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Study on treatment efficacy for patients with obstructive sleep apnea using heart rate variability

심박변이도 분석을 활용하여 폐쇄성수면무호흡증 환자의 치료 유효성 평가에 관한 연구

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July 2020

The Department of Otorhinolaryngology,
Seoul National University
College of Medicine
Woo Hyun Lee

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지도교수 김 정 훈

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이 우 현

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위원	원 준 연	(인)
위원	김 현 직	(인)

Study on treatment efficacy for patients with obstructive sleep apnea using heart rate variability

By

Woo Hyun Lee

A Thesis Submitted to the Department of Otorhinolaryngology in Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Medical Science at the Seoul National University College of Medicine

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Approved by thesis committee

Professor _____Chairman

Professor _____Vice chairman

Professor _____

Professor _____

Professor _____

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논문 제목	**심박변이도 분석을 활용하여 폐쇄성수면무호흡증 환자의 치료 유효성 평가에 관한 연구** **Study on treatment efficacy for patients with obstructive sleep apnea using heart rate variability**
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1. 본인은 서울대학교가 위 저작물을 인터넷 등 정보통신망을 통해 복제·전송·배포하는 것에 동의합니다.

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Abstract

Study on treatment efficacy for patients with obstructive sleep apnea using heart rate variability

Woo Hyun Lee

Otorhinolaryngology, College of Medicine

Seoul National University

Introduction: The aim of this study is (Chapter 1) to evaluate the effects of mandibular advancement device (MAD) on nocturnal heart rate variability (HRV) in obstructive sleep apnea (OSA) and (Chapter 2) to compare the treatment efficacy between sleep surgery and MAD using HRV.

Material and methods: (Chapter 1) We retrospectively reviewed anthropometric data, questionnaire results, and HRV parameters (evaluated using time- and frequency-domain methods) of 58 adult patients with OSA treated via MAD therapy. (Chapter 2) Subjects treated for OSA with sleep surgery or MAD (n = 30/group) were matched for sex, body mass index (BMI), and baseline apnea–hypopnea index (AHI). The efficacy of these treatments according to HRV time- and frequency-domain parameters were compared between pre-treatment and 3-months post-treatment.

Results: (Chapter 1) The average normal-to-normal (NN) interval, standard deviation of the NN interval, low-frequency power in normalized units (LFnu), and high-frequency power in normalized units (HFnu) showed significant changes with MAD therapy. Based on the criteria for success (decrease in the apnea-hypopnea index by >50% and value <20/h), 34 and 24 patients were classified into the response and nonresponse groups, respectively. No differences in baseline characteristics were detected between groups, except for higher body mass index and lower minimal oxygen saturation in the

nonresponse group. A subgroup analysis indicated that the average NN interval and HFnu significantly increased, and that Total power (TP), very low frequency, low frequency (LF), low frequency/high frequency and LFnu significantly decreased compared to baseline in the response group; however, no HRV changes were found in the nonresponse group. After adjusting for age, sex, and BMI, the response group showed significant changes from baseline in TP and LF compared to the nonresponse group. (Chapter 2) In time-domain HRV analysis, average NN intervals increased significantly in the surgery (942.2 ± 140.8 to 994.6 ± 143.1, P = 0.008) and MAD (901.1 ± 131.7 to 953.7 ± 123.1, P = 0.002) groups. LF decreased significantly in the surgery group (P = 0.012). The LF/HF ratio decreased in both groups (2.9 ± 1.8 to 2.3 ± 1.7, P = 0.017, vs 3.0 ± 1.8 to 2.4 ± 1.4, P = 0.025). HFnu increased significantly in both groups (31.0 ± 13.2 to 36.8 ± 13.7, P = 0.009, vs. 29.1 ± 10.7 to 33.7 ± 12.5, P = 0.024), in contrast to LFnu. However, no HRV parameter changes differed significantly between the groups after adjusting for age, BMI, and AHI.

Conclusion: (Chapter 1) HRV may be useful for determining the efficacy of MAD therapy in OSA. (Chapter 2) Sleep surgery and MAD are equally effective treatments for OSA according to cardiac autonomic activity.

Key words: Obstructive sleep apnea, Heart rate variability, Mandibular advancement device, Sleep surgery, Efficacy, Cardiac autonomic activity

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List of abbreviations and symbols

Analysis of covariance (ANCOVA)

Apnea–hypopnea index (AHI)

Apnea index (AI)

Body mass index (BMI)

Continuous positive airway pressure (CPAP)

Electrocardiography (ECG)

Epworth sleepiness scale (ESS)

Heart rate variability (HRV)

High frequency (HF)

High-frequency power in normalized units (HFnu)

Hypopnea index (HI)

Low frequency (LF)

Low-frequency power in normalized units (LFnu)

Mandibular advancement device (MAD)

Normal-to-normal (NN)

Number of pairs of adjacent NN intervals greater than 50 ms (NN50)

Obstructive sleep apnea (OSA)

Oxygen desaturation index (ODI)

Pittsburgh sleep quality index (PSQI)

Polysomnography (PSG)

Rapid eye movement (REM)

Square root of the mean of the squared differences of adjacent NN intervals (RMSSD)

Standard deviation of NN intervals (SDNN)

Total power (TP)

Very low frequency (VLF)

CHAPTER 1

Nocturnal heart rate variability may be useful for determining the efficacy of mandibular advancement devices for obstructive sleep apnea

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway obstruction during sleep associated with arterial blood desaturation, sympathetic nervous system activation, and cardiovascular impairment [1]. Untreated patients with OSA have increased mortality rates compared to the general population [2, 3]. Laboratory polysomnography (PSG) is accepted as a standard method of diagnosing OSA [4]. However, PSG can be cumbersome because of its time, space, equipment, and tester requirements.

Heart rate variability (HRV) measures the variation in the time interval between heartbeats and reflects cardiac sympathetic and parasympathetic modulation. It can be measured using the single-lead electrocardiography (ECG) signal and is also called cycle length variability, RR variability, or heart period variability [5]. Reduced HRV was found to be related to increased mortality after myocardial infarction, congestive heart failure, diabetic neuropathy, depression, and poor survival in premature infants [5-9]. Because patients with OSA show abnormal cardiac autonomic modulation, the association between OSA and changes in HRV has been reported by several studies [10-13].

A mandibular advancement device (MAD) is an oral device that has been recommended as an alternative therapy for OSA [14]. It can effectively reduce the collapsibility of the upper airway during sleep by advancing the mandible [15]. MAD was found to have positive effects on cardiac autonomic modulation measured by HRV in OSA that are similar to those of other treatments such as continuous positive airway pressure (CPAP) therapy [16-18]. However, there is still insufficient evidence for HRV changes occurring

with successful MAD therapy for OSA. Furthermore, the positive effects of MAD on cardiac autonomic modulation are less clear than those of CPAP. Therefore, studies of the effects of MAD on cardiac morbidities are warranted. We attempted to identify whether MAD can affect cardiac autonomic modulation during an entire night. Our hypothesis was that a positive treatment response to MAD therapy may be associated with positive changes in HRV. This study evaluated the effects of MAD on HRV changes according to the response of treatment in patients with OSA.

Methods

Subjects

We retrospectively reviewed the data of patients who visited a sleep center of a tertiary hospital because of snoring and sleep apnea. We selected subjects according to inclusion and exclusion criteria. The inclusion criteria were as follows: (1) adult patients (age ≥18 years); (2) patients who were diagnosed with OSA (AHI >5/h); (3) patients who were treated with MAD (SomnoDent; SomnoMed Ltd, New South Wales, Australia) (Fig. 1-1); and (4) patients who underwent follow-up PSG after 3 months of MAD therapy and had the results of two PSG tests (baseline and with MAD) available. The exclusion criteria were the follows: (1) significant arrhythmias; (2) low-quality data (artefact >20% of total sleep time); (3) total sleep time less than 5 h; (4) awake more than 30 minutes from midnight to 5 AM; (5) combined sleep disorders (i.e., insomnia or narcolepsy); (6) habitual use of sedatives and hypnotics; and (7) history of specific pathology related to HRV changes (i.e., myocardial infarction, diabetic neuropathy, cardiac transplantation, myocardial dysfunction, or tetraplegia). Based on the inclusion and exclusion criteria, a total of 58 patients with OSA were included in this study. The anthropometric data of subjects were evaluated. Daytime sleepiness and subjective sleep quality of subjects were evaluated using the Epworth sleepiness scale (ESS) and Pittsburgh sleep quality index (PSQI), respectively. The ethics committee of Seoul National University Bundang Hospital (IRB No. B-1902-522-111) approved the use of these data. The need for written informed consent was waived by the Institutional Review Board.

Analyses of nocturnal heart rate variability

The HRV was measured using exported ECG data and commercially available PSG software (RemLogic 3.0 HRV analyzer; Embla Systems, San Carlos, CA). The HRV analysis was performed without any information regarding PSG results except for the ECG signal. To prevent inappropriate comparisons, we analyzed the ECG signal from midnight to 5 AM. In other words, ECG signals exported before midnight and after 5 AM were not included in the HRV analysis. The signals were interpolated and resampled at 5.0 Hz; NN intervals more than 2,400 ms and less than 400 ms were omitted.

Calculations of the time domain and frequency domain parameters were performed according to the standard methods for HRV measurements [5]. The following parameters measured using time domain methods were included: (1) average NN interval; (2) standard deviation of NN intervals (SDNN); (3) standard deviation of the 5-minute averages of NN intervals (SDANN); (4) square root of the mean of the squared differences of adjacent NN intervals (RMSSD); (5) number of pairs of adjacent NN intervals more than 50 ms (NN50 count); (6) the rate of NN50 in the total number of NN intervals (pNN50); and (7) HRV triangular index and geometric measurements. Frequency domain variables were presented as the average of the values calculated every 5 minutes. The parameters of the frequency domain and their brief descriptions were as follows: total power, power of approximately ≤0.4 Hz; VLF, power ≤0.04 Hz; LF, power of 0.04–0.15 Hz; HF, power of 0.15–0.4 Hz; LF/HF ratio, LF divided by HF; LFnu, LF power of normalized units [LF / (LF + HF) × 100]; and HFnu, HF power of normalized units [HF / (LF + HF) × 100].

Definition of treatment outcomes

Apnea was defined as the complete cessation of airflow for at least 10 s. Hypopnea was defined as a substantial reduction in airflow (≥30 %) for at least 10 s associated with electroencephalographic arousal or oxygen desaturation (≥3%). AHI was defined as the total number of apnea incidents and hypopnea incidents per hour of sleep. Snoring was measured with a snore sensor (Piezo; Pro-Tech, Woodinville, Washington, USA). The sensor was attached around the neck of patients at the larynx level and detected whether vibration of the larynx was sufficient. The snoring rate was defined as the ratio of snoring time to total sleep time. The response to treatment was defined as an AHI that decreased by more than 50% and had a value less than 20/h with MAD compared to baseline [19]. Subjects who did not meet these criteria were included in the nonresponse group. The success to treatment was defined as an AHI that decreased by more than 50% and had a value less than 10/h with MAD compared to baseline. Subjects who did not meet these criteria were included in the failure group.

Statistical Analysis

Most values obtained during this study were continuous variables expressed as mean ± standard deviation, except for sex, which was a categorical variable presented as a ratio. The paired *t* test was used to compare the differences between the baseline values of parameters and those after MAD. The independent *t* test or chi-squared test was performed for the comparative analysis of baseline characteristics of the response and nonresponse groups. Differences in the change from baseline between the response and nonresponse groups were tested using an analysis of covariance (ANCOVA) with age, sex, and body mass index as covariates. Data analyses were

performed using SPSS software (version 18; SPSS Inc., Chicago, IL), and $P < 0.05$ was considered statistically significant.

Results

Changes in polysomnography statistics

PSG parameters related to the respiratory index were significantly improved by MAD when compared to baseline. MAD treatment significantly decreased the apnea-hypopnea index (AHI), apnea index (AI), hypopnea index (HI), and oxygen desaturation index (ODI). The minimal and average oxygen saturations significantly increased; however, the snoring rates were not changed with MAD. The incidence of sleep stage N3 and REM sleep significantly increased from 4.8 ± 5.5% to 7.2 ± 6.8% ($P < 0.001$) and from 15.6 ± 5.8% to 18.5 ± 6.2% ($P < 0.001$), respectively (Table 1-1).

Changes in nocturnal heart rate variability

MAD treatment resulted in changes in HRV. Among the time domain measures, the average normal-to-normal (NN) interval significantly increased from 949.3 ± 134.1 ms to 988.4 ± 127.0 ms ($P = 0.001$), and the standard deviation of the NN interval (SDNN) significantly decreased from 96.8 ± 32.6 ms to 87.4 ± 26.8 ms ($P = 0.042$). Regarding the frequency domain values, the low-frequency (LF) power in normalized units (LFnu) and high-frequency (HF) power in normalized units (HFnu) showed statistically significant changes. LFnu decreased from 70.5 ± 11.9 to 67.4 ± 13.8 ($P = 0.022$) and HFnu increased from 29.5 ± 11.9 to 32.6 ± 13.8 ($P = 0.022$) with the use of MAD (Table 1-2).

Subgroup analyses of response and nonresponse groups

According to the response criteria, 34 subjects were classified into the response group and 24 were classified into the nonresponse group. No

significant differences in baseline characteristics were found between the two subgroups except for higher body mass index (P =0.004) and lower minimal oxygen saturation (P = 0.048) in the nonresponse group (Table 1-3). However, significant HRV differences were detected between the two groups. Regarding the time domain measures, the average NN interval significantly increased in the response group (from 947.7 ± 152.0 ms to 998.9 ± 140.0 ms; P = 0.003); however, no significant difference was found in the nonresponse group (from 951.8 ± 106.6 ms to 973.6 ± 107.2 ms; P = 0.111). Other time domain variables did not significantly change in both groups. Among the frequency domain values, total power (TP, P = 0.007), very low frequency (VLF, P = 0.010), LF (P = 0.004), LF/HF (P = 0.031), and LFnu (P = 0.015) significantly decreased in the response group, but not in the nonresponse group. There was also a significant change in HFnu in the response group (from 28.8 ± 10.1 to 33.4 ± 12.6; P = 0.015), but not in the nonresponse group (from 30.6 ± 14.3 to 31.3 ± 14.3; P = 0.686). The remaining frequency domain variable (HF) did not change with MAD in either group (Table 1-4). According to the success criteria of AHI that decreased by more than 50% and had a value less than 10/h, 24 subjects were classified to success group and 34 subjects were classified to failure group. In analyzing the change in HRV of each group, the average NN interval, TP, VLF, LF, LFnu, and HFnu significantly changed in the success group, while average NN interval and SDNN significantly change in the failure group (Table 1-5). Finally, the response group showed significant changes from baseline in the TP [-11004.00 (95% CI, -21448.00 to -559.85) in the response group and 5162.16 (95% CI, -7804.99 to 18129.00) in the nonresponse group; P = 0.02] and LF [-3483.21 (95% CI, -6690.23 to -276.19) and 2057.00 (95% CI, -1924.82 to 6038.81); P = 0.012] compared to the nonresponse group after adjusting for age, sex, and body mass index. However,

changes in the sleep stage did not differ between the response and nonresponse groups (Table 1-6).

Discussion

This study revealed that MAD treatment significantly changed cardiac autonomic modulation represented by nocturnal HRV and that the changes were significant only in the treatment response group. MAD reduces AHI less effectively than CPAP, but it has been associated with higher compliance [20]; therefore, it has been widely used as an alternative treatment for patients with OSA. However, few studies have assessed the effects of MAD on cardiac autonomic modulation. A previous study that included 10 patients with OSA treated with MAD showed significant changes in the NN interval, HF, and the LF/HF ratio [16]. However, our findings showed significant changes in the NN interval, SDNN, LFnu, and HFnu. This discrepancy could be related to the difference in the number of subjects (10 vs. 58), HRV measurement time (day vs. night), and the treatment success rate (100% success group vs. 62.1% response group). Two previous studies that compared CPAP and MAD also described changes in HRV after MAD treatment. One study showed that MAD significantly decreased TP compared to baseline, and that the decrease was greater than that resulting from the use of a placebo oral appliance but lower than that resulting from CPAP [17]. Another study found no difference between MAD and CPAP regarding cardiac autonomic function changes during the day, although CPAP was more effective than MAD for eliminating respiratory events [18].

Although these previous comparative studies showed that MAD treatment induced significant HRV changes, their results were limited by the relatively small numbers of subjects (29 and 40) and restricted numbers of parameters that were used to assess HRV. Because we included 58 subjects and evaluated most HRV parameters, our results are likely to provide more concrete evidence

regarding the effects of MAD on HRV. However, the difference in HRV changes was weakened between success and failure groups. HRV significantly changed on average NN interval, TP, VLF, LF, LFnu, and HFnu in the success group, while changed on average NN interval and SDNN in the failure group. Considering the average AHI (41.0/h) of our study subjects, the success criteria of AHI (decreased by more than 50% and had a value less than 10/h) was too strict. Accordingly, some subjects who had a good therapeutic effect on MAD were classified to failure group could be a reason for weakened difference between success and failure groups.

HRV varies considerably between individuals and is affected by age and physical condition [21]. Therefore, there is no uniform definition of the normal HRV range, and it is more difficult to determine a cutoff value for diagnosing OSA. Previous studies have reported the results of various HRV parameters for the diagnosis of OSA through various research methods. One previous study presented the LF/HF ratio as a useful parameter for diagnosing OSA in correlation with AHI [11]. Another study that examined the difference between HRV during the day and that during the night found that day and night SDNN were able to screen for OSA with high sensitivity and specificity [22]. Another study suggested that the NN interval was the best index among the time and frequency domain parameters because only the mean NN interval was shorter in the OSA group than in the control group [23]. As previously mentioned, studies that used HRV to diagnose OSA showed generally inconsistent results. These different reasons were due to the lack of uniform study methods and HRV characteristics that varied with age and physical condition. Therefore, to clarify the relationship between OSA and HRV, a well-designed research method is needed.

It seems that HRV is more useful for determining treatment results than for

diagnosing OSA. A few studies have reported changes in HRV after OSA treatment. One study on changes in HRV after CPAP therapy reported that the SDNN of non-REM sleep decreased after CPAP [24]. We also found that the SDNN was decreased regardless of the sleep stage after MAD treatment. However, it was impossible to determine the response or nonresponse to treatment using the SDNN. A decrease in the LF/HF ratio was reported for 18 children after adenotonsillectomy [25]. We also found a change in the LF/HF ratio with response group of MAD therapy. Despite the differences in the age of the subjects (children vs. adults) and treatment modality (adenotonsillectomy vs. MAD) between studies, the change in the LF/HF ratio was similar. Choi et al [26] concluded that HRV showed significant changes in the success group of OSA patients who underwent upper airway surgery, but not in the failure group of OSA patients. They reported that the changes in VLF, LF, LFnu, and HFnu were meaningful, and these findings were in partial agreement with our results. We found that TP, VLF, LF, LFnu, and HFnu showed significant changes among the frequency domain parameters in the response group.

HRV is easier and less expensive to evaluate than PSG. The final model of our study showed that the TP and LF significantly changed in the response group compared to those in the nonresponse group after adjusting for age, sex, and body mass index. Taken together, changes in HRV, including decreased TP and decreased LF, possibly used to determine the response of MAD treatment through the further well-designed study.

Previous studies that have analyzed the changes in HRV and evaluated treatment success have not included time domain parameters [26] or only described the results of short-term analyses [24]. However, after analyzing the time domain parameters during 5 nights h according to the standard method,

we found that the NN interval had significantly changed in the response group, which was a strength of our study.

This study had several limitations. First, various success criteria were applied in different studies. Among many definitions of OSA treatment success, we used commonly accepted criteria, namely more than a 50% decrease in AHI and a value less than 20/h with MAD treatment. Therefore, the results of this study might differ from those of studies that used other success criteria. Second, the time domain method was applied during 5 h during the night. The HRV Task Force has indicated that it seems appropriate to analyze time domain method results using nominal 24 h long-term recordings [5]. To overcome this limitation, we used recordings of ECG during the same 5-h periods to analyze the time domain method results according to alternative recommendations. Third, selection bias could not be excluded because patients with better outcomes were more likely to participate in follow-up testing. A prospective study is needed to validate the effects of MAD treatment on cardiac autonomic modulation in OSA. Fourth, the sleep stage may influence the HRV values. However, in this study, we did not perform a detailed analysis of HRV according to sleep stage. Instead, we found that changes in the sleep stage did not differ between the response and nonresponse groups. Therefore, the sleep stage may have had a minor effect on the differences in HRV values between groups. Nevertheless, follow-up studies of HRV according to the sleep stage are needed.

Conclusion

The present study showed that MAD treatment for OSA significantly changed cardiac autonomic modulation as represented by nocturnal HRV. Among the assessed parameters, the average NN interval and HFnu increased,

while TP, VLF, LF, LF/HF ratio, and LFnu decreased. However, the changes were observed only in the response group. Moreover, after adjusting for age, sex, and body mass index, the response group showed significant changes in the TP and LF compared to the nonresponse group. Therefore, nocturnal HRV may be a useful screening tool for determining the efficacy of MAD.

CHAPTER 2

Effectiveness of sleep surgery versus a mandibular advancement device for obstructive sleep apnea in terms of nocturnal cardiac autonomic activity

Introduction

Obstructive sleep apnea (OSA) is prevalent disorder that affects 2% to 4% of the adult population [27]. Patients with OSA experience partial or complete cessation of respiratory flow due to periodic collapse of the upper respiratory tract during sleep, and the condition has been associated with cardiovascular morbidities, such as hypertension, ischemic heart disease, congestive heart failure, arrhythmias, as well as with cardiovascular mortality [28-31].

Continuous positive airway pressure (CPAP) is a treatment of choice for OSA, regardless of severity. Oral appliances and surgical treatments may be individual alternative treatments in OSA patients, who despite all efforts are not treatable with CPAP therapy, such as when patients decline CPAP therapy or CPAP therapy is ineffective in eliminating OSA. Evidence of clinical efficacy for sleep surgery and mandibular advancement devices (MAD) is limited and their efficacy is inferior to the gold standard of CPAP, but sleep surgery and MAD may represent a therapeutic option in individual patients with good compliance [32, 33].

MAD are a type of oral appliance that can effectively reduce the collapsibility of the upper airway during sleep for mild to moderate OSA [15] [34], and as sleep surgery and MAD are not directly comparable, they may have significance in selected cases. Many previous studies have reported that sleep surgery and MAD could lower risk of cardiovascular mortality in OSA patients by reducing the respiratory flow limitation during sleep [34, 35]. However, it is difficult to define which of sleep surgery or MAD is a more effective alternative for OSA.

Classically, polysomnography (PSG) and sleep questionnaires are objective and subjective methods, respectively, for evaluating the efficacy of treatments for OSA although sleep questionnaires are known to be imprecise in cardiovascular patients [36]. Heart rate variability (HRV), which can be measured from a single-lead electrocardiography (ECG) signal, reflects cardiac autonomic activity and reflects the quantitative variation between normal-to-normal heartbeats [5]. The clinical implications of HRV were first proposed in 1965, and since then, the association between OSA and increased sympathetic activity in HRV has been well described [37, 38]. Moreover, adequate treatment of OSA may reverse the deterioration in cardiac autonomic activity [18, 26]. Therefore, evaluation of HRV could be used to assess treatment efficacy in OSA. However, cardiac autonomic activity has rarely been used to evaluate treatment efficacy between sleep surgery and MAD for OSA.

We hypothesized that there might be a difference between sleep surgery and MAD from the perspective of improvement of cardiac autonomic activity in patients with OSA. This study aimed to compare the efficacy between sleep surgery and MAD in terms of cardiac autonomic activity, using HRV analysis.

Methods

Subjects

We retrospectively reviewed patients who underwent sleep surgery for OSA in our clinic from January 2013 to December 2017. Sleep surgery included tonsillectomy, uvulo-palato-pharyngoplasty, expansion sphincter pharyngoplasty, lateral pharyngoplasty, tongue-base resection, and a combination of these procedures. Each surgical procedure was performed according to whether the patient had upper airway collapse, which was evaluated by physical examinations, such as sleep videofluoroscopy, Muller's maneuver, and Friedman grading system. In brief, we conducted tonsillectomy for patients with OSA who had tonsil enlargement. Enlarged tonsil and velopharyngeal collapse were indications for uvulo-palato-pharyngoplasty. Patients with observed velopharyngeal lateral collapse in physical exam underwent expansion sphincter pharyngoplasty or lateral pharyngoplasty. Tongue-base resection was applied to patients with oropharyngeal collapse by a tongue base. Furthermore, multi-level surgery was performed for patients with velopharyngeal and oropharyngeal collapse simultaneously. Among these, we selected patients according to the following inclusion and exclusion criteria. We included adult patients (age ≥ 18 years); patients diagnosed with OSA (apnea–hypopnea index, AHI > 5/h); patients who had a follow-up PSG at 3 months after treatment, and who had two PSG datasets (baseline and 3-months post-treatment) available. We excluded patients with significant arrhythmias; low-quality data (artefacts exceeding 20% of total sleep time); total sleep time < 5 hours; awakening more than 30 minutes from midnight to 5 AM; patients with combined sleep disorders (i.e., insomnia or narcolepsy); habitual use of sedatives and hypnotics; history of specific pathology related

to HRV changes (i.e., myocardial infarction, diabetic neuropathy, cardiac transplantation, myocardial dysfunction, or tetraplegia).

Forty-two patients who met the criteria were identified. During this period, 54 patients who met the inclusion and exclusion criteria were treated for OSA by MAD. These patients were matched for sex, body mass index (BMI, ± 0.5 kg/m^2), and baseline AHI (± 5/hour) with patients treated by sleep surgery. The matching process was performed with blinding to the result of follow-up PSG. Thirty patients were enrolled in the sleep surgery or MAD group. The ethics committee of Seoul National University Bundang Hospital (IRB No. B-1907/555-108) approved the use of the data. The need for written informed consent was waived by the institutional review board.

Classical evaluation of treatment efficacy

Embla^{TM} N7000 (Embla, Reykjavik, Iceland), a commercially available recording PSG system with standard electrodes and sensors, was used to perform the procedure, under the supervision of a skilled technician. Apnea was defined as the complete cessation of airflow for at least 10 seconds. We defined hypopnea as a substantial reduction in airflow (≥ 50 %) for at least 10 seconds or a moderate reduction in airflow for at least 10 seconds associated with oxygen desaturation (≥ 4 %) or electroencephalographic arousals. The AHI was defined as the total number of apneas and hypopneas per hour of sleep.

Sleep questionnaires, completed by subjects, were also analyzed. Daytime sleepiness was evaluated using the Epworth sleepiness scale (ESS); subjective sleep quality was measured using the Pittsburgh sleep quality index (PSQI).

HRV analysis

The single-lead ECG data exported from the PSG system were used to measure HRV, using commercially available software (RemLogic 3.0 HRV analyzer; Embla Systems, San Carlos, CA). The ECG signal from midnight to 5 AM were analyzed for comparison under identical conditions (signals from before midnight and after 5 AM were not included in analysis) and interpolated and resampled at 5.0 Hz. Normal-to-normal heartbeat intervals < 400 milliseconds and > 2,400 milliseconds were omitted. We used the standard methods of HRV measurement to calculate the time-domain and frequency-domain parameters [38].

Time-domain measures

The time-domain parameters included were the average normal-to-normal (NN) interval, standard deviation of NN intervals (SDNN), square root of the mean of the squared differences of adjacent NN intervals (RMSSD), and number of pairs of adjacent NN intervals greater than 50 ms (NN50).

Frequency-domain measures

The frequency-domain parameters used in the present study were total power (variance of all normal-to-normal intervals), very low frequency (VLF; power in 0.003–0.04 Hz range), low frequency (LF; power in 0.04–0.15 Hz range), high frequency (HF; power in 0.15–0.4 Hz range), normalized LF [LFnu; LF / (LF + HF) × 100], normalized HF [HFnu; HF / (LF + HF) × 100], and LF/HF ratio. LF activity reflects a mixture of both sympathetic and parasympathetic activity, while HF has been linked to parasympathetic activity. The LF/HF ratio is considered to reflect the balance between sympathetic and parasympathetic activity and is correlated with the degree of AHI in OSA [40]. LFnu and HFnu are regarded as markers of sympathetic and parasympathetic activity, respectively.

Statistical Analysis

Data obtained in this study for continuous variables were presented as mean ± standard deviation (SD), while sex, a categorical variable was presented as ratio of male to female. The independent *t*-test or chi-squared test was performed to evaluate the differences in baseline characteristics between sleep surgery and MAD groups. The paired *t*-test was used to evaluate differences between baseline values of parameters and those at 3 months' post-treatment. Differences in baseline to post-treatment HRV changes between sleep surgery and MAD groups were tested by analysis of covariance (ANCOVA), with age, BMI, and baseline AHI as covariates. In ANCOVA, values were expressed as least-squares means (LSmeans) and 95% confidence intervals. We used SPSS software, version 18 (SPSS Inc., Chicago, IL, USA) to perform the data analysis; *P* values < 0.05 were considered statistically significant.

Results

Patient characteristics

Most baseline characteristics between the sleep surgery group and MAD group showed no statistically significant difference; except for age and sleep stage (Table 2-1). Because subjects were matched, BMI and AHI were comparable, and the male to female ratio was equal to 27:3 in both groups. The age of the patients in the sleep surgery group was significantly younger than that of those in the MAD group and the N3 sleep stage was higher in the sleep surgery than in the MAD group.

Changes in polysomnography parameters

Both groups had significantly decreased BMI after treatment (from 26.8 ± 3.4 to 26.3 ± 3.1 in sleep surgery group, $P = 0.013$; from 26.7 ± 2.9 to 26.5 ± 2.9 in MAD group, $P = 0.010$). However, no difference was found between the two groups in BMI changes, ($P = 0.798$). We performed follow-up PSG evaluation at 3 months after treatment. Among the parameters, AHI, apnea index, oxygen desaturation index, and arousal were decreased, and minimal oxygen saturation was increased statistically significantly in both groups. In the proportion of total sleep time, stage N1 (decreased, $P = 0.029$), stage N2 (increased, $P = 0.035$), and rapid eye movement (REM) stage (increased, $P = 0.034$) changed significantly in the sleep surgery group at 3-months post-treatment. In the MAD group, stages N2 ($P = 0.045$) and N3 ($P = 0.027$) were significantly increased after treatment (Table 2-2).

Changes in sleep questionnaires

Subjective sleep quality analysis was performed using ESS and PSQI. ESS

decreased in the sleep surgery group (from 7.6 ± 2.4 to 5.4 ± 2.5, $P < 0.001$) and PSQI decreased in both groups (from 10.9 ± 3.1 to 6.9 ± 3.4, $P < 0.001$ in the sleep surgery group; from 11.1 ± 5.1 to 9.2 ± 5.1, $P = 0.012$ in the MAD group) after treatment, as compared to baseline (Figure 2-1).

Changes in heart rate variability

Among time-domain indices, the average NN interval significantly increased in both sleep surgery ($P = 0.008$) and MAD ($P = 0.002$) groups after treatment. However, other time-domain parameters did not change in either group.

In frequency-domain analysis, LF significantly decreased in the sleep surgery group ($P = 0.012$), while HF was unchanged in both groups at 3-months post-treatment. The LF/HF ratio had decreased significantly in both the sleep surgery ($P = 0.017$) and MAD ($P = 0.025$) groups after treatment, as compared to baseline. Moreover, in both groups, HFnu increased significantly ($P = 0.009$ in the sleep surgery group; $P = 0.024$ in the MAD group), and as HFnu increased, LFnu decreased (Table 2-3).

Comparison of changes of heart rate variability between groups

Finally, changes in HRV from baseline to post-treatment were compared between the sleep surgery and MAD groups. These changes were not significantly different between groups after adjusting for age, BMI, and baseline AHI (Table 2-4).

Discussion

Since CPAP was introduced by Sullivan in 1981 as a safe treatment for OSA, it has been considered as a gold-standard modality [39]. Furthermore, a recent study reported that CPAP therapy improved cardiac ventricular function through reduced pulmonary hypertension [40]. According to many studies to date, there is consensus about the efficacy and importance of CPAP for OSA, but its lower patient compliance and poor long-term acceptance have been limitations to its implementation. To overcome the limitation of CPAP, new devices, such as hypoglossal nerve stimulation, have been developed until recently [41]. Sleep surgery and MAD are the most widely used alternative treatments for patients who decline CPAP; the usefulness of these two modalities has been well described in many studies. However, to the best of our knowledge, few studies have compared the efficacy between sleep surgery and MAD for OSA. The present study evaluated the efficacy of these two treatments, which were matched for sex, BMI, and AHI at baseline, in terms of cardiac autonomic activity and identified positive effects in both groups. However, we found both sleep surgery and MAD to be equally efficacious, because there was no difference in HRV changes from baseline to 3 months after treatment between the two therapies after adjusting for confounding factors.

The cardiac autonomic nervous system consists of a parasympathetic and a sympathetic branch, and heartbeat is modulated by a balance between these two branches. If parasympathetic nerves are suppressed and sympathetic nerves are activated, the heartbeat converges to the intrinsic heart rate (approximately 100 beats/min) and results in reduced HRV. Reduced HRV is associated with congestive heart failure, diabetic neuropathy, sudden cardiac

death, and post-cardiac transplant. Theoretically, HRV could be a method for evaluating the efficacy of OSA treatment, as it reflects cardiac autonomic activity. The improvement in HRV post-OSA treatment, such as sleep surgery, MAD, and CPAP, has been reported in previous studies. A study related to sleep surgery reported that VLF, LF, and LFnu changes were significant in successful upper airway surgery patients [26]. Another study demonstrated that expansion sphincter pharyngoplasty decreased the LF/HF ratio in the successful surgery group [42]. In a comparative study that was presented, even though CPAP proved to be more effective at reducing AHI, both MAD and CPAP significantly decreased the total power of HRV [17]. Moreover, CPAP significantly decreased SDNN in patients with OSA even at the first night of use [24].

A study suggested that time-domain HRV analysis was a useful index for assessing a sympathovagal balance in OSA, because OSA patients showed a shorter average NN interval than healthy subjects. Our study showed that the average NN interval significantly increased in both groups after treatment, and this reflected improvement of sympathovagal balance by both therapies. Our study results also demonstrated improvement in the frequency-domain in both groups. An increased LF/HF ratio in OSA patients compared to healthy subjects has been reported in previous studies and is considered a useful parameter to evaluate severity of the condition [43]. Moreover, adequate application of treatment modalities for OSA could correct the increased LF/HF ratio in OSA patients [16, 44]. In our study, the LF/HF ratio was significantly decreased in both sleep surgery and MAD groups, and it represented decreased OSA severity in subjects or change in the autonomic nerve system balance to a parasympathetic dominance. Among the other frequency-domain indices, we found a significant decrease in LFnu as well as an increase in HFnu by both

therapies. As mentioned earlier, LFnu and HFnu are regarded as markers of sympathetic and parasympathetic modulation, respectively. Briefly, considering the frequency-domain changes, the effects of both therapies on cardiac autonomic activity were associated with an increase in parasympathetic activity and a decrease in sympathetic activity.

HRV measurement can provide information about the risk of cardiovascular diseases in patients with OSA because it is considered as a strong predictor of cardiovascular mortality [45]. Moreover, the sympathetic hyperactivity and imbalance of the cardiovascular autonomic nervous system during sleep may play a critical role in development of cardiovascular diseases [46, 47]. Therefore, both alternative OSA therapies attenuate the cardiovascular risk by re-adjustment of the imbalance of the autonomic nerve system in OSA.

PSG parameters and sleep questionnaires are representative classical evaluation methods of the efficacy of OSA treatments. In the present study, because subjects were matched in terms of sex, BMI, and AHI, the baseline PSG parameters, and HRV indices showed no differences between sleep surgery and MAD groups. However, age was younger and N3 sleep stage was increased in sleep surgery group. This might reflect the patient's desire or the physicians' preference for performing surgery in younger OSA patients. The difference in N3 sleep stage between groups might be associated with the age difference, because the duration of slow-wave sleep gradually decreases by 2% per decade from young to middle-age [48].

In PSG parameters, respiration-related indices, such as AHI, oxygen desaturation index, and minimal oxygen saturation were significantly improved after treatment in both groups. AHI was decreased by more than 50% after treatment as compared to baseline (from 45 to 22 in the sleep surgery group, from 44 to 21 in the MAD group) and the change was accepted as a

response to treatment in some previous studies [49-51]. The proportion of REM stage sleep in the sleep surgery group and N3 sleep stage in the MAD group were significantly increased, and REM and slow-wave sleep rebound was associated with successful treatment of OSA [52, 53]. Therefore, our study also confirmed the efficacy of these two alternative therapies in terms of PSG parameters.

Some studies have reported issues with inter-test reliability and a need for further validation of the ESS and PSQI; nevertheless, these are currently representative questionnaires for subjective sleep quality evaluations [54, 55]. A decrement in the ESS score reflects improvement in daytime sleepiness, which is associated with motor-vehicle accidents, work-related accidents, and increased risk of diabetes, myocardial infarction, and stroke [54]. In this study, ESS scores were significantly decreased in the sleep surgery group and PSQI scores were decreased in both groups post-treatment; thus, the subjective symptom improvement based on these questionnaires also demonstrated the efficacy of both alternative OSA treatments.

This study had several limitations. First, the study was performed with patients who underwent follow-up PSG at 3 months after treatment. The efficacy of treatment may be exaggerated because patients with better outcomes tended to participate in the follow-up test. Second, this was a retrospective study, and selection bias may have been present. A well-designed randomized control study or cross-over study would be ideal for comparing the efficacy of sleep surgery and MAD. However, a cross-over study was not possible for surgical intervention, and such experiments could have ethical implications. To minimize bias, we matched the groups for sex, BMI, and AHI after blinding the results of follow-up PSG. Third, this study did not evaluate compliance with the therapies. The compliance of sleep surgery is not a

consideration, but adherence to using the MAD is an important factor in determining treatment efficacy. For a more valid analysis of the treatment efficacy for OSA, a future prospective comparative study is warranted, considering compliance. Fourth, patients who underwent heterogeneous surgery, such as tonsillectomy, uvulo-palato- pharyngoplasty, expansion sphincter pharyngoplasty, and so on, were considered among the sleep surgery group. We performed sleep surgery according to the sites of the upper airway collapse. Therefore, the purpose of each sleep surgery was homogeneous to improve autonomic nervous system imbalance by preventing upper airway collapse, same as the purpose of CPAP therapy [56].

Conclusion

Both treatment modalities were considered useful for OSA in terms of cardiac autonomic activity. The observed changes in HRV indices may indicate that both therapies could attenuate OSA-related cardiovascular mortality. However, the superiority of sleep surgery or MAD in terms of cardiac autonomic activity was not identified. Further studies are needed to compare the efficacy between sleep surgery and MAD for OSA.

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Figure 1-1. Mandibular advancement device.

Table 1-1. Laboratory full-night polysomnographic parameters without and with the use of a mandibular advancement device for patients with obstructive sleep apnea

	Baseline	With MAD	*P* value
Sleep parameters			
Total sleep time, min	384.2 ± 55.0	389.2 ± 58.0	0.627
WASO, min	69.4 ± 40.8	59.1 ± 36.9	0.076
Sleep latency, min	15.8 ± 24.8	11.5 ± 9.6	0.152
Sleep efficiency, %	81.8 ± 9.9	83.1 ± 13.1	0.448
Arousal, per hour	31.5 ± 21.0	11.3 ± 12.8	< 0.001*
Sleep stage, % of total sleep time			
N1	16.0 ± 7.9	12.2 ± 18.0	0.132
N2	48.6 ± 10.3	51.8 ± 9.9	0.077
N3	4.8 ± 5.5	7.2 ± 6.8	< 0.001*
REM sleep	15.6 ± 5.8	18.5 ± 6.2	< 0.001*
Respiratory index			
AHI, per hour	41.0 ± 20.1	19.6 ± 17.1	< 0.001*
Hypopnea index, per hour	16.1 ± 7.5	11.8 ± 8.9	0.001*
ODI, per hour	30.6 ± 20.7	12.8 ± 15.0	< 0.001*
Minimal O_2, %	80.1 ± 6.9	83.4 ± 6.3	< 0.001*
Average O_2, %	94.8 ± 1.8	95.5 ± 1.5	< 0.001*
Snoring, %	33.0 ± 18.2	30.1 ± 18.9	0.287

MAD, mandibular advancement device; WASO, wake time after sleep onset; REM, rapid eye movement; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; * $P < 0.05$

Table 1-2. Changes in nocturnal heart rate variability after the use of a mandibular advancement device for patients with obstructive sleep apnea

Variable	Baseline	With MAD	*P* value
Time domain measures			
Average NN interval, ms	949.3 ± 134.1	988.4 ± 127.0	0.001*
SDNN, ms	96.8 ± 32.6	87.4 ± 26.8	0.042*
SDANN, ms	65.2 ± 30.7	67.6 ± 43.2	0.728
RMSSD, ms	58.3 ± 45.5	48.4 ± 36.8	0.140
NN50 count	3,089 ± 3,175	2,860 ± 2,944	0.519
pNN50, %	11.2 ± 11.2	11.0 ± 11.8	0.839
HRV triangular index	16.5 ± 5.0	16.0 ± 4.3	0.473
Frequency domain measures			
Total power, ms^2	51,905 ± 25,730	48,241 ± 25,666	0.243
VLF, ms^2	29,058 ± 18,160	26,480 ± 17,101	0.166
LF, ms^2	15,884 ± 7,984	14,929 ± 9,359	0.320
HF, ms^2	5,790 ± 2,619	6,140 ± 2,720	0.310
LF/HF ratio	3.0 ± 1.9	2.8 ± 2.0	0.242
LFnu	70.5 ± 11.9	67.4 ± 13.8	0.022*
HFnu	29.5 ± 11.9	32.6 ± 13.8	0.022*

MAD, mandibular advancement device; SDNN, standard deviation of NN intervals; SDANN, standard deviation of the 5-min averages of NN intervals; RMSSD, the square root of the mean of the squared differences of adjacent NN intervals; NN50 count, number of pairs of adjacent NN intervals more than 50 ms; pNN50, rate of NN50 in the total number of NN intervals; VLF,

very low frequency; LF, low frequency; HF, high frequency; LFnu, LF power in normalized units; HFnu, HF power in normalized units; * $P < 0.05$

Table 1-3. Baseline characteristics of the treatment response and nonresponse groups

	Response (N=34)	Nonresponse (N=24)	*P* value
Age, years	52.9 ± 9.7	53.3 ± 8.3	0.858
Male/female ratio	29/5	22/2	0.688
Body mass index, kg/m^2	24.9 ± 3.0	27.4 ± 3.0	0.004*
Waist-to-hip ratio	0.93 ± 0.05	0.91 ± 0.19	0.639
AHI (per hour)	37.8 ± 15.7	45.4 ± 24.8	0.193
Apnea index, per hour	22.3 ± 16.7	28.7 ± 24.1	0.269
Minimal oxygen saturation, %	81.6 ± 6.8	78.0 ± 6.6	0.048*
ODI, per hour	26.4 ± 16.2	36.5 ± 25.0	0.090
ESS	10.1 ± 4.8	10.6 ± 5.6	0.733
PSQI	6.4 ± 3.2	6.7 ± 3.7	0.793

MAD, mandibular advancement device; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; ESS, Epworth sleepiness scale; PSQI, Pittsburgh sleep quality index; * $P < 0.05$

Table 1-4. Changes in nocturnal heart rate variability after the use of a mandibular advancement device in the response and nonresponse groups

	Response (N = 34)			Nonresponse (N = 24)		
Variable	Baseline	With MAD	*P* value	Baseline	With MAD	*P* value
Polysomnographic data						
AHI, per hour	37.8 ± 15.7	9.6 ± 4.9	<0.001*	45.4 ± 24.8	33.7 ± 18.3	0.003*
Apnea index, per hour	22.3 ± 16.7	2.7 ± 2.9	<0.001*	28.7 ± 24.1	15.1 ± 16.2	<0.001*
Hypopnea index, per hour	15.6 ± 7.6	7.0 ± 3.6	<0.001*	16.8 ± 7.5	18.7 ± 9.6	0.302
ODI, per hour	26.4 ± 16.2	4.6 ± 3.4	<0.001*	36.5 ± 25.0	24.4 ± 17.3	0.006*
Minimal O_2, %	81.6 ± 6.8	84.9 ± 7.0	0.001*	78.0 ± 6.6	81.3 ± 4.5	0.002*
Average O_2, %	95.3 ± 1.6	96.0 ± 1.5	0.010*	94.0 ± 1.8	94.8 ± 1.1	0.021*
Sleep stage, %						
N1	15.2 ± 7.9	11.6 ± 23.1	0.391	17.2 ± 8.0	12.8 ± 6.0	0.007*
N2	47.9 ± 9.3	52.7 ± 9.9	0.047*	49.6 ± 11.7	50.0 ± 10.2	0.894
N3	6.0 ± 6.0	7.3 ± 6.1	0.114	3.1 ± 4.2	7.1 ± 7.8	0.003*
REM sleep	15.2 ± 6.6	19.2 ± 6.2	0.001*	16.1 ± 4.7	17.3 ± 6.3	0.378
Time domain						

Average NN interval, ms	947.7 ± 152.0	998.9 ± 140.0	0.003*	951.8 ± 106.6	973.6 ± 107.2	0.111
SDNN, ms	98.0 ± 34.7	89.9 ± 25.1	0.175	95.0 ± 30.1	84.0 ± 29.2	0.136
SDANN, ms	61.4 ± 26.2	76.6 ± 48.1	0.075	70.5 ± 36.0	54.7 ± 32.0	0.137
RMSSD, ms	55.1 ± 46.1	45.6 ± 25.7	0.184	62.8 ± 45.2	52.5 ± 48.7	0.421
NN50 count	2,998 ± 2,882	2,639 ± 2,634	0.449	3,218 ± 3,611	3,172 ± 3,370	0.933
pNN50, %	11.0 ± 10.4	10.4 ± 11.2	0.760	11.7 ± 12.5	11.8 ± 12.9	0.962
HRV triangular index	16.7 ± 5.5	16.1 ± 4.5	0.513	16.2 ± 4.4	16.0 ± 4.1	0.767
Frequency domain						
Total power, ms^2	54,810 ± 26,689	45,169 ± 20,785	0.007*	47,789 ± 24,260	52,594 ± 31,288	0.385
VLF, ms^2	31,706 ± 19,169	24,731 ± 13,606	0.010*	26,393 ± 16,517	28,960 ± 21,171	0.475
LF, ms^2	16,487 ± 8,011	13,616 ± 7,906	0.004*	15,031 ± 8,036	16,790 ± 11,010	0.335
HF, ms^2	5,871 ± 2,644	6,153 ± 2,589	0.523	5,676 ± 2,635	6,121 ± 2,954	0.431
LF/HF ratio	3.1 ± 2.0	2.5 ± 1.5	0.031*	2.9 ± 1.7	3.2 ± 2.5	0.331
LFnu	71.2 ± 10.1	66.6 ± 12.6	0.015*	69.4 ± 14.3	68.7 ± 14.3	0.686
HFnu	28.8 ± 10.1	33.4 ± 12.6	0.015*	30.6 ± 14.3	31.3 ± 14.3	0.686

MAD, mandibular advancement device; AHI, apnea-hypopnea index; REM, rapid eye movement; ODI, oxygen desaturation index; REM, rapid eye movement; SDNN, standard deviation of NN intervals; SDANN, standard deviation of the 5-min averages of NN intervals; RMSSD, the square root of the mean of the squared differences of

adjacent NN intervals; NN50 count, number of pairs of adjacent NN intervals more than 50 ms; pNN50, rate of NN50 in total number of NN intervals; VLF, very low frequency; LF, low frequency; HF, high frequency; LFnu, LF power in normalized units; HFnu, HF power in normalized units; * $P < 0.05$

Table 1-5. Changes in nocturnal heart rate variability after the use of a mandibular advancement device in the success and failure groups

	Success (N = 24)			Failure (N = 34)		
Variable	Baseline	With MAD	*P* value	Baseline	With MAD	*P* value
Time domain						
Average NN interval, ms	968.4 ± 136.3	1004.8 ± 130.0	0.031*	935.9 ± 132.9	976.9 ± 125.5	0.010*
SDNN, ms	95.3 ± 33.6	89.0 ± 24.4	0.447	97.8 ± 32.4	86.3 ± 28.7	0.035*
SDANN, ms	62.3 ± 24.7	71.6 ± 36.2	0.213	67.3 ± 34.5	64.7 ± 47.9	0.799
RMSSD, ms	52.0 ± 49.2	41.6 ± 22.8	0.293	62.7 ± 42.9	53.2 ± 43.8	0.302
NN50 count	2,545 ± 2,913	2,248 ± 2,210	0.615	3,473 ± 3,337	3,291 ± 3,332	0.688
pNN50, %	9.2 ± 10.0	8.4 ± 8.4	0.686	12.7 ± 11.9	12.8 ± 13.5	0.929
HRV triangular index	15.8 ± 4.6	15.4 ± 4.6	0.746	17.0 ± 5.3	16.5 ± 4.1	0.507
Frequency domain						
Total power, ms^2	54,330 ± 26,087	44,123 ± 18,974	0.017*	50,193 ± 25,727	51,148 ± 29,426	0.828
VLF, ms^2	31,474 ± 19,753	24,367 ± 12,701	0.032*	28,120 ± 17,113	27,973 ± 19,677	0.960
LF, ms^2	16,324 ± 7,501	13,156 ± 7,487	0.008*	15,574 ± 8,405	16,181 ± 10,407	0.664
HF, ms^2	5,822 ± 2,292	5,960 ± 2,482	0.796	5,768 ± 2,861	6,266 ± 2,907	0.278

LF/HF ratio	3.1 ± 2.2	2.5 ± 1.6	0.083	3.0 ± 1.6	3.0 ± 2.2	0.801
LFnu	71.2 ± 10.4	66.8 ± 11.2	0.049*	69.9 ± 13.0	67.9 ± 15.5	0.214
HFnu	28.8 ± 10.4	33.2 ± 11.2	0.049*	30.1 ± 13.0	32.1 ± 15.5	0.214

MAD, mandibular advancement device; SDNN, standard deviation of NN intervals; SDANN, standard deviation of the 5-min averages of NN intervals; RMSSD, the square root of the mean of the squared differences of adjacent NN intervals; NN50 count, number of pairs of adjacent NN intervals more than 50 ms; pNN50, rate of NN50 in total number of NN intervals; VLF, very low frequency; LF, low frequency; HF, high frequency; LFnu, LF power in normalized units; HFnu, HF power in normalized units; * $P < 0.05$

Table 1-6. Comparison of changes from baseline in nocturnal heart rate variability after the use of a mandibular advancement device between the response and nonresponse groups

Variable	Response (N = 36)	Nonresponse (N = 22)	*P* value
Time domain measures			
Average NN interval, ms	44.48(6.02 to 82.94)	-0.37(-48.12 to 47.38)	0.086
SDNN, ms	-8.78(-25.02 to 7.47)	-3.75(-23.92 to 16.42)	0.645
SDANN, ms	23.84(1.30 to 46.39)	-1.21(-29.21 to 26.79)	0.101
RMSSD, ms	-7.34(-31.41 to 16.73)	-2.20(-32.08 to 27.68)	0.750
NN50 count	25.82(-1263.01 to 1314.66)	367.47(-1232.73 to 1967.68)	0.692
pNN50, %	1.01(-3.59 to 5.61)	1.93(-3.79 to 7.64)	0.766
HRV triangular index	-1.16(-3.39 to 1.07)	-0.08(-2.85 to 2.70)	0.470
Frequency domain measures			
Total power, ms^2	-11004.00(-21448.00 to -559.85)	5162.16(-7804.99 to 18129.00)	0.024*
VLF, ms^2	-7695.10(-15021.00 to -368.97)	2580.36(-6515.71 to 11676.00)	0.061
LF, ms^2	-3483.21(-6690.23 to -276.19)	2057.00(-1924.82 to 6038.81)	0.012*
HF, ms^2	197.72(-1049.70 to 1445.13)	404.02(-1144.76 to 1952.80)	0.805
LF/HF ratio	-0.55(-1.25 to 0.16)	0.33(-0.55 to 1.21)	0.069

LFnu	-4.53(-9.13 to 0.07)	-1.28(-7.00 to 4.43)	0.295
HFnu	4.53(-0.07 to 9.13)	1.28(-4.43 to 7.00)	0.295
Sleep stage, % of total sleep			
N1	-6.41(-15.18 to 2.36)	-5.94(-16.83 to 4.95)	0.937
N2	2.21(-4.23 to 8.65)	-2.98(-10.98 to 5.01)	0.231
N3	2.78(0.34 to 5.23)	5.12(2.08 to 8.15)	0.157
REM sleep	3.66(1.08 to 6.25)	1.18(-2.03 to 4.39)	0.156

MAD, mandibular advancement device; SDNN, standard deviation of NN intervals; SDANN, standard deviation of the 5-min averages of NN intervals; RMSSD, the square root of the mean of the squared differences of adjacent NN intervals; NN50 count, number of pairs of adjacent NN intervals more than 50 ms; pNN50, rate of NN50 in total number of NN intervals; VLF, very low frequency; LF, low frequency; HF, high frequency; LFnu, LF power in normalized units; HFnu, HF power in normalized units; REM, rapid eye movement.

Values are reported as least squares means (LS-means) and the 95% confidence intervals from the ANCOVA adjusted for age, sex, and body mass index; * $P < 0.05$

Table 2-1. Comparison of baseline characteristics between the sleep surgery group and mandibular advancement device group in polysomnographic parameters and heart rate variability

Variable	Sleep surgery (N = 30)	MAD (N = 30)	*p* value
Age, years	42.5 ± 11.8	51.6 ± 9.2	0.001*
Sex, male/female	27/3	27/3	1.000
Body mass index, kg/m^2	26.8 ± 3.4	26.7 ± 2.9	0.945
Polysomnographic parameters			
AHI, /hour	44.7 ± 25.9	44.0 ± 20.3	0.897
REM AHI, /hour	37.7 ± 22.2	31.2 ± 22.0	0.259
AI, /hour	32.5 ± 25.3	31.9 ± 19.6	0.916
ODI, /hour	39.4 ± 26.4	37.6 ± 20.8	0.772
Minimal Oxygen sat, %	77.0 ± 11.3	81.3 ± 6.1	0.076
Average Oxygen sat, %	93.6 ± 3.5	94.9 ± 1.6	0.081
Snoring, %	23.2 ± 22.1	32.8 ± 20.0	0.086
TST, min	393.8 ± 45.8	384.8 ± 62.8	0.526
WASO, min	71.6 ± 44.6	73.8 ± 43.2	0.847
SL, min	11.6 ± 10.3	15.7 ± 25.2	0.411
SE, %	82.8 ± 9.7	81.0 ± 11.3	0.517
Arousal, /hour	37.2 ± 24.7	29.9 ± 22.0	0.232
Sleep stage, % of TST			
N1	16.0 ± 10.4	14.6 ± 5.8	0.523
N2	45.0 ± 11.0	47.3 ± 9.5	0.378
N3	8.5 ± 6.4	4.5 ± 5.8	0.014*
REM	15.4 ± 4.7	17.8 ± 5.4	0.074
Heart rate variability index			
Time-domain			

Average NN interval	940.2 ± 140.8	901.1 ± 131.7	0.248
SDNN	101.2 ± 32.7	95.6 ± 35.0	0.527
RMSSD	62.1 ± 36.4	60.1 ± 55.2	0.899
NN50	3569.6 ± 2675	3072.0 ± 3510.8	0.539
Frequency-domain			
Total power, ms^2	52,849 ± 33,237	51,941 ± 25,358	0.906
VLF, ms^2	27,992 ± 22,449	29,241 ± 16,997	0.706
LF, ms^2	16,812 ± 10,531	15,590 ± 7,962	0.614
HF, ms^2	7,083 ± 3,963	5,743 ± 2,755	0.134

MAD; Mandibular advancement device, AHI; Apnea–hypopnea index, REM; Rapid eye movement, AI; Apnea index, ODI; Oxygen demand index, TST; Total sleep time, WASO; Wake time after sleep onset, SL; Sleep latency, SE; Sleep efficiency, NN; normal-to-normal, SDNN; standard deviation of NN intervals, RMSSD; square root of the mean of the squared differences of adjacent NN intervals, NN50; number of pairs of adjacent NN intervals greater than 50 ms, VLF; Very low frequency, LF; Low frequency, HF; High frequency, * $P < 0.05$

Table 2-2. Changes in polysomnographic parameters after treatment in patients with obstructive sleep apnea

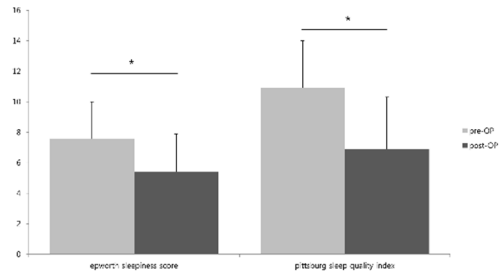
	Sleep surgery (N = 30)			MAD (N = 30)		
Parameter	Baseline	After surgery	*p* value	Baseline	With MAD	*p* value
AHI, /hour	44.7 ± 25.9	21.9 ± 20.1	<0.001*	44.0 ± 20.3	21.3 ± 19.5	<0.001*
REM AHI, /hour	37.7 ± 22.2	25.4± 22.1	0.010*	31.2 ± 22.0	25.1 ± 19.4	0.126
AI, /hour	32.5 ± 25.3	13.9 ± 17.9	<0.001*	31.9 ± 19.6	9.8 ± 13.8	<0.001*
ODI, /hour	39.4 ± 26.4	19.3 ± 18.7	<0.001*	37.6 ± 20.8	17.1 ± 18.0	<0.001*
Minimal Oxygen sat, %	77.0 ± 11.3	82.0 ± 8.0	0.002*	81.3 ± 6.1	83.0 ± 5.1	0.020*
Average Oxygen sat, %	93.6 ± 3.5	95.6 ± 1.8	0.002*	94.9 ± 1.6	95.2 ± 1.3	0.159
Snoring, %	23.2 ± 22.1	14.6 ± 14.2	0.016*	32.8 ± 20.0	28.3 ± 16.9	0.212
TST, min	393.8 ± 45.8	407.2 ± 46.1	0.100	384.8 ± 62.8	377.7 ± 61.0	0.636
WASO, min	71.6 ± 44.6	54.0 ± 39.8	0.017*	73.8 ± 43.2	59.2 ± 37.6	0.081
SL, min	11.6 ± 10.3	14.0 ± 17.7	0.448	15.7 ± 25.2	11.7 ± 10.8	0.392
SE, %	82.8 ± 9.7	85.8 ± 9.1	0.044*	81.0 ± 11.3	84.0 ± 8.8	0.135
Arousal, /hour	37.2 ± 24.7	16.8 ± 17.8	<0.001*	29.9 ± 22.0	13.7 ± 14.0	<0.001*
Sleep stage, % of TST						
N1	16.0 ± 10.4	12.5 ± 9.3	0.029*	14.6 ± 5.8	15.4 ± 24.2	0.870
N2	45.0 ± 11.0	48.8 ± 11.9	0.035*	47.3 ± 9.5	51.7 ± 8.5	0.045*

N3	8.5 ± 6.4	9.6 ± 7.1	0.183	4.5 ± 5.8	6.4 ± 5.6	0.027*
REM	15.4 ± 4.7	17.9 ± 5.6	0.034*	17.8 ± 5.4	17.8 ± 7.0	0.968

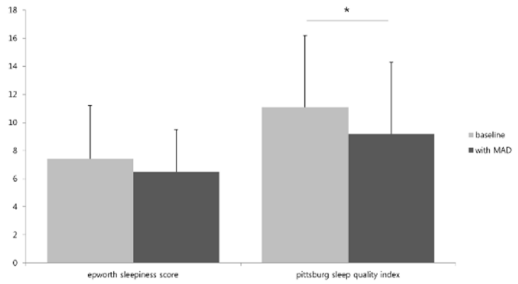
MAD; Mandibular advancement device, AHI; Apnea-hypopnea index, REM; Rapid eye movement, AI; Apnea index, ODI; Oxygen demand index, TST; Total sleep time, WASO; Wake time after sleep onset, SL; Sleep latency, SE; Sleep efficiency, * $P < 0.05$

Figure. 2-1 Changes in the mean of sleep questionnaires before and 3 months after sleep surgery or mandibular advancement device.

a. Epworth sleepiness scale and Pittsburgh sleep quality index scores were significantly decreased after sleep surgery as compare to baseline. **b**. The Pittsburgh sleep quality index score was significantly decreased after mandibular advancement device treatment. The Epworth sleepiness scale score tended to decrease after mandibular advancement device treatment, but this change was not statistically significant. * $P < 0.05$



(a)



(b)

Table 2-3. Changes in heart rate variability indices after treatment in patients with obstructive sleep apnea

	Sleep surgery (N = 30)			MAD (N = 30)		
Index	Baseline	After surgery	*p* value	Baseline	With MAD	*p* value
Time-domain						
Average NN interval	942.2 ± 140.8	994.6 ± 143.1	0.008*	901.1 ± 131.7	953.7 ± 123.1	0.002*
SDNN	101.1 ± 32.7	93.6 ± 31.6	0.173	95.6 ± 35.0	88.7 ± 29.7	0.363
RMSSD	62.1 ± 36.4	67.9 ± 53.0	0.427	60.6 ± 55.2	53.7 ± 43.5	0.568
NN50	3569.6 ± 2675.0	3672.1 ± 2794.9	0.832	3072.0 ± 3510.8	2927.2 ± 3284.5	0.759
Frequency-domain						
LF, ms^2	16,812 ± 10,531	13,710 ± 8,381	0.012*	15,590 ± 7,962	13,599 ± 8,906	0.213
HF, ms^2	7,083 ± 3,963	7,348 ± 3,517	0.618	5,743 ± 2,755	6,087 ± 2,625	0.486
LF/HF ratio	2.9 ± 1.8	2.3 ± 1.7	0.017*	3.0 ± 1.8	2.4 ± 1.4	0.025*
LFnu	69.0 ± 13.2	63.2 ± 13.7	0.009*	70.9 ± 10.7	66.3 ± 12.5	0.024*
HFnu	31.0 ± 13.2	36.8 ± 13.7	0.009*	29.1 ± 10.7	33.7 ± 12.5	0.024*

NN; normal-to-normal, SDNN; standard deviation of NN intervals, RMSSD; square root of the mean of the squared differences of adjacent NN, NN50; number of pairs of adjacent NN intervals greater than 50 ms, LF; Low frequency, HF; High frequency, LFnu; Low frequency normalized unit, HFnu; High frequency normalized unit, * $P < 0.05$

Table 2-4. Comparative efficacy of sleep surgery versus mandibular advancement device in terms of heart rate variability

Index	Sleep surgery (N = 30)	MAD (N = 30)	*p* value
Change in time-domain			
Average NN interval	54.7(19.8 to 89.5)	50.3(15.5 to 85.2)	0.867
SDNN	-4.9(-18.6 to 8.8)	-9.6(-23.3 to 4.1)	0.643
RMSSD	10.2(-10.7 to 31.1)	-11.3(-32.2 to 9.6)	0.170
NN50	287.5(-697.7 to 1272.7)	-329.8(-1315.0 to 655.4)	0.400
Change in frequency-domain			
LF, ms^2	-2961.3(-5886.4 to -36.3)	-2131.0(-5056.0 to 794.1)	0.702
HF, ms^2	215.8(-743.7 to 1175.2)	394.0(-565.5 to 1353.4)	0.802
LF/HF ratio	-0.6(-1.1 to -0.1)	-0.6(-1.1 to -0.1)	0.931
LFnu	-5.4(-9.4 to -1.5)	-5.0(-8.9 to -1.0)	0.876
HFnu	5.4(1.5 to 9.4)	5.0(1.0 to 8.9)	0.876

NN; normal-to-normal, SDNN; standard deviation of NN intervals, RMSSD; square root of the mean of the squared differences of adjacent NN intervals, NN50; number of pairs of adjacent NN intervals greater than 50 ms, LF; Low frequency, HF; High frequency, LFnu; Low frequency normalized unit, HFnu; High frequency normalized unit, Values

are reported as least squares means (LS-means) and the 95% confidence intervals from ANCOVA adjusted for age, body mass index, and baseline apnea–hypopnea index

국문 초록

서론: 본 연구의 목표는 (1 장) 심박변이도 분석을 통하여 하악구강전진 장치의 효능을 평가해 보는 것과 (2 장) 심박변이도 분석을 활용하여 수면수술과 하악전진장치의 효능에 관하여 비교 분석하는 것이다.

대상 및 연구 방법: (1 장) 폐쇄성수면무호흡증의 치료를 위해 하악전진장치를 사용한 총 58 명의 환자의 치료 이전과 치료 3 개월 후의 심박변이도 분석 및 설문조사의 결과를 비교하였다. (2 장) 폐쇄성수면무호흡증의 치료를 위하여 수면수술을 시행 받은 환자와 하악전진장치를 사용한 환자의 성별, 나이, 수면무호흡-저호흡 지수를 대응시켜 각각 30 명의 환자를 선별하였고 선별 환자의 심박변이도 변화를 측정하여 치료 방법 간의 우월성에 관한 평가를 시행하였다.

결과: (1 장) 심박변이도 분석 항목 중 NN interval, SDNN, LFnu, HFnu 가 치료 전에 비해 하악전진장치의 사용 후 유의미하게 변하였다. 더 자세한 분석을 위하여 환자들을 치료의 성공 및 실패 기준(수면무호흡-저호흡 지수가 치료 후 치료 이전 대비 50% 이상 감소하고 동시에 절대치가 20 이하로 감소)에 따라 치료 반응군 및 비반응군으로 분류하여 각 군의 심박변이도의 변화를 측정하였다. 반응군에서 NN inverval, HFnu 는 유의하게 증가하였고, TP, VLF, LF, LF/HF 비율, LFnu 는 유의하게 감소한 반면 비반응군에서는 HRV 의 유의한 변화가 전혀 관찰되지 않았다. 나이와 성별 및 BMI 에 HRV 의 변화를 보정한 결과에도 TP, LF 가 반응군에서 비반응군에 비해 유의한 변화를 보였다. (2 장) 심박변이도의 시간 변이 분석 상 NN interval 평균값의 변화가 수면수술군(942.2 ±

140.8 to 994.6 ± 143.1, P = 0.008)과 하악전진장치군(901.1 ± 131.7 to 953.7 ± 123.1, P = 0.002)에서 모두 유의하게 관찰되었다. LF/HF 비율도 두 군 모두 유의하게 감소(2.9 ± 1.8 to 2.3 ± 1.7, P = 0.017, vs 3.0 ± 1.8 to 2.4 ± 1.4, P = 0.025)하였고 HFnu 는 LFnu 의 감소와 반비례하여 유의한 증가(31.0 ± 13.2 to 36.8 ± 13.7, P = 0.009, vs. 29.1 ± 10.7 to 33.7 ± 12.5, P = 0.024) 양상을 두 군 모두에서 확인할 수 있었다. 하지만 심박변이도의 변화를 나이, BMI 및 수면무호흡-저호흡 지수에 보정하여 변화를 비교해 본 결과 심박변이도의 변화에는 군간의 우열이 관찰되지 않았다.

결론: (1 장) 하악전진장치를 이용한 폐쇄성수면무호흡증의 치료는 심박변이도의 변화를 가져오며 이러한 변화는 치료 효과를 예측할 수 있는 지표로 사용될 가능성이 있다. (2 장) 수면수술과 하악전진장치는 심장자율신경활성도의 측면에서 동등한 효능을 가지고 있는 치료이다.

주요어: 폐쇄성수면무호흡, 심박변이도, 하악전진장치, 수면수술, 치료 효능, 심장자율신경활성도

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