Can Nasal Continuous Positive Airway Pressure Decrease Clinic Blood Pressure in Patients with Obstructive Sleep Apnea ?

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TUN, Y., HIDA, W., OKABE, S., OGAWA, H., KIKUCHI, Y., OIKAWA, M., KITAMURO, T. and SHIRATO, K. *Can Nasal Continuous Positive Airway Pressure Decrease Clinic Blood Pressure in Patients with Obstructive Sleep Apnea ?* Tohoku J. Exp. Med., 2003, **201** (3), 181-190 — Obstructive sleep apnea (OSA) is commonly associated with systemic hypertension and now recognized as an independent risk factor for daytime hypertension. We aimed to study the short- and long-term effect of nasal continuous positive airway pressure (CPAP) in hypertensive and normotensive patients with OSA. Forty-six patients with moderated to severe OSA were treated with nasal CPAP and followed after one year of treatment. Clinic blood pressure, heart rate, and body weight were taken before and followed up for one year after beginning nasal CPAP. In this study 25 patients with OSA were found to have hypertension (54.3%). The hypertensive group showed a significant reduction in clinic blood pressure after nasal CPAP, whereas the normotensive group showed no changes. The subgroup of hypertensive patients with OSA who had no anti-hypertensive medication revealed a decrease in clinic blood pressure comparable to those with anti-hypertensive drugs. The heart rate was not significantly changed in any patients. There was no significant correlation between the decrease in body weight and the reduction in blood pressure. These results suggest that nasal CPAP alone might have a substantial blood pressure lowering effect in hypertensive patients with OSA. This effect could decrease the morbidity and mortality related to cardiovascular complications in patients with OSA. ——— sleep apnea syndrome; hypoxemia; nasal CPAP; clinic blood pressure

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Received July 3, 2003; revision accepted for publication September 29, 2003.

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Systemic hypertension occurs in nearly one half of patients with obstructive sleep apnea (OSA) and conversely, 20–30% of patients with essential hypertension are found to have OSA (Fletcher 1995). Previously, the association of these two common conditions was thought to be coincidental. Now it has become evident that OSA is an independent risk factor for daytime hypertension in population-based studies (Grote et al. 1999; Peppard et al. 2000). The reason for developing daytime hypertension in OSA is not precisely known but possible underlying mechanisms may include a continuation of the high asleep blood pressure into the daytime period (Weiss et al. 1996; Tun et al. 1999), a sustained rise in daytime sympathetic activities (Carlson et al. 1993) and deranged baroreflex mechanisms due to repeated nocturnal hypoxia (Ziegler et al. 1995). The elimination of the nocturnal events by nasal continuous positive airway pressure (CPAP) reduces the daytime sleepiness and improves the quality of life in patients with OSA (Bennett et al. 1999; D'Ambrosio et al. 1999). Nasal CPAP can suppress the episodic rise in blood pressure following apnea during sleep (Ali et al. 1992). With the treatment of nasal CPAP daytime sympathetic activities in patients with OSA were normalized after 6 months (Narkiewicz et al. 1999). Based on these findings it is plausible that nasal CPAP should lower the blood pressure during the daytime in such patients.

However, previous studies showed inconsistent findings regarding the effects of nasal CPAP on the blood pressure during the daytime in patients with OSA (Rauscher et al. 1993; Suzuki et al. 1993; Worsnop et al. 1993; Davies et al. 1994; Dimsdale et al. 2000). Some studies showed beneficial effects but others did not. Most studies were conducted in a small population of patients with OSA and then, the patients were followed for only a relatively short period after the nasal CPAP treatment (Worsnop et al. 1993). Moreover, some studies investigated the effect of nasal CPAP on blood pressure in

patients with OSA who were normotensive during the daytime (Davies et al. 1994). It is still unclear whether nasal CPAP alone has a blood pressure lowering effect without medication in hypertensive patients with OSA. In this study we aimed to examine the lowering effect of nasal CPAP on the blood pressure during the daytime in patients with OSA, and to clarify the independent effect of nasal CPAP in hypertensive patients with OSA.

PATIENTS AND METHODS

Patients

This study includes 53 consecutive patients with moderate to severe OSA who attended our sleep clinic from 1996 to 1998. All patients had snoring and excessive daytime sleepiness. The Epworth sleepiness scale (ESS) was used to score the daytime sleepiness of the patients (Johns 1991). All patients were newly diagnosed as OSA and had not been previously treated by nasal CPAP or other measures. We followed these patients for up to one year after beginning treatment with nasal CPAP. Among them, 7 patients were excluded since one patient used an oral appliance for treatment and others did not come regularly to the sleep clinic in the follow up period. The remaining 46 patients visited the sleep clinic regularly at least once a month for one year, and fulfilled the study. The 17 patients of these finally enrolled patients had already taken anti-hypertensive drugs when they visited our sleep clinic, and the other patients had not taken any medication. The medication had not been changed throughout the follow up period. Each patient gave informed consent to this study.

Blood pressure measurement

Blood pressure measurement was performed on the non-dominant arm by the use of mercury sphygmomanometer while the patients was in the sitting position. After they arrived at the sleep clinic the patients were asked to rest for 30 minutes before the measurement of the

blood pressure. An appropriate cuff size for each individual was used in the blood pressure measurement. Systolic blood pressure was defined by phase I, and diastolic blood pressure by phase V of Korotkoff's sound. The mean blood pressure was calculated as one-third of the systolic pressure plus two-thirds of the diastolic pressure. Three measurements were done and the average value was taken for data analysis. The same physician measured the blood pressure at the same daytime period i.e., morning or afternoon. To reduce the white coat effect (Verdecchia et al. 2002), doctors talked cordially with the patients before performing the blood pressure measurement. Hypertensive patient was defined as a patient with blood pressure $\geq 140/90$ mmHg in the sitting position as the average value of three measurements (Peppard et al. 2000).

Overnight sleep polysomnography and nasal CPAP titration

All patients were hospitalized for overnight sleep polysomnography and nasal CPAP titration. An overnight polysomnography was carried out in darkened quiet room using standard equipment. Briefly, electroencephalography (C4/A1, C3/A2), electro-oculography, submental electromyography, and electrocardiography with surface electrodes, air flow at the nose and mouth with thermistors, respiratory movement of the rib cage and abdomen with inductive plethysmography (Respirace; Ambulatory Monitoring; Ardsley, NY, USA), and percutaneous arterial oxygen saturation (SpO_2) with a finger pulse oximeter (Biox 3700; Ohmeda, Boulder, CO, USA) were simultaneously measured. All variables were recorded on an eight-channel thermal chart recorder (Model 360; NEC San-ei; Tokyo) and a personal computer using MacLab with a chart 3.5 system (AD Instruments, Castle Hill, Australia) (Tun et al. 1999).

Apnea is defined as a cessation of airflow lasting 10 seconds or more, while hypopnea is

defined as a more than 50% decrease in the thoracoabdominal amplitude (Respirace signal) associated with a decline in SpO_2 of more than 4% from the preceding value (Gould et al. 1988). The apnea-hypopnea index (AHI) was calculated according to the definition of Guilleminault and associates (1976). Nasal CPAP titration was performed under standard polysomnography on the following day after the diagnostic polysomnography. The pressure with which the patients continued to use nasal CPAP was determined on the titration night. All patients in this study were hospitalized for 2 weeks and managed with a supervised program that included dietary therapy.

Spirometry and arterial blood gas analysis

Vital capacity (VC) and forced expiratory volume in one second (FEV_1) were measured with a rolling-seal spirometry (Fudac-70s, Fukuda, Tokyo). A 2-ml arterial blood sample was anaerobically taken, and blood gas analysis including arterial oxygen tension (PaO_2), arterial carbon dioxide tension (PaCO_2), and pH was performed with a pH/blood gas analyzer (Model 213, Instrumentation Laboratories, Lexington, MA, USA) at 30 minutes before spirometry.

Follow up in the sleep clinic

In the follow up, the patients were interviewed concerning trouble with the use of the mask, regular use of nasal CPAP, daytime sleepiness and other symptoms, status of anti-hypertensive medications, and dietary conditions. Blood pressure and body weight data at the sleep clinic were taken before and 3 monthly for up to one-year after beginning treatment with nasal CPAP.

Data analysis

All data were expressed as means $\pm$ s.d. Blood pressure data were taken before, after 3 months, 6 months, 9 months, and 12 months of nasal CPAP for data analysis. One-way analy-

sis of variance (ANOVA) was applied and if significant, paired *t* test as a post-hoc test was used to compare the blood pressure among before and at each period after beginning nasal CPAP. Paired *t*-test was used to compare between the body weights before and after one-year CPAP treatment. Unpaired *t*-test was performed to compare between hypertensive and normotensive patients with OSA as well as between those taking anti-hypertensive drugs and those not. A two-tailed *p*-value of less than 0.05 was regarded as significant.

RESULTS

All patients showed a significant decrease in AHI (53.7 ± 23.4 vs. 4.1 ± 4.2 ; $p < 0.01$) after 2 weeks of nasal CPAP treatment. These patients used nasal CPAP regularly an average 5 days per week and had no major trouble with the use. Among them 25 patients were found to be hypertensive, constituting 54.3% of this study group. The 17 patients treated by anti-hypertensive drugs were included in the hypertensive group, because they showed hyperten-

sion before nasal CPAP.

Normotensive and hypertensive patients with OSA were comparable in age, height, body weight, body mass index, spirometry, and blood gas data (Table 1). AHI and the pressure of nasal CPAP were not different in these two groups. After one-year treatment with nasal CPAP the hypertensive group showed a significant reduction in clinic systolic, diastolic and mean blood pressure, whereas the normotensive group revealed no significant changes in the blood pressure (Fig. 1). The body weight after one-year treatment with nasal CPAP, compared with the values before nasal CPAP treatment, decreased significantly to 86.1 ± 13.9 kg ($p < 0.01$) and 85.5 ± 14.8 kg ($p < 0.01$) in the normotensive OSA group and the hypertensive OSA group, respectively. Fig. 2 shows the individual change in the body weight and in the blood pressure. There were not significant correlations between changes in body weight and mean blood pressure both in the normotensive and hypertensive patients ($r = 0.19$ and $r = 0.17$, respectively). The heart rate was not signifi-

TABLE 1. *Characteristics of patients with OSA*

	Normotensive OSA (<i>n</i> = 21)	Hypertensive OSA (<i>n</i> = 25)
Age (years)	44.8 ± 9.5	49.2 ± 11.5
Sex (m/f)	21/0	22/3
Height (cm)	168.1 ± 6.2	166.3 ± 8.1
Body weight (kg)	91.5 ± 18.5	90.2 ± 17.7
Body mass index (kg/m ²)	32.3 ± 5.6	32.6 ± 5.6
%VC (%predicted)	106.1 ± 17.1	102.8 ± 17.1
%FEV ₁ (%predicted)	99.1 ± 14.1	94.1 ± 19.2
FEV ₁ /VC (%)	81.4 ± 7.1	75.6 ± 7.9
PaO ₂ (mmHg)	79.7 ± 8.5	80.0 ± 10.3
PaCO ₂ (mmHg)	44.7 ± 3.3	44.5 ± 5.0
pH	7.39 ± 0.03	7.39 ± 0.04
Apnea-hypopnea index (/hour)	55.1 ± 24.0	52.5 ± 23.3
CPAP (cmH ₂ O)	9.6 ± 2.9	9.6 ± 2.5

OSA, Obstructive sleep apnea; VC, Vital capacity; FEV₁, Forced expiratory volume in one second; PaO₂, Arterial oxygen tension; PaCO₂, Arterial carbon dioxide tension; CPAP, Continuous positive airway pressure.

Values are means $\pm$ S.D.

Fig. 1. Effect of long-term nasal CPAP on clinic systolic, diastolic, mean blood pressure in hypertensive ($n=25$, ●) and normotensive ($n=21$, ○) OSA patients. A significant decrease in the blood pressures of the hypertensive group was found after one year of nasal CPAP treatment. There was no significant change in blood pressure in the normotensive group. Means $\pm$ s.d. ^aSignificantly different from the value before nasal CPAP; $p < 0.01$.

Fig. 2. Individual change in body weight (one year after CPAP—before) and change in mean blood pressure (one year after CPAP—before). Negative value means the reduction in body weight or blood pressure after CPAP. There were not significant correlations between changes in body weight and mean blood pressure both in normotensive (○; $r=0.19$) or hypertensive (●; $r=0.17$) groups.

TABLE 2. Comparison between hypertensive patients with OSA taking drugs and those not taking drugs

	Hypertensive patients taking drugs (n=17)	Hypertensive patients not taking drugs (n=8)
Age (years)	50.1±11.3	47.3±12.5
Sex (m/f)	14/3	8/0
Body mass index (kg/m ²)	34.2±5.1	29.2±5.4 ^a
Decrease in body weight (kg)	6.5±6.8	4.3±5.0
Apnea-hypopnea index (/hour)	51.1±19.9	55.5±30.6
CPAP (cmH ₂ O)	9.5±2.4	9.7±2.8
Before nasal CPAP		
Systolic BP (mmHg)	161.3±22.3	156.5±10.9
Diastolic BP (mmHg)	99.5±17.3	99.3±10.0
Mean BP (mmHg)	120.1±16.8	118.3±8.5
Heart rate (beat/min)	75.8±14.9	72.6±11.9
After nasal CPAP		
Systolic BP (mmHg)	141.3±16.4 ^b	136.0±11.3 ^b
Diastolic BP (mmHg)	85.1±9.9 ^b	90.5±2.8 ^b
Mean BP (mmHg)	103.8±10.5 ^b	105.7±3.7 ^b
Heart rate (beat/min)	82.5±10.5	78.7±9.9

BP, blood pressure.

^aSignificantly different from the value of the drug-taking group at $p < 0.05$.

^bSignificantly different from the corresponding value before nasal CPAP at $p < 0.01$.

Fig. 3. Serial clinic systolic (●), diastolic (▲), mean blood pressure (■) changes in hypertensive patients with OSA during one year of nasal CPAP treatment. All blood pressure start to fall after 3 months of treatment. There was a significant change in all blood pressures after nasal CPAP (ANOVA, < 0.01). Means±s.d. ^aSignificantly different from the value before nasal CPAP; $p < 0.01$.

cantly changed after nasal CPAP both in the normotensive (81.6 ± 10.5 vs. 78.7 ± 9.9 beats/min; NS) and hypertensive OSA groups (77.9 ± 11.3 vs. 74.8 ± 12.2 beats/min; NS).

The hypertensive patients were classified to two groups based on the medication. One group consisted of the 17 patients who had taken anti-hypertensive drugs, such as calcium antagonist, angiotensin converting enzyme inhibitor, β -blocker, diuretic or direct vasodilator. About modalities of treatment, patients who had taken single drug were four, and patients who had taken two and more drugs were thirteen. Another group consisted of the remaining 8 patients who were drug-free during the follow up period. The mean age was similar in those taking such drugs and those not. Although the base line body mass index was higher in those with drugs than in those without, the changes in body weight after one-year nasal CPAP was not significantly different between the two groups. The pressure of nasal CPAP used by both groups was comparable. The blood pressures before treatment in both those with drugs and those without were not significantly different and both groups showed a significant reduction in the blood pressures after one year (Table 2).

Serial blood pressure measurements of the hypertensive patients with OSA are showed in Fig. 3. A significant reduction in the blood pressure was found at each period of follow up after beginning nasal CPAP (ANOVA, $p < 0.01$) in these patients.

DISCUSSION

This study has found that clinic blood pressures (both systolic and diastolic) were decreased by nasal CPAP treatment in the hypertensive OSA group. In addition, the reduction of blood pressure after one year of treatment was similar both in patients with anti-hypertensive drugs and those without such drugs. Normotensive patients with OSA showed no significant changes in blood pressure

after nasal CPAP treatment.

The use of clinic blood pressure in this study may be criticized for methodological reason. The ambulatory 24-hour blood pressure measurement has some advantages over the clinic blood pressure in the diagnosis and monitoring of the management of hypertension (Clement and De Buyzere 1998; Clement et al. 2003). However, this measurement is somewhat cumbersome to use in routine clinical practice. The clinic blood pressure measured in well-standardized circumstances is still useful in the evaluation of patients with hypertension (Fagard et al. 1995). The clinic blood pressure is associated more with the alerting component than the ambulatory blood pressure and may detect the early part of hypertension (Middeke and Lemmer. 1996). Furthermore, the clinic blood pressure, especially diastolic pressure, has been extensively used to evaluate the therapeutic outcome in clinical practice as well as research practice (Kraiczi et al. 2000). In this study patients were asked to take adequate rest and the attending doctors persuaded them not to be tense at the time of measurement. Moreover, the blood pressure measured at home and the previous blood pressure were also checked, and if there was a substantial different in these values the blood pressure measurement was repeated after a 20 minutes interval. To limit observation variations three measurements were conducted and the average value was used for data analysis. We measured the clinic blood pressure at the same daytime period and by the same physician to minimize diurnal and observer variations. Comparison of the clinic blood pressure obtained by the same method was done before and after treatment. For these reasons we believe that the findings of our study were not invalidated by the method of blood pressure measurement.

Unfortunately, it was impossible to enroll patients with sham treatment of nasal CPAP as control study in this study, because moderate or severe OSA patients could not continue to be

free from nasal CPAP treatment up to one year ethically. Therefore, the effect of the regression to the mean on the decrease in blood pressure after nasal CPAP may not be neglected. However, this effect is unlikely, because all hypertensive OSA patients who had taken anti-hypertensive drugs were referred to the sleep clinic due to the poor control of blood pressure, and they showed consistent hypertension before nasal CPAP.

In this study, the patients in 54.3% of the studied OSA patients showed the daytime hypertension, but others did not. This incidence of hypertension was quite similar to that of other studies (Fletcher 1995; Peppard et al. 2000). The mechanisms of daytime hypertension in some OSA patients are yet unknown. The difference of sympathetic activity or baroreceptor function between the hypertensive and normotensive OSA groups may be plausible explanation. Patients with OSA reveal a sustained rise in sympathetic activity during the daytime (Minemura et al. 1998; Narkiewicz et al. 1999), or nocturnal hypoxia due to repeated apnea-hypopnea may induce a daytime hypertension and a deranged baroreceptor function during the daytime (Ziegler et al. 1995). These factors could induce the daytime hypertension.

Furthermore, we found that hypertensive OSA patients showed a reduction in blood pressure with nasal CPAP similar to the previous studies (Suzuki et al. 1993; Worsnop et al. 1993). The reasons of the effects of nasal CPAP on the blood pressure were also unknown. There are three possible underlying mechanisms for our finding of a lowering of the blood pressure during the daytime: namely (1) the nasal CPAP effect, (2) anti-hypertensive medication, and (3) weight reduction.

Nasal CPAP suppresses the nocturnal rise in blood pressure, which could contribute to the blood pressure lowering effect in patients with OSA during the daytime. Patients with OSA reveal a sustained rise in sympathetic activity during the daytime and long-term nasal CPAP

can decrease the sympathetic activity in such patients (Minemura et al. 1998; Narkiewicz et al. 1999). Therefore, it is speculated that the decrease in clinic blood pressure in these patients might be due to the fall in the sympathetic activity by nasal CPAP treatment. An improvement of nocturnal hypoxia by the nasal CPAP may correct the dysfunction of baroreceptor during the daytime and be associated with the reduction in blood pressure during the daytime in hypertensive OSA patients. In addition, the lowering of nocturnal blood pressure by nasal CPAP may contribute to the decrease in blood pressure during the daytime (Ali et al. 1992).

The decrease in clinic blood pressure may be due to the effect of anti-hypertensive medication used in some hypertensive patients. However, nearly half of the patients with anti-hypertensive drugs were referred to sleep clinic for poor control of the blood pressure, and they showed the sustained hypertension before nasal CPAP treatment. In addition, neither the dosages nor the kinds of drugs were changed during the follow up period. The hypertensive patients with OSA without medication showed similar reduction in blood pressure to those taking anti-hypertensive drugs (Table 2). Therefore, the effect of anti-hypertensive drugs on the blood pressure in hypertensive OSA patients would be unlikely.

The next consideration is the effect of weight reduction on clinic blood pressure in patients with OSA. A previous study stressed that the weight reduction rather than the nasal CPAP effect was a statistically significant factor in the lowering of blood pressure in patients with OSA (Rauscher et al. 1993). On the contrary, there were reports that OSA itself could be associated with daytime hypertension independently of obesity (Carlson et al. 1994), and nasal CPAP treatment with 10 nights was associated with a decrease in blood pressure during the daytime in hypertensive OSA patients without a significant change in body weight

(Worsnop et al. 1993). The present study that the body weight reduction was not significantly correlated with the decrease in blood pressure would support the latter papers.

Thus, nasal CPAP treatment itself seemed to have a substantial effect on the blood pressure during the daytime in hypertensive OSA patients. However, as we could not distinguish clearly the effect of nasal CPAP on blood pressure from that of weight loss, we would not deny the weight reduction may additionally contribute to this effect of nasal CPAP in such patients.

In this study patients with OSA treated with nasal CPAP could be followed closely every month up to one year. The effect of nasal CPAP on the blood pressure was available at least after 3 months of treatment. We could carefully check the status of all patients concerning troubles with using the machine, daily activities, control of blood pressure, body weight and sleep conditions. This is the first study that includes a one-year follow up of the blood pressure during the daytime in a relatively large sample of OSA patients treated by nasal CPAP.

In conclusion, patients with OSA are frequently associated with daytime systemic hypertension, which could account for the cardiovascular morbidity and mortality (Lindberg et al. 1998). Long-term use of nasal CPAP treatment is effective in lowering of the high blood pressure during the daytime in patients with OSA by eliminating nocturnal events. Nasal CPAP treatment would contribute to a decrease in the morbidity and mortality in patients with OSA (Veale et al. 2000).

Acknowledgments

The authors are indebted to Mr. B. Bell for reading this manuscript.

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