As the correlation between AHI and cardiovascular complications is well established, whether the sleep quality based upon CPC analysis is related with co-morbidities should be more studied. Thirdly, because this was a retrospective study, a selection bias was likely to be present. However, because comparisons were made between before and after treatment in the same patients, the bias may not be great. In a future study, it would be better to design a prospective study and set a control group.

CONCLUSIONS

This is the first study to analyze the outcome of MAD therapy for OSA based upon the CPC parameters. We could identify that MAD treatment increased HFC and decreased LFC, suggesting that sleep became more stable and the quality of sleep was improved. In addition to the conventional polysomnographic analysis, the CPC analysis may also be used to assess treatment outcomes including sleep quality in patients treated with a MAD for their OSA. In future, a controlled prospective study is needed to validate the change in sleep quality based upon CPC analysis and to identify the relationship between CPC parameters and occurrence of co-morbidities of OSA.

CHAPTER 2

Defining success of non-CPAP treatment for obstructive sleep apnea in terms of sleep quality using cardiopulmonary coupling analysis.

INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent disease characterized by repeated episodes of partial or complete obstruction of the upper airways during sleep. [20] Many treatment methods such as weight loss, continuous positive airway pressure (CPAP), oral appliances, and surgery of the upper airway have been proposed for OSA since the first description in the medical literature. [21-23] Among them, CPAP is regarded as the gold standard in treatment of OSA in many countries after introduced in 1981 by Sullivan.[24]

It is essential to define a success in treatment of OSA, because the effective management of OSA results in decreased co-morbidities such as hypertension, heart failure, arrhythmia, coronary artery disease, and stroke. [25-29] Since CPAP is titrable to make apnea hypopnea index (AHI) less than 5, adherence is a major problem of successful treatment. [30] Unfortunately, the compliance and long-term acceptance of CPAP is relatively low. On contrary, compliance rate is 70% to 90% in the oral appliance, [31-33] even it is meaningless to argue on compliance in the sleep surgery. For this reason, efficacy is a major concern of non-CPAP therapy in evaluation of treatment success. However, there is no established definition of success and the criteria of success in non-CPAP therapy vary depending on the studies. There is need for standard criterion to compare the effects of successful sleep surgery or oral appliance therapy. Nevertheless, it is too difficult to define the success in sleep surgery or oral appliance therapy because of the lack of evidence from randomized controlled trials or the ethical limitations of this trial.

Cardiopulmonary coupling (CPC) measures coupling between heart rate variability (HRV) and electrocardiogram derived respiration (EDR) amplitude modulations and thresholds this behavior to correlate with sleep stability states. [8] CPC could evaluate the sleep quality as well as the sleep stage with parameters and shows a closer relationship with cyclic alternating pattern (CAP) scoring system. [8,11,16] We hypothesized that significant improvement in

sleep quality could be a landmark for successful outcome in non-CPAP therapy, while unsuccessful treatment would not be associated with remarkable changing in sleep quality. The aim of this study was to define the success criteria of non-CPAP therapy for OSA in terms of sleep quality using CPC analysis.

MATERIALS & METHODS

Subjects

We retrospectively screened 1464 patients who underwent full-night attended polysomnography (PSG) at our sleep center between January 2011 and March 2013. Among them, total of 804 patients were diagnosed having OSA. Of them, 96 patients were underwent sleep surgery (uvulopalatal flap, uvulopalatopharyngoplasty, expansion sphincter pharyngoplasty, lingual tonsillectomy, lateral pharyngoplasty, tongue base radiofrequency, genioglossus advancement and/or partial epiglottectomy) and 143 patients were treated with mandibular advancement device (MAD). According to the protocol of the center, the follow-up PSG was performed at least 3months after surgery or MAD application. Total of 119 patients underwent full-night attended PSG at both baseline and 3 months after treatment. Patients who developed significant arrhythmias including atrial fibrillation, had low quality data (artifact more than 20% of total sleep time), total sleep time less than 4 hours, and/or sleep efficiency less than 80% were excluded. Of this process, 17 patients were excluded. Patients with history of major cardiovascular disease (angina, myocardial infarction, or stroke), insomnia, peripheral vascular disease, neuropathy, or previous history of sleep surgery were also excluded. Four patients were excluded because of the past medical history. Finally, a total of 98 patients (33 with sleep surgery and 65 with MAD) with OSA were included in this study. To estimate the sleep quality, we extracted the CPC indices from each PSG. Subjective sleep quality of the patient was evaluated by the Epworth Sleepiness Scale (ESS) and the Pittsburgh Sleep Quality Index (PSQI).

Cardiopulmonary Coupling Analysis

CPC was measured on the exported single-lead ECG data using the commercially available PSG software RemLogic 2.0 CPC analyzer (Embla Systems, San Carlos, CA, USA). Thomas

and his colleagues described technical details regarding how to process the data in the previous study. [8] Combining HRV and EDR produce high (HFC; 0.1-0.4 Hz), low (LFC; 0.01-0.1 Hz), very low frequency (VLFC; 0.001-0.01 Hz), and elevated-low frequency coupling (e-LFC). HFC is associated with breath-to-breath stability of tidal volume and physiologic respiratory sinus arrhythmia, so it is a biomarker of stable and consolidated sleep. While, LFC is related to breath-to-breath cycles of fluctuation tidal volumes and cyclic variation in heart rate, thus it reflects unstable and fragmented sleep. [11] From these backgrounds, successful treatment of OSA is associated with a switch from LFC to HFC. [8,11] Thus, we considered sleep quality improvement as HFC increment (HFC_{inc}) and LFC decrement (LFC_{dec}) were induced simultaneously after treatment.

Assessment of treatment results

Subjects were divided into success and failure groups depending on 7 success criteria, respectively. Success was defined as followed;

1) A post-treatment AHI lower than 10

2) A post-treatment AHI lower than 20

3) More than 50% reduction of AHI and a post-treatment AHI lower than 10

4) More than 50% reduction of AHI and a post-treatment AHI lower than 15

5) More than 50% reduction of AHI and a post-treatment AHI lower than 20

6) More than 50% reduction of AHI

7) Subjective symptom improvement after treatment

Those who did not meet these criteria were included in the failure group.

Sleep quality evaluation using questionnaire

We performed estimation of day time sleepiness with Epworth Sleepiness Scale (ESS), and

also evaluation of subjective sleep quality with Pittsburgh Sleep Quality Index (PSQI). The ESS is an eight-item self-reported questionnaire asking the subject how patient is to doze off or fall asleep in different situations using a 4-pont likert scale. [34] The PSQI is a self-reported questionnaire which assesses sleep quality and disturbances over a 1-month time interval using likert and open-ended response formats. Seven component scores of the PSQI questionnaire are generated from 19 individual items and the sum of scores for these 7 components yields one composite score. [35] Eighty-four of 98 (85.7%) patients answered the questionnaire at both the baseline and 3 month after treatment. We defined subjective symptom improvement as both ESS and PSQI score declined more than 1 point after treatment.

Statistical Analysis

Data analysis was performed using SPSS (version 18, Chicago, IL). All the values are expressed as means ± standard deviation unless otherwise specified. We used paired *t* test to evaluate the differences on the CPC parameters between the success and the failure group depending on 7 success criteria. We also performed logistic regression analysis to determine the optimal success criterion of non-CPAP therapy which represented improvement of sleep quality in the success group, while it did not induced in the failure group. Another statistical analysis was performed to determine an adequate cut-off point for the best correlation between the optimal success criterion and the CPC parameters. The cut-off value was calculated using a receiver operating characteristic (ROC) curve. Statistical significance was attributed to mean differences with P values < 0.05.

RESULTS

Demographics

Of the 98 patients, there were 85 males (86.7 %) and 13 females (13.3 %) with a mean age of 51.5 ± 9.9 (range, 19-74) years. The mean BMI of enrolled patients was 25.6 ± 2.6 kg/m^2. There was no significant difference between the sleep surgery and the MAD group in demographics, except age (45.2 ± 6.4 years, sleep surgery group; 53.4 ± 10.0 years, MAD group; $P < 0.001$).

Baseline versus MAD application

The results of full-night attended PSG, CPC analysis, and subjective symptom score are summarized in **Table 1**.

	Baseline	With therapy	*P*-value
Polysomnographic index			
TST, min	394.5 ± 50.2	404.8 ± 48.3	0.101
WASO, min	57.3 ± 37.0	47.3 ± 31.1	0.009
Respiratory arousal, /hour	25.7 ±17.1	10.9 ± 12.0	< 0.001
AHI, /hour	34.3 ± 18.0	16.3 ± 15.6	< 0.001
AI, /hour	19.8 ± 18.1	6.9 ± 12.2	< 0.001
Average apnea duration, sec	26.6 ± 8.7	21.8 ± 10.6	< 0.001
HI, /hour	14.5 ± 8.3	9.4 ± 7.3	< 0.001
ODI, /hour	25.4 ± 16.7	11.5 ± 12.6	< 0.001
Minimal Oxygen saturation, %	79.8 ± 6.5	83.3 ± 6.0	< 0.001
Average Oxygen saturation, %	95.1 ± 1.8	95.6 ± 1.4	0.002
Snoring, %	34.9 ± 19.6	29.1 ± 20.0	0.005
Cardiopulmonary coupling index			
HFC, %	30.2 ± 17.1	37.4 ± 16.7	< 0.001
LFC, %	57.4 ± 17.7	46.9 ± 16.5	< 0.001
VLFC, %	12.2 ± 7.0	15.2 ± 8.4	0.002
e-LFC, %	42.2 ± 18.6	31.5 ± 17.5	< 0.001
Other, %	0.4 ± 0.5	0.5 ± 1.0	0.166
Subjective symptom index			
ESS	10.6 ± 4.5	8.4 ± 4.3	< 0.001
PSQI	5.7 ± 3.1	4.7 ± 2.4	0.004

Table 1. Changes in the sleep-related parameters before and after treatment in patient with obstructive sleep apnea.

Among the PSG parameters, the total sleep time (TST) of the baseline was not significantly different from that of post-therapy. However, wake after sleep onset (WASO) and most of the respiratory index (AHI; apnea-hypopnea index, AI; apnea index, average apnea duration, HI; hypopnea index, ODI; oxygen desaturation index, minimal oxygen saturation, average oxygen saturation and snoring) were significantly decreased after non-CPAP therapy. The parameters of the sleep quality using CPC analysis also showed significant change after treatment. HFC and VLFC were significantly increased ($P < 0.001$ and $P = 0.002$, respectively), while LFC and e-LFC were significantly decreased ($P < 0.001$, respectively) after non-CPAP therapy. Participants' mean ESS score was 10.6 ± 4.6 at the baseline. ESS scores significantly decreased to 8.4 ± 4.3 after non-CPAP therapy ($P < 0.001$). On the PSQI, the mean score also significantly decreased after therapy (5.7 ± 3.1 to 4.7 ± 2.4, $P = 0.004$). In the subgroup analysis, the MAD and the surgery group showed no differences in most of parameters except AHI decrement (19.6 ± 13.4 versus 12.6 ± 16.8, P = 0.042).

The rate of success ranged from 44.0% to 70.4% depending on the criteria and metric used to define a successful outcome (**Table 2**). With the criterion of a post-treatment AHI lower than 20, 69 of 98 (70.4%) patients met the criteria of success. However, 44% (37 of 84) patients were classified as the success group with the criterion of subjective symptom improvement.

Success criteria	Success	Failure	Percentages of success
AHI<10/h	47	51	48.0 %
AHI<20/h	69	29	70.4 %
AHI<10/h and 50% reduction	44	54	44.9 %
AHI<15/h and 50% reduction	54	44	55.1 %
AHI<20/h and 50% reduction	59	39	60.2 %
50% reduction	65	33	66.3 %
Subjective symptom improvement	37	47	44.0 %

Table 2. Percentages of patients reported as having a successful outcome where success is defined according to the different success criteria.

CPC analysis according to the success criteria

Change in parameters of CPC with non-CPAP therapy

Subjects were divided to the success and the failure group depending on the different 7 success criteria. Among the criteria, when we adapted 3 criteria; a post-treatment AHI lower than 20; more than 50% reduction of AHI and a post-treatment AHI lower than 20; more than 50% reduction of AHI, sleep quality improvement of the success group was differ from that of the failure group. However, with others criteria; a post-treatment AHI lower than 10; more than 50% reduction of AHI and a post-treatment AHI lower than 10, both the success and the failure

		Success			Failure		
Success criteria	CPC parameters	Baseline	With therapy	*P*-value	Baseline	With therapy	*P*-value
AHI<10/h	HFC, %	35.9 ± 13.1	43.2 ± 15.2	< 0.001	25.0 ± 18.7	32.1 ± 16.4	0.006
	LFC, %	51.0 ± 13.8	41.2 ± 13.6	< 0.001	63.3 ± 18.9	52.1 ± 17.3	< 0.001
AHI<20/h	HFC, %	33.4 ± 14.4	41.1 ± 16.1	< 0.001	22.7 ± 20.5	28.8 ± 15.2	0.108
	LFC, %	54.3 ± 15.2	41.9 ± 13.7	< 0.001	64.6 ± 21.0	58.8 ± 16.7	0.130
AHI<10/h and 50% reduction	HFC, %	35.7 ± 13.4	43.4 ± 15.1	< 0.001	25.8 ± 18.5	32.6 ± 16.5	0.006
	LFC, %	51.7 ± 13.9	40.8 ± 13.0	< 0.001	62.0 ± 19.1	51.8 ± 17.5	< 0.001
AHI<15/h and 50% reduction	HFC, %	33.5 ± 14.4	42.4 ± 16.0	< 0.001	26.1 ± 19.2	31.3 ± 15.6	0.071
	LFC, %	54.3 ± 15.0	40.6 ± 13.1	< 0.001	61.1 ± 20.1	54.5 ± 17.1	0.027
AHI<20/h and 50% reduction	HFC, %	33.5 ± 15.0	42.0 ± 16.3	< 0.001	25.2 ± 18.8	30.5 ± 14.9	0.072
	LFC, %	54.5 ± 15.6	40.8 ± 13.2	< 0.001	61.7 ± 19.9	56.1 ± 16.8	0.083
50% reduction	HFC, %	30.9 ± 16.7	41.1 ± 16.4	< 0.001	29.0 ± 17.9	30.3 ± 15.0	0.629
	LFC, %	57.5 ± 17.7	42.4 ± 14.4	< 0.001	57.1 ± 17.9	55.8 ± 16.8	0.642
Subjective symptom improvement	HFC, %	24.3 ± 12.6	31.2 ± 15.3	0.088	28.5 ± 20.6	36.5 ± 18.6	0.011
	LFC, %	64.0 ± 14.1	48.0 ± 12.1	0.001	59.0 ± 20.8	48.1 ± 18.7	0.001

Table 3. Changes in parameters of electrocardiogram-based cardiopulmonary coupling on treatment according to the success criteria.

group showed significant improvement in sleep quality. With the criterion of more than 50% reduction of AHI and a post-treatment AHI lower than 15, the success group significantly improved in sleep quality while the failure group partly improved (LFC change, $P = 0.027$). In contrast, the success group partly improved (LFC change, $P = 0.001$), while the failure group showed significant improvement in sleep quality with the criterion of subjective symptom improvement (**Table 3**).

The optimal success criteria in terms of sleep quality

In the logistic regression model (**Table 4**), the success group showed significant improvement in sleep quality with the criterion of more than 50% reduction of AHI. However, the rest of 6 criteria were related with partly or not significant improvement in sleep quality. After adjustment for age, sex, body mass index, and treatment modality (sleep surgery or MAD), the success group who responsible for the criterion of more than 50% reduction of AHI still showed only significant effects on the sleep quality improvement (adjusted OR, 1.041; 95% CI, 1.008-1.076 for HFC_{inc} and adjusted OR, 1.061; 95% CI, 1.025-1.099 for LFC_{dec}) (**Table 4**).

The best cutoff value for success criteria

Among the 7 success criteria, ′More than 50% reduction of AHI′ after non-CPAP therapy showed the most discriminable results between the success and the failure group in CPC parameters. Using this criterion, ROC (receive operation characteristics) studies were conducted for HFC_{inc} (HFC increment) and LFC_{dec} (LFC decrement) to find an optimal thresholds. Both CPC parameters attained significant power to discriminate success from patients who treated with non-CPAP therapy. By comparing the area under curve (AUC) of ROC, the best overall single predictive parameter was LFC_{dec} (AUC = 0.717; 95% CI, 0.609-

0.825). When selecting 10.1% as the optimal cut-off point for LFC_{dec}, a specificity of 66.2% and sensitivity of 66.7% were obtained (**Figure 1**).

Success criteria	CPC change	Crude (95% CI)	*P*-value	Adjusted (95% CI)	*P*-value
AHI<10/h	HFC_{inc}	1.001 (0.975-1.027)	0.960	0.997 (0.969-1.026)	0.835
	LFC_{dec}	0.995 (0.971-1.019)	0.668	0.989 (0.963-1.015)	0.392
AHI<20/h	HFC_{inc}	1.007 (0.979-1.036)	0.634	1.003 (0.972-1.034)	0.860
	LFC_{dec}	1.025 (0.997-1.053)	0.078	1.022 (0.992-1.054)	0.146
AHI<10/h and 50% reduction	HFC_{inc}	1.004 (0.978-1.030)	0.774	1.001 (0.973-1.030)	0.956
	LFC_{dec}	1.002 (0.979-1.027)	0.840	0.998 (0.973-1.024)	0.885
AHI<15/h and 50% reduction	HFC_{inc}	1.016 (0.990-1.043)	0.233	1.012 (0.983-1.042)	0.418
	LFC_{dec}	1.028 (1.001-1.054)	0.039	1.023 (0.995-1.052)	0.104
AHI<20/h and 50% reduction	HFC_{inc}	1.013 (0.986-1.040)	0.340	1.010 (0.981-1.040)	0.512
	LFC_{dec}	1.032 (1.005-1.060)	0.021	1.030 (1.001-1.060)	0.040
50% reduction	HFC_{inc}	1.041 (1.010-1.073)	0.009	1.041 (1.008-1.076)	0.016
	LFC_{dec}	1.061 (1.027-1.096)	< 0.001	1.061 (1.025-1.099)	0.001
Subjective symptom improvement	HFC_{inc}	1.005 (0.978-1.033)	0.708	1.007 (0.977-1.037)	0.668
	LFC_{dec}	1.008 (0.983-1.034)	0.536	1.011 (0.983-1.040)	0.430

Table 4. The changes in cardiopulmonary coupling parameters for the success according to the different success criteria

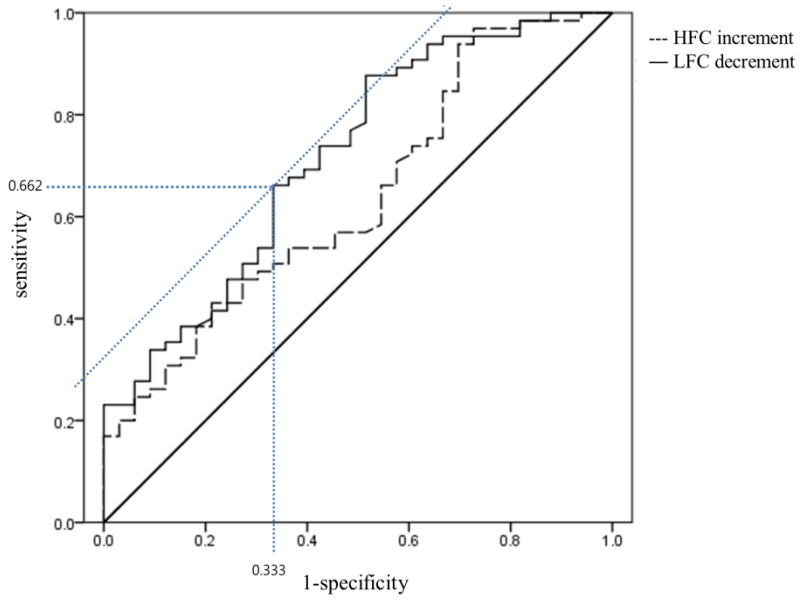

Figure 1. A receiver operating characteristic (ROC) curve for change in CPC parameters. The best cutoff value for successful treatment was at $LFC_{dec} \geq$ 10.1% with a sensitivity of 66.2% and specificity of 66.7%.

DISCUSSION

CPAP is the treatment of choice for OSA, however, sleep surgery or oral appliance could be alternative therapies for the OSA. [36] Consistent CPAP treatment has proven to be effective in improving the cardiovascular morbidity in OSA patients. [37] However, despite the potentially high effectiveness of CPAP, the compliance and long-term acceptance is relatively low and even 20% to 40% of CPAP user will discontinue within 3 months, resulting in a limited clinical effectiveness. [38,39] In our study, non-CPAP therapy significantly improved sleep disordered breathing (**Table 1**). Sleep quality which was measured by both subjective (questionnaire) and objective (CPC analysis) method were also significantly improved with non-CPAP therapy. Regarding the relatively high compliance of non-CPAP therapy, these results represent the sleep surgery or the oral appliance is eligible therapy for the OSA treatment. In the subgroup analysis, the MAD group showed significant effect on AHI than the sleep surgery group. However, inequality of subject (33 with sleep surgery versus 65 with MAD) and age difference (45.2 years in sleep surgery group versus 53.4 years in MAD) would weaken the discrepancy of AHI change between groups.

There is no absolute definition of successful outcome with non-CPAP therapy and the criteria of success are various depending on the studies. [40] Some physicians adapted subjective symptom improvement as a criterion of successful treatment[41], another thought a percentage of reduction of AHI [33,42], others proposed success based on absolute decreased value of AHI [43-46], and the others defined combination of those[47,48,31,49-58] (**Table 5**). Since the diversity of criteria, the rate of success ranged also varies depending on the criteria and metric used to define a successful outcome. [59]

We applied 7 criteria which are used in previous other studies for evaluation of the treatment efficacy in sleep surgery or oral appliance. In our study, the rate of success raged from 44.0%

to 70.4% according to the definition of treatment success. Elshaug[60] also reported that the success rate was different according to criteria. Phase I surgical procedures is 55% with traditional success criteria (AHI<20/h and 50% reduction), 31.5% with AHI $\leq$ 10, and 13% with AHI $\leq$ 5 defined as success. Consensus is needed among the arbitrary cut-off definition of success to make an objective assessment for non-CPAP therapy.

To determine the optimal criteria of successful OSA therapy among the different criteria, randomized control trial or large population-based cohort study is ideal which prove how much AHI improvement on therapy is related to the decreased mortality or morbidity of OSA. However, it is not so simple study, since these kinds of studies need a large amount of time and dedication. Moreover, it is unethical to leave the patients in the treatment failure group untreated for a longer time. [61] To overcome these limitations, we applied CPC parameters as an experimental verification of defining the success criteria for OSA therapy.

Study	Treatment modality	Definition of success
Woodson BT et al. 2000[41]	Pharyngeal suspension	SSI
Liu Y et al. 2000[43]	MR	RDI<10/h
Bettega G et al. 2000[47]	Maxillofacial surgery	AHI<15/h and≥50% reduction
Verse T et al. 2000[56]	Tonsillectomy	AHI<20/h and≥50% reduction
Yoshida K 2001[46]	Oral appliance	AHI<10/h
Vilaseca I et al. 2002[58]	UPPP + GA + HS	AHI<20/h and SSI
W-E ML et al. 2002[42]	UPPP or dental appliance	≥50% reduction of AI
Marklund M et al. 2004[44]	MAD	AHI<10/h
Friedman M et al. 2005[49]	UPPP	AHI<20/h and≥50% reduction
Vicente E et al. 2006[57]	TBS + UPPP	AHI<20/h and≥50% reduction and SSI
Yin SK et al. 2007[45]	UPPP + GA + HS	AHI<20/h
Foltan R et al. 2007[48]	GA + HM	AHI<20/h and ≥50% reduction
Lettieri CJ et al. 2011[54]	Oral appliance	AHI<5/h, AHI<10/h and SSI
Lee CH et al. 2011[53]	UPPP	AHI<20/h and≥50% reduction
Tanyeri H et al. 2012	UPPP	AHI≥50% reduction and SSI
Hou T et al. 2012[51]	Tongue coblation	AHI<20/h and≥50% reduction
Friedman M et al. 2012[31]	MAD	AHI<20/h and≥50% reduction
Lee CH et al. 2012[52]	MAD	AHI<10/h and≥50% reduction
Gunawardena I et al. 2013[50]	Lingualplasty	AHI<15/h and≥50% reduction
Lee WH et al. 2013[33]	MAD	≥50% reduction of AHI

Table 5. The criteria of success vary depending on the studies.

With 3 criterion (AHI<20/h, AHI<20/h and 50% reduction, and AHI 50% reduction), improvement of the all CPC parameters showed only in the success group, while failure group showed any differences between baseline and non-CPAP therapy (**Table 3**). However, with AHI<10 or AHI<15, some CPC parameter was improved even in the failure group. This result supports the success criteria of AHI<10 or AHI<15 is strict criteria in terms of sleep quality. For example, 48 years old man classified to the failure group with criteria of AHI limitation (less than 10 or 15) even though remarkable decreased in AHI (74.3 to 19.8/h), though the sleep quality were significantly improved (HFC; 3.1 to 42.3 % and LFC; 91.2 to 36.0 %) with sleep surgery. Given that our result showed the criterion of the success which is defined as AHI of less than 20 is more applicable than less than 10 or 15 in terms of the sleep quality. Subjective symptom improvement is important because of patients often seek physician with recognizing their symptom. However, lots of OSA patients do not know their symptoms at night and some patients unrecognized their day time symptom, such as morning headache or sleepiness. [62,63] From this point of view, subjective symptom is not enough to fulfill the successful treatment. Our study once again confirmed the discrepancy between improvement of subjective symptom and objective sleep quality. Inversely, HFC significantly increased in the failure group which was divided according to the criteria of subjective symptom improvement and LFC significantly decreased regardless symptom improvement.

In a logistic model, we found ‘more than 50% reduction of AHI’ is the optimal criterion to represent the successful outcome of therapy in terms of sleep quality. Applying this criterion, 1% HFC_{inc} increased the success rate 1.041 times and 1% LFC_{dec} elevated the success rate 1.061 times with statistical significance. After adjusting for age, sex, BMI, and treatment modality (surgery or MAD), CPC changes still have significant effects on the successful outcome of therapy with this criterion. Becker[64] reported that a 50% reduction in AHI induced minimal reduction in arterial blood pressure, while a 95% reduction in AHI made

significant drop in arterial blood pressure on CPAP therapy for OSA. Ever since, there has been no report on how much percentage reduction in AHI is related with efficacy of OSA therapy. We found ‘more than 50% reduction of AHI’ was sufficient to represent successful outcome of non-CPAP therapy in terms of sleep quality.

Using the success criterion of ‘more than 50% reduction of AHI’, $LFC_{dec} \geq 10.1$ % demonstrated intermediate sensitivity (66.2%) and specificity (66.7%) suggesting that it is an possible measure that could be integrated into clinical practice as a screener for identification of patients who resulted in successful or unsuccessful outcome for non-CPAP therapy. These findings have important clinical implications since CPC may be potential surrogates for evaluating a treatment outcome for OSA, though it is simpler, cheaper, and more accessible testing method than PSG.

Our study has several important limitations. Firstly, there is some confusion in a word of ‘non-CPAP therapy’ or it could be a misnomer. Non-CPAP therapy includes not only sleep surgery or oral appliance therapy but behavioral therapy or adjunctive therapies (bariatric surgery or pharmacologic therapy). However, most of previous other studies argued on success rate of sleep surgery or oral appliance depending on the various criteria. In this point of view, non-CPAP therapy considers as sleep surgery or oral appliance is reasonable. Secondly, the numbers of each treatment modality clearly spell out the disparities (33 with sleep surgery versus 65 with MAD). In addition, age was different between the modalities. However, this study aimed not to make a comparison between sleep surgery and oral appliance therapy but to define the success criteria of non-CPAP therapy. Moreover, criteria of success in both therapies make no difference in many previous studies. Nevertheless, further study is needed to reveal the discrepancy of sleep quality according to the treatment modalities.

CONCLUSIONS

A uniform definition of treatment success should be established with non-CPAP therapy for OSA. In this point of view, our result provide clue to make a criteria of success on non-CPAP therapy for OSA. Traditionally, success was defined as ‘more than 50% reduction of AHI and a post-treatment AHI lower than 20’ after using it for evaluation success of sleep surgery by Sher. [65] Others have recently proposed to tighten these criteria to ‘a post-treatment AHI lower than 5 and/or 10’. [60] However, we found ‘more than 50% reduction of AHI’ is sufficient improvement of non-CPAP therapy for OSA in terms of sleep quality. Moreover, this criterion is the optimal to determine the treatment success. Using this criterion of success, LFCdec $\geq$ 10.1% cutoff represented clinical value in identifying successful non-CPAP therapy.

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초 록

Cardiopulmonary coupling 분석을 이용한 폐쇄성수면무호흡증에서 수면의 질에 관한 연구

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서론: 하악구강전진장치를 이용하여 폐쇄성수면무호흡증을 치료하였을 때 치료 전후의 수면의 질의 변화를 Cardiopulmonary coupling (CPC) 분석을 통하여 알아보는 것과(Chapter 1), CPC 분석법을 활용하여 비양압기치료(non CPAP therapy)의 성공적인 치료의 기준을 정의하는 것이 (Chapter 2) 이 연구의 목적이다.

방법: (Chapter 1) 총 52명의 폐쇄성수면무호흡 환자(연령, 53.7 ± 9.6 세)를 대상으로 하악구강전진장치의 치료 전과 치료 3개월 후의 수면다원검사에 나타난 심전도 신호로부터 추출한 CPC 결과를 활용하여 수면의 질을 비교하였다.

(Chapter 2) 폐쇄성수면무호흡의 치료로써 비양압기치료의 일종인 수면수술과 하악구강전진장치를 받은 98명의 환자(연령, 51.6 ± 9.5 세)를 대상으로 치료 전후의 CPC 결과를 비교하여 여러 가지 다양한 성공의 기준 중 가장 수면의 질 변화를 유의하게 반영하는 기준을 찾아 보았다.

결과: (Chapter 1) 하악구강전진장치의 사용으로 수면 중 호흡장애와 관련된 지표는 개선되었으나, N3 수면단계(3.7 ± 4.3 to 6.9 ± 6.4 %, $p < 0.001$)를 제외한 수면의 단계에는 차이가 없었다. CPC를 활용한 수면 질 역시 향상되었는데, LFC (59.5 ± 16.1 to 47.7 ± 14.8 %, $p < 0.001$)와 e−LFC (44.6 ± 18.4 to 32.6 ± 15.7 %, $p < 0.001$)는

하악구강전진장치의 사용에 의해 감소한 반면 HFC (28.6 ± 16.0 to 36.5 ± 15.7 %, p = 0.004)와 VLFC (11.7 ± 7.2 to 15.3 ± 6.6 %, p = 0.028)는 통계적으로 유의한 증가를 보였다.

(Chapter 2) 다양한 수면치료의 성공의 기준 중 술 후 50%의 수면무호흡-저호흡지수(AHI)의 감소가 비양압기치료에 의한 수면의 질의 유의한 향상을 보였다. 이 기준을 적용하여 비양압기치료 후 LFC의 10.1% 이상의 감소를 보인 경우 66.2%의 민감도와 66.7%의 특이도로 성공적인 치료의 결과를 예상할 수 있다.

결론: (Chapter 1) 하악구강전진장치를 이용한 폐쇄성수면무호흡의 치료는 수면의 질을 향상 시킴을 알 수 있었고, CPC 분석을 통하여 환자가 체감하지 못하는 수면 질의 향상을 알아낼 수 있었다.

(Chapter 2) 비양압기치료 후 50%의 수면무호흡저호흡지수의 감소가 수면의 질의 향상 측면에서 유의한 성공적인 치료의 기준임을 알 수 있었고, LFC의 10.1% 이상의 감소를 비양압기치료의 성공적인 치료 결과로 평가하게 하는 예측값으로 사용할 수 있다.

주요어: 폐쇄성수면무호흡, 하악구강전진장치, Cardiopulmonary coupling, 성공적인 치료, 수면의 질

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