

Long Term Effects of Continuous Positive Airway Pressure in Obstructive Sleep Apnea Patients: Apnea-Hypopnea Index and Blood Pressure Changes

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Background and Objective Obstructive sleep apnea (OSA) is characterized by repetitive episodes of complete or partial upper airway obstruction during sleep. Although, optimal treatment of OSA with continuous positive airway pressure (CPAP) reduce the number of respiratory events during sleep, and thus improve daytime sleepiness, quality of life, and cardiovascular risk, there are few studies that address the long term effects of CPAP treatment. This study aims to determine the long term effects of positive airway pressure (PAP) in compliant OSA patients.

Methods Forty OSA patients naïve to PAP treatment were included. Polysomnography for apnea-hypopnea index, sleep structure, and desaturation index, blood pressure, Epworth Sleepiness Scale (ESS) for excessive daytime sleepiness, and Beck Depression Inventory (BDI) for depressive mood were initially administered before the PAP treatment and after the long term PAP treatment. We have excluded immediate pneumatic effects of the PAP treatment, by administrating a follow up study after 7 days of PAP treatment withdrawal.

Results A total of 40 (male: 92.5%, mean age: 54.4 ± 10.4 yr) patients were enrolled. The duration of PAP treatment was 3.4 ± 1.4 years. The initial apnea-hypopnea index (AHI) was 50.8 ± 22.6 /hr which decreased to 34.4 ± 19.1 /hr ($p \leq 0.001$). These significant reductions in AHI were seen without Body Mass Index changes ($p = 0.707$). The sleep architecture revealed no significant changes between the initial and follow up study. The systolic and diastolic blood pressure (DBP) decreased significantly after the long term CPAP treatment (systolic blood pressure pre: 138.5 ± 18.1 , post: 122.3 ± 13.7 , $p \leq 0.001$, DBP pre: 88.7 ± 13.6 , post: 78.5 ± 11.1 , $p \leq 0.001$). ESS and BDI decreased significantly after years of PAP treatment compared to the baseline study (ESS pre: 11.5 ± 5.3 , post: 8.3 ± 4.7 , $p \leq 0.001$, BDI pre: 12.7 ± 11.6 , post: 6.3 ± 7.0 , $p = 0.019$).

Conclusions This study confirmed that after years of faithful PAP treatment for OSA, the severity of OSA significantly improved. In addition, blood pressure, daytime sleepiness, and depression levels also decreased significantly.

Sleep Med Res 2012;3:20-26

Key Words OSA, CPAP, Body weight, Blood, Pressure.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of complete or partial upper airway obstruction occurring during sleep. Excessive daytime sleepiness (EDS), the major presenting complaint, is associated with an increased risk of traffic accidents.^{1,2} It also impairs quality of life by increasing the risk of hypertension (HTN) and cardiovascular disease.³⁻⁷ OSA can be treated with continuous positive airway pressure (CPAP). The CPAP working as a pneumatic splint to relieve airway obstruction during sleep eliminates respiratory events.^{8,9} Reduction of respiratory events during sleep improves daytime sleepiness, quality of life, and cardiovascular risk in randomized-controlled trials.^{1,10}

Previously, baseline and follow up sleep studies of CPAP treatment revealed significant improvement of the apnea-hypopnea index (AHI) index even after the discontinuation of treatment.¹¹⁻¹³ However, the follow up studies done in these studies were only after one night of treatment withdrawal, and the duration of CPAP treatment was less than 1 year (few months

Received: August 27, 2012

Revised: October 22, 2012

Accepted: November 17, 2012

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to 1 year). Further, there is only one randomized controlled study investigating the CPAP withdrawal on OSA severity, sleepiness, psychomotor performance, and measures of cardiovascular risk.¹⁴

This study investigated the long term effects of OSA after compliant positive airway pressure (PAP)(CPAP, or AutoPAP) therapy. The included subjects are naïve to CPAP treatment with good compliance defined by more the 4 hours use per night. The authors studied the baseline and follow up measurements of severity of OSA syndrome, sleep architectures, subjective daytime sleepiness, cardiovascular risk factors, and mood changes.

METHODS

Study Population

The patients were recruited from June 2006 to January 2009 in a Sleep Clinic at the Samsung Medical Center, Korea. All patients were diagnosed with moderate to severe OSA by the initial overnight polysomnography (PSG)(AHI > 15/hr) and were naïve to CPAP treatment. All the patients underwent complete medical examination, and were screened for underlying HTN, diabetes, dyslipidemia, atrial fibrillation, heart failure, stroke and any other disabling medical condition. Body weight, height, and body mass index (BMI) were calculated. We excluded those with localized anatomical defects of the upper respiratory pathway, or with neurological and endocrine disease known to be associated with OSA. We also excluded patients taking drugs active on the central nervous system and those who suffered from chronic alcoholism. All patients, after diagnosis of OSA were treated with PAP either by CPAP or AutoPAP. Finally, forty compliant PAP users were able to have the follow PSG study. The compliant user indicating averages of at least four hours of use per night were ultimately included.

These patients went through initial studies of overnight PSG, blood pressure, Epworth Sleepiness Scale (ESS), and Beck Depression Inventory (BDI) measurements. The same studies were repeated for a follow up study after years of PAP treatment, however to avoid the immediate effects of PAP treatment, patients were withdrawn from the treatment for 1 week prior to the follow up study.

The overnight PSG was conducted including a 6 channel electroencephalogram (EEG)(F4-M1, F3-M2, C3-M2, C4-M1, O1-M2, O2-M1), a 2 channel electrooculogram, a 4 channel electromyogram for the chin, intercostals muscles, right and left anterior tibialis, and electrocardiogram (ECG)(Embla Co., Broomfield, CO, USA). The EEG and ECG signals were digitized at a sampling rate of 200 Hz. Nasal pressure, plethysmography, thoracic and abdominal breathing movement were also recorded. All PSG studies were manually sleep-staged in 30 second epochs by experienced sleep technologists according to

the American Academy of Sleep Medicine (AASM) criteria.¹⁵ Respiratory events including obstructive apnea and hypopnea were scored manually based on the AASM criteria. The obstructive sleep apnea syndrome (OSAS) was defined when the AHI was more than 5/hr. Nine patients underwent full-night PSG and 31 patients underwent split-night PSG. Split night PSG is a sleep study during which the first two or more hours of the sleep period are used to assess OSA, and if criteria are met, CPAP titration is performed during the remainder of the night. Criteria for switch over to the CPAP titration is when the AHI > 10/hr. The same procedure was done for the follow up PSG study and of them 7 patients underwent split night PSG and 33 patients underwent full night PSG. The follow-up PSG study was done after CPAP treatment was interrupted for 7 days.

Questionnaires for EDS and depressive mood were done at the initial evaluation of PSG, and at follow up. The severity of EDS was evaluated by using the ESS questionnaire.¹⁶ The ESS questionnaire requires subjects to rate the likelihood that they might doze off or fall asleep in eight different everyday situations. The sleepiness is scored from 0 to 3 points, where 3 represent a high likelihood of dozing or falling asleep. BDI contains 21 groups of four statements regarding cognitive, biologic and emotional symptoms of depression, each scored between 0 and 3.¹⁷ The ESS scores high when the subject reports sleepiness and BDI scores high when the subject reports a depressive mood. A BDI score of 10 or more indicates mild depressive mood, and 16 or more suggests depression.

Blood pressure was documented in all the enrolled patients regardless of previously diagnosed HTN. Patients were asked to abstain from caffeine containing products, and remain in a stable resting state before the systolic blood pressure (SBP), and diastolic blood pressure (DBP) measurement. Blood pressures were measured in the sitting position during the outpatient clinic visits, baseline during the initial visit and follow up during the last visit before the second PSG study.

Statistical Analysis

Continuous data are expressed as mean (\pm standard deviation) or median and categorical data are presented as percent frequencies and percentages. The difference in the pre-PAP treatment and post-PAP treatment values were compared. The variables were compared by paired t-test before and after CPAP therapy. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Forty OSA patients successfully used PAP for mean 3.4 ± 1.4 years. The mean age was 54.4 ± 10.4 years, and there was a sig-

Table 1. Clinical characteristics, sleep parameters, sleepiness, and depressive mood of enrolled patients

(n = 40)	Baseline	Follow-up	p-value
Age, years (SD)	54.4 (10.4)		
Male gender, n (%)	37 (92.5)		
Weight, kg (SD)	73.2 (8.6)	73.6 (9.1)	0.537
BMI, kg/m ² (SD)	26.1 (2.7)	26.1 (2.7)	0.908
Underlying vascular risk factors			
Hypertension, n (%)	10 (25.0)		
Systolic BP, mm Hg (SD)	138.5 (18.1)	122.3 (13.7)	< 0.001
Diastolic BP, mm Hg (SD)	88.7 (13.6)	78.5 (11.1)	< 0.001
Diabetes mellitus, n (%)	1 (2.5)		
Dyslipidemia, n (%)	6/39 (15.0)		
Previous ischemic stroke, n (%)	1 (2.5)		
Ischemic heart disease, n (%)	3 (7.5)		
Valvular heart disease, n (%)	2 (5.0)		
Cardiac arrhythmia, n (%)	3 (7.5)		
Sleep parameters, Sleepiness, Depressive mood			
AHI, /hr (SD)	50.8 (22.6)	34.4 (19.1)	< 0.001
Arousal index, /hr (SD)	45.3 (20.8)	33.4 (15.8)	< 0.001
Lowest SpO ₂ , % (SD)	78.0 (9.30)	82.3 (5.3)	< 0.001
ESS, (SD)	11.5 (5.3)	8.3 (4.7)	< 0.001
BDI, (SD)	12.7 (11.6)	6.3 (7.0)	0.019
≤ 9, n (%)	20 (50)	32 (80)	
10-15 n (%)	2 (5)	4 (10)	
≥ 16 n (%)	18 (45)	4 (10)	
CPAP treatment profile			
Total time of CPAP use, years (SD)	3.5 (1.3)		
Mean time of CPAP use per night, minutes (SD)	356.0 (68.0)		
Percent days of use, % (SD)	92.8 (19.0)		
AHI on PAP use, /hr (SD)	4.2 (3.4)		
Mean PAP pressure, mm Hg (SD)	9.7 (1.7)		
Type of mask			
Nasal mask, n (%)	30 (75.0)		
Nasal pillows, n (%)	9 (22.5)		
Full face, n (%)	1 (2.5)		

SD: standard deviation, BMI: Body Mass Index, AHI: apnea hypopnea index, ESS: Epworth Sleepiness Scale, BDI: Beck Depression Inventory, PAP: positive airway pressure.

nificant male predominance (n = 37, 92.5%). The baseline characteristics of the subjects studied are described in Table 1. The mean BMI index was 26.1 ± 2.7 kg/m². The mean ESS score was 11.5 ± 5.3 . Among 40 enrolled patients, 10 patients were diagnosed with HTN, 1 with diabetes mellitus, 6 dyslipidemia, 1 ischemic stroke, 3 ischemic heart diseases, 3 atrial fibrillation, 2 valvular heart diseases and none of the patients had a history of congestive heart failure.

All the enrolled patients underwent baseline and follow up sleep studies. The initial baseline PSG results of 40 patients re-

vealed mean AHI of 50.8 ± 22.6 /hr (min: 16.9/hr, max: 118.3/hr). The mean lowest nocturnal desaturation levels were $78.6 \pm 9.30\%$ (min: 61%, max: 89%), which demonstrated that the majority of patients were in the moderate or severe OSA range. After the initial sleep study, 16 patients were treated with CPAP and 24 patients were treated with AutoPAP. We confirmed from the downloaded data regarding the PAP device during the follow up period that these patients were treated with optimal pressure and duration, suggested by mean AHI < 10/hr, and mean time used per day > 4/hr.

The average duration of the PAP uses since the diagnosis were 3.4 ± 1.4 years. It is remarkable that there was no significant change in BMI (pre: 26.1 ± 2.7 , post: 26.1 ± 2.7 , $p = 0.91$) during the course of follow up (Table 1, Fig. 1).

Among 40 enrolled patients, there were 7 patients who went through paired full night PSG initially and at follow up. Sleep structures were compared among these 7 patients. The sleep architecture revealed no significant changes between the initial and follow up PSG (Table 2). The AHI reduction was also seen among 7 selected patients (pre-PAP AHI = 45.0 ± 7.1 /hr, post-PAP AHI = 27.0 ± 15.5 /hr, $p = 0.014$). The significant changes between pre- and post-PAP PSGs in sleep stage I, rapid eye movement (REM) sleep, slow wave sleep (SWS), sleep latency, sleep efficiency, lowest desaturation and arousal index were not seen. The changes between the pre- and post-PAP PSGs were time in bed (TIB)(pre: 320.3 ± 94.1 , post: 421.2 ± 55.2 $p = 0.044$), and decrease in wake after sleep onset (WASO)(pre: 32.3 ± 21.6 , post: 15.4 ± 10.6 , $p = 0.018$).

All the patients administered the PAP treatment: minimum of 4 hours per night were required for the enrollment. The average PAP per day was 356.0 ± 68.0 minutes, and the rate of days of use were 92.8 ± 19.0 percent. The faithful PAP treatment of these patients was supported by the findings that during the PAP use the mean pressure was 9.7 ± 1.7 (min: 6.9, max: 13.5), and mean AHI was 4.2 ± 3.4 (min: 1.4, max: 22.4). The type of mask used was chosen based on the patients' preference. 30 used a nasal mask, 9 used nasal pillows, and one used a full face mask.

A significant improvement in AHI was seen compared to the initial AHI, as illustrated in Fig. 1. The average baseline AHI was 50.8 ± 22.6 /hr, which decreased to 34.4 ± 19.1 /hr ($p \leq 0.001$). Among them 5 had an AHI below 15/hr, and none below 5/hr: the majority still remained in a range of moderate to severe OSA. Total of 12 (30.0%) patients had more than a 50% reduction from baseline, 21 (52.5%) patients had < 50% reduction from baseline and 7 (17.5%) patients had an increase

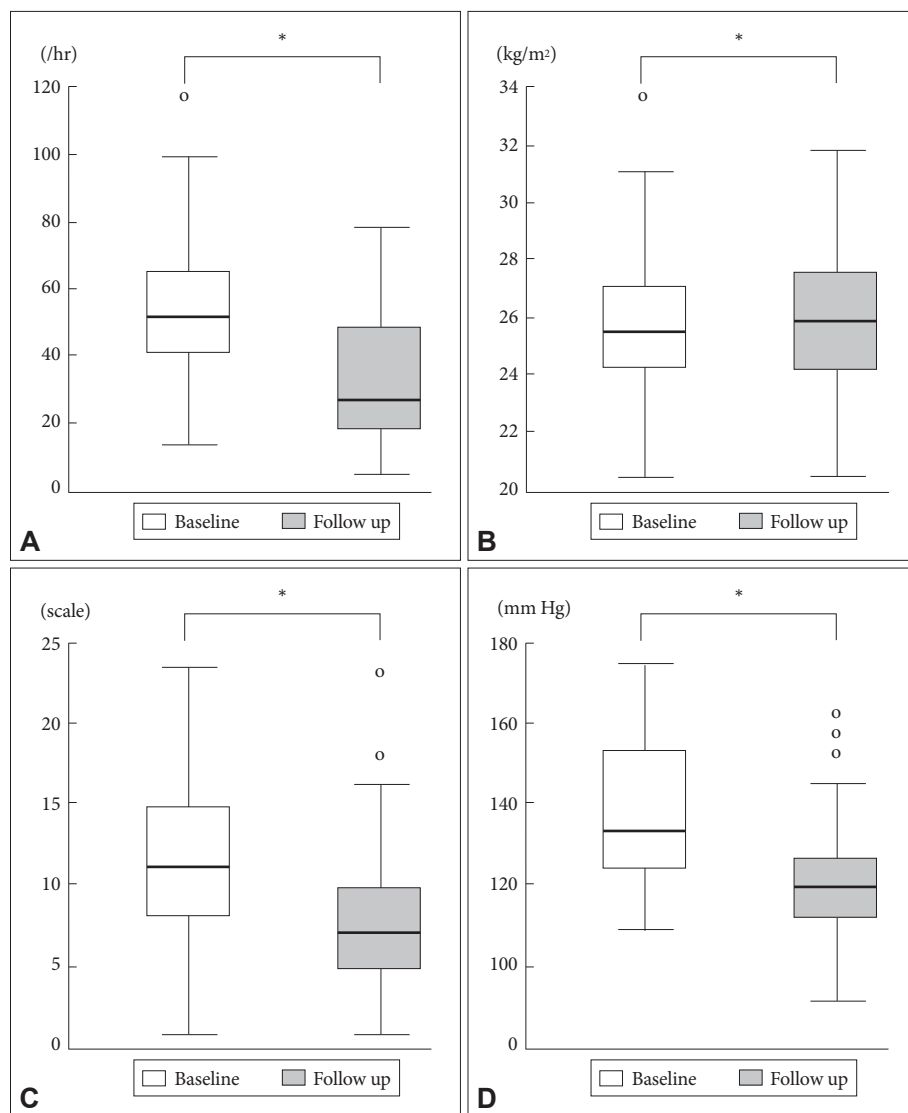


Fig. 1. Comparative illustration of changes between initial and follow up studies. A: Apnea hypopnea index. B: Body Mass Index. C: Epworth Sleepiness Scale. D: Systolic blood pressure. *Statistically significant changes.

Table 2. Sleep parameters in patients with full night PSG

(Total n = 7)	Baseline PSG study	Follow-up PSG study after CPAP treatment	p-value
Age, years (SD)	53.0 (11.0)		
Male gender, n (%)	7 (100)		
BMI, kg/m ² (SD)	25.0 (3.0)	25.2 (2.8)	0.707
TST, minutes (SD)	311.4 (121.0)	350.0 (60.0)	0.412
TIB, minutes (SD)	320.3 (94.1)	421.2 (50.2)	0.044
Sleep efficiency, minutes (SD)	73.1 (20.2)	83.0 (10.4)	0.055
WASO, /hr (SD)	32.3 (21.6)	15.4 (10.6)	0.018
Arousal index, /hr (SD)	33.4 (13.3)	28.8 (11.3)	0.297
Sleep latency, minutes (SD)	11.6 (6.9)	7.6 (8.0)	0.194
REM sleep latency, minutes (SD)	151.6 (74.0)	135.1 (83.2)	0.398
AHI, /hr (SD)	45.0 (7.1)	27.0 (14.5)	0.014
Sleep stage distribution			
NREM 1, % (SD)	28.8 (9.9)	27.2 (10.0)	0.729
NREM 2 % (SD)	51.7 (5.8)	51.5 (8.7)	0.947
SWS, % (SD)	1.7 (2.9)	3.0 (3.9)	0.434
REM, % (SD)	17.8 (6.4)	18.3 (7.0)	0.866
Lowest SpO ₂ , % (SD)	72.3 (14.3)	82.7 (6.3)	0.060
PLMS, /hr (SD)	12.2 (20.9)	4.7 (5.7)	0.465
MAI, /hr (SD)	0.8 (1.6)	0.6 (1.4)	0.180
Snoring score, (SD)	1.8 (0.3)	1.7 (0.3)	0.317

PSG: polysomnography, CPAP: continuous positive airway pressure, SD: standard deviation, TST: total sleep time, TIB: time in bed, WASO: wake after sleep onset, REM: rapid eye movement, AHI: apnea hypopnea index, NREM: non rapid eye movement, SWS: slow wave sleep, PLMS: periodic limb movements in syndrome, MAI: movement arousal index.

in AHI compared to baseline despite optimal use. Each subgroup had no significant BMI between baseline and follow up studies. The exposure to hypoxemia at night improved not only due to a decrease in the frequency of obstructive events but also to an improvement in the mean nocturnal desaturation. The lowest nocturnal desaturation revealed significant change from $78.0 \pm 9.0\%$ before PAP treatment to $82.3 \pm 5.3\%$ after PAP treatment.

After PAP treatment, SBP and DBP significantly decreased by -16.2 and -10.2 mm Hg, respectively (SBP pre: 138.5 ± 18.1 , post: 122.3 ± 13.7 , $p \leq 0.001$, DBP pre: 88.7 ± 13.6 , post: 78.5 ± 11.1 , $p \leq 0.001$)(Table 1, Fig. 1). Subgroup analysis revealed that 10 patients who were diagnosed with HTN and were on anti-hypertensive medication had statistically significant SBP reduction (pre: 140.4 ± 17.6 , post: 126.4 ± 10.7 , $p = 0.008$), but no significant changes in DBP ($p = 0.114$). The 30 normotensive patients had statistically significant SBP, and DBP reduction (SBP pre: 138.0 ± 18.2 , post: 120.8 ± 14.3 , $p < 0.001$, DBP pre: 87.9 ± 13.3 , post: 76.5 ± 11.6 , $p < 0.001$)

The ESS indicating subjective daytime sleepiness also decreased (pre: 11.5 ± 5.3 , post: 8.3 ± 4.7 , p value < 0.001)(Table 1, Fig. 1). The BDI score significantly decreased after PAP treatment (pre: 12.7 ± 11.6 , post: 6.3 ± 7.0 , p value $= 0.019$)(Table 1). The initial BDI score revealed that the prevalence of undetect-

ed mild depression (BDI score 10-15) was 5% at base line and 10% after PAP treatment, and depression (BDI score ≥ 16) at baseline was 50% and 10% after PAP treatment (Table 1).

DISCUSSION

This study investigated the long term average use (3.5 years) effects of PAP in compliant OSA patients. We evaluated the severity of OSA, sleep architectures, subjective daytime sleepiness, blood pressure, and depressive mood by BDI score. Similar studies have been reported the change of pre- and post-CPAP treatment; however these reports were focused on the immediate changes caused by withdrawal of nasal CPAP after only a few months of use. This study explored the long term effects of compliant PAP treatment compared to baseline data. Furthermore, to exclude residual PAP effects, follow-up studies were done after PAP treatment withdrawal for 1 week.

The baseline and follow-up PSG indicated a statistically significant decrease of AHI after PAP treatment. Similar studies have been previously reported which indicated that OSA patients, optimally treated for months, show improvement of AHI severity even after the withdrawal of CPAP treatment,¹¹⁻¹³ These studies were designed in patients with CPAP treatment

less than 1 year (a few months to 1 year), and follow-up PSG studies done only after one night of PAP treatment withdrawal. Since these studies have relatively short PAP treatment duration and only one night of treatment withdrawal, it is not clear whether it was a long term effect or an immediate pneumatic effect of the CPAP treatment for AHI reduction. Only one study focuses on the CPAP withdrawal for 2 weeks in OSA patients who have already been on optimal treatment for at least 12 months. The rapid return of OSA on the first night off CPAP was seen, with further changes until the first week of trial, and not much after a week.¹⁴ This supports that CPAP withdrawal for 7 days, as in this study, is sufficient enough to represent changes in OSA severity of the subjects after long term treatment.

The strength of this study is that the enrolled patient population was naïve to PAP treatment initially and had an average of 3.5 years of PAP use, much longer than the previous studies and withdrawal of PAP treatment was for 7 days. The results of follow-up studies indicate that a long term PAP treatment may have an enlarging effect of the airway or reduce the progression of OSA. There is evidence that OSA worsens over time when left untreated.^{18,19} Further on, this study had excluded the effect of anatomical changes caused by weight gain or loss during the follow-up period. Thus, relatively independent effects of long term PAP use were seen. The CPAP treatment can improve AHI and may halt and reverse the progression of the underlying pathophysiology of OSA. It provides a physical “pneumatic splint” to relieve upper airway obstruction during sleep, thus eliminating respiratory events.¹³ Further contribution of CPAP treatment has been proposed by the partial reversibility of sensory impairment, due to neuropathy. Previously, it has been proposed that the upper airway neuropathy in OSA is due to the mechanical trauma associated with snoring and apneas, oxidative stress related to hypoxia-oxygenation, and inflammation resulting from both of these insults.^{9,13,14,20-22} The partial improvement of OSA, can in part be explained by the reversibility of such a mechanism after long term treatment with PAP. Furthermore, increased intra-airway pressure during PAP treatment for several years may enlarge the airway opening although we did not follow-up the airway magnetic resonance imaging study.

The sleep structure of patients with OSAS is characterized by the loss of physiological REM/NREM alternation as well as by a deficit of REM and SWS and excess of sleep stages 1 and 2.²³⁻²⁵ This can be caused by sleep fragmentation as a result of the high amount of arousals related to respiratory events.²³ The disturbance of sleep structures have been reported to improve with CPAP treatment.^{12,23} However, long term PAP did not improve the disturbed sleep structure that was seen at the initial sleep study. However, only 7 patients had both pre- and post-PAP full night PSG and post-PAP AHI was still abnormal. This result correlates well with previous studies of sleep structure changes after CPAP withdrawal for 1 and 14 days.¹²⁻¹⁴ However, WASO decreased after long term PAP treatment in the present study.

Cardiovascular risk factor assessments by changes in blood pressure revealed a significant decrease in SBP and DBP after PAP treatment. In our study, compared to the pre-PAP period, SBP and DBP measured at post-PAP treatment decreased significantly by 16.2 and 10.2 mm Hg, respectively. Remarkably, the reductions of blood pressure were also seen in the normotensive patients. There are numerous reports on the effects of CPAP on the reduction of BP in patients with OSA and sustained HTN. The decrease of blood pressure after 1 or 2 months of CPAP treatment varies from 2.5 to 8 mm Hg depending on the AHI severity, and initial blood pressure.²⁶ Furthermore, significant increase in systolic (+ 8.5 mm Hg) and diastolic (+ 6.9 mm Hg) blood pressure after 2 week of CPAP treatment withdrawal have been reported.¹⁴ However, this study was focused on the changes of blood pressure between the optimal CPAP treatment period and after CPAP withdrawal. Our results, which compared blood pressures between pre- and post-PAP treatment periods in long term compliant users, indicated a significant decrease in blood pressure after PAP treatment. Although, rapid returns of blood pressure after CPAP withdrawal are also reported, years of effective PAP use and AHI decrease post-PAP treatment may have contributed to the stable reduction of the baseline blood pressure.

The EES scores indicating subjective daytime sleepiness in this study have decreased from an average of 11.5 to 8.3. This is contrary to previous studies, which indicated a rapid increase in ESS scores after CPAP treatment withdrawal.^{11,12} However, these studies represent only 1 night of treatment withdrawal, in patients who have been on treatment for a few months to 1 year. Furthermore, sudden withdrawal might have induced rebound sleepiness.

The BDI has been used to assess depressive mood.²⁷ The BDI scores are reported to be high in 20-25% of OSA patients.²⁸ However, the results of studies on BDI changes following CPAP treatment were controversial. Some studies have reported a decrease in BDI score after CPAP treatment^{29,30} whereas others have not.^{31,32} Our results indicated a significant decrease of BDI score after 3.5 years of PAP treatment and one week withdrawal of PAP treatment.

Our study is not without limitations: First, this study does not have a sub-therapeutic or placebo group for comparison. We excluded partially treated or inadequately used patients by enrolling patients who are compliant PAP users. Second, BDI, and ESS scores are based on the patients subjective measurements, other confounding factors should be considered, and straightforward association requires cautious interpretation. Especially, BDI can be scored higher with other related factors such as fatigue, loss of interest, decreased libido, and poor concentration, which have not been evaluated in our study. Third, although we have compared PSG parameters between baseline, and follow up studies, cautious interpretation is needed because follow up full night or split night PSG were selected re-

ardless of which were done for the baseline study.

This study confirmed that after years of faithful PAP treatment for OSA, one week of PAP treatment withdrawal demonstrated a significant decrease of AHI. Moreover, long term PAP treatment induced the improvement in blood pressure, daytime sleepiness, and depressive mood, even after the withdrawal of treatment.

Conflicts of Interest

The authors have no financial conflicts of interest.

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