Acute Effects of Nasal Continuous Positive Airway Pressure on 24-Hour Blood Pressure and Catecholamines in Patients with Obstructive Sleep Apnea

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To assess the acute effects of nasal continuous positive airway pressure (CPAP) on the 24-hour blood pressure and the secretion of catecholamines in urine and plasma, we investigated the changes in the 24-hour blood pressure and urinary and plasma concentrations of epinephrine (E) and norepinephrine (NE) in 26 men with obstructive sleep apnea (OSA) with and without nasal CPAP. Nasal CPAP resulted in significant decreases in the daytime diastolic pressure (from 86 ± 16 mmHg to 83 ± 12 mmHg), the nighttime diastolic pressure (from 81 ± 12 mmHg to 77 ± 9 mmHg) and the nighttime systolic pressures (from 125 ± 15 mmHg to 120 ± 10 mmHg). There was no significant difference between patients with and without CPAP in the daytime or nighttime urinary E level, but patients who received CPAP showed a significant decrease in daytime urinary NE level (from 156 ± 112 μg/14h to 119 ± 101 μg/14h) and nighttime urinary NE level (from 143 ± 91 μg/10h to 112 ± 65 μg/10h). The morning plasma level of NE also decreased (from 371 ± 181 pg/ml to 273 ± 148 pg/ml) in patients who received nasal CPAP (p<0.02), but the plasma level of E remained unchanged. There were no correlations between PSG parameters and the reductions in blood pressure and the catecholamine levels induced by nasal CPAP. These findings suggest that OSA contributes, at least in part, to the development of systemic hypertension by increasing sympathetic nervous activity.

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Key words: daytime blood pressure, nighttime blood pressure, urinary catecholamine, plasma catecholamine

Introduction

Although there is no direct evidence of an association between systemic hypertension and obstructive sleep apnea (OSA) (1–5), successful treatment of OSA improves daytime hypertension, suggesting that there is a causal link between hypertension and OSA (6–9). We previously found that the application of short-term nasal continuous positive airway pressure (CPAP) reduces the daytime blood pressure in OSA patients (10). However, because blood pressure fluctuates during sleep and nasal CPAP is applied only during sleep, it is important to investigate changes in the nighttime blood pressure during nasal CPAP. Wilcox et al (8) and Suzuki et al (9) reported that 5- to 8-week treatment with nasal CPAP significantly reduced both the daytime and nighttime blood pressure. However, the acute effect of nasal CPAP on blood pressure has not been examined.

The mechanisms of blood pressure elevation during sleep in OSA patients are not fully understood, but marked oxygen desaturation following an episode of OSA or an increase in sympathetic nervous activity due to microarousal may be involved (11–13). However, the effect of catecholamines on blood pressure in OSA patients is controversial. Some studies have shown that the urinary level of norepinephrine (NE) during sleep is significantly reduced in OSA patients after tracheostomy or nasal CPAP (14, 15), but Marrone et al (16) reported that the urinary level of epinephrine (E) is decreased and the NE level remains unchanged in patients treated with nasal CPAP.

We investigated the acute effects of nasal CPAP on 24-hour blood pressure using a noninvasive blood pressure monitoring system, and also the changes in the daytime and nighttime
Patients and Methods

We studied 26 men with OSA (47.8 ± 11.1 years) in whom the diagnosis of OSA had been confirmed by polysomnography (PSG) in an outpatient sleep clinic. This study was permitted by the Institutional Human Investigation Committee of Niho University. All subjects were hospitalized during the present study and received a standard hospital diet (2,100 Kcal/day, 10 g of sodium/day). Subjects were asked to moderate their consumption of fluids and snacks. Renal function was within normal limits in all subjects (Creatinine: 1.0 ± 0.1 mg/ml, blood urea nitrogen (BUN): 18 ± 2 mg/ml). Six subjects were being treated with antihypertensive medication (calcium antagonist in 4 patients and angiotensin converting enzyme (ACE) blockers in 2 patients). Antihypertensive medications were withdrawn 3 days before the study. Informed consent was obtained from all subjects.

Each subject underwent overnight PSG from 10 PM to 8 AM using standard techniques as previously described (10). Analysis and interpretation of the sleep study were performed using standard criteria (17). Blood pressure was monitored at 30-minute intervals during a 24-hour period using an ambulatory blood pressure monitoring system (SpaceLabs 90207, Nihon Koden Co., Tokyo) without nasal CPAP. The 24-h blood pressure was used as the “control day” value. “Daytime” was defined as the period from 8 AM to 10 PM and “nighttime” as the period from 10 PM to 8 AM. We calculated the average daytime and nighttime blood pressure.

Daytime and nighttime urine samples were collected for measurement of NE and E by high-performance liquid chromatography (18). Venous blood samples were obtained by a trained nurse at 8 AM after completion of the PSG recording. Blood pressure was monitored at 30-minute intervals during a 24-hour period using an ambulatory blood pressure monitoring system (SpaceLabs 90207, Nihon Koden Co., Tokyo) without nasal CPAP. The 24-h blood pressure was used as the “control day” value. “Daytime” was defined as the period from 8 AM to 10 PM and “nighttime” as the period from 10 PM to 8 AM. We calculated the average daytime and nighttime blood pressure.

Nasal CPAP titration was performed to completely abolish snoring and apnea and to maintain a saturation of oxygen (SaO2) >90% during sleep using a commercial CPAP device (Tranquility Plus, Healthdyne, GA). The mean CPAP was 10.9 ± 2.7 cmH2O. Twenty-four-hour blood pressure monitoring and measurements of urinary and plasma levels of catecholamines were repeated during nasal CPAP, which was administered at night on the day after CPAP titration (treatment day).

Results

Severe OSA was detected in all subjects. The average nighttime blood pressure was significantly lower than the average daytime blood pressure (p<0.01) (Table 1). Daytime hypertension (defined as an average systolic pressure >140 mmHg or an average diastolic pressure >90 mmHg) was present in 9 patients, 4 of whom had been taking antihypertensive medications (calcium antagonist in 3 patients and an ACE blocker in 1 patient). There were no significant differences in blood pressure and catecholamine levels among the 4 subjects who had been receiving antihypertensive medication and the 22 subjects who had not been taking these drugs. There were no correlations between daytime and nighttime blood pressure and PSG parameters. The 24-hour blood pressure profile with and without nasal CPAP is shown in Fig. 1. The systolic pressures at 2 and 4 AM and the diastolic pressures at 4 PM, 4 AM, and 6 AM were significantly decreased during nasal CPAP (p<0.05). Nasal CPAP significantly reduced the average nighttime systolic and diastolic blood pressure (from 125 ± 15/81 ± 12 to 120 ± 11/77 ± 9 mmHg) and the daytime diastolic blood pressure (from 86 ± 16 to 83 ± 10 mmHg) (Fig. 2).

The average daytime and nighttime blood pressures in 9 of the hypertensive subjects were 144 ± 10/97 ± 5 mmHg and 139 ± 12/92 ± 12 mmHg, respectively. There were no differences in age, body mass index (BMI), or PSG parameters between hypertensive and normotensive subjects. The average nighttime systolic and diastolic pressures decreased significantly (from 139 ± 12/92 ± 12 mmHg to 132 ± 7/86 ± 9 mmHg) during CPAP in hypertensive subjects (p<0.05).

No correlations were observed between PSG parameters and urinary and plasma catecholamine levels before treatment. There were no significant differences between patients with and without nasal CPAP both in the daytime and nighttime urinary E levels (Fig. 3). Nasal CPAP significantly reduced the daytime and nighttime urinary NE levels from 156 ± 112 to 119 ± 101 µg/14h and from 143 ± 91 to 112 ± 65 µg/10h, respectively (Fig. 4). Nasal CPAP did not significantly alter the plasma level of E, but significantly reduced the NE level (from 385 ± 192 to 270 ± 146 pg/ml; p<0.02) (Fig. 5). The CPAP-induced changes in

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BMI: body mass index, RDI: respiratory disturbance index, BP: blood pressure, S: systolic, D: diastolic.
Figure 1. The 24-hour blood pressure profile with and without CPAP. *p<0.05.

Figure 2. Changes in daytime and nighttime blood pressures with and without CPAP. N.S.: not significant.

Figure 3. Changes in daytime and nighttime urinary levels of epinephrine with and without CPAP. N.S.: not significant.

Figure 4. Changes in daytime and nighttime urinary levels of norepinephrine with and without CPAP.

Figure 5. Changes in the early-morning plasma levels of epinephrine and norepinephrine with and without CPAP.

blood pressure were not correlated with the urinary and plasma levels of NE (Fig. 6). In hypertensive subjects, CPAP was associated with a decrease in the daytime urinary NE level in the range of 199±11 µg/14h to 128±75 µg/14h and with a decrease in the nighttime NE level in the range of 105±65 µg/10h to 89±71 µg/10h, but these changes were not significant. CPAP also reduced the plasma NE level in hypertensive subjects, but the change was not significant. The urinary and plasma E levels did not change significantly during nasal CPAP in hypertensive subjects.

Discussion

The relationship between hypertension and OSA remains controversial (1–5). In the present study, blood pressures did not correlate with PSG parameters of the severity of OSA, suggesting that OSA is not directly related to hypertension. However, nasal CPAP significantly reduced the nighttime systolic and diastolic blood pressure and the daytime diastolic pressure. Nasal CPAP caused a greater decrease in nighttime
blood pressure than in daytime blood pressure. Although the daytime systolic blood pressure did not change significantly after short-term nasal CPAP (from 131 ± 14 mmHg to 127 ± 15 mmHg), a tendency to decrease was found (p<0.1). If nasal CPAP is applied for a longer duration, the reduction of the nighttime blood pressure may be fixed and the daytime systolic pressure may decrease significantly as well as daytime diastolic pressure. We previously found that 1- to 2-week treatment periods with nasal CPAP were associated with decreases in the daytime blood pressure in OSA patients (10). Wilcox et al (8) and Suzuki et al (9) also found that a 5- to 8-week treatment period with nasal CPAP was associated with significant decreases in nighttime blood pressures. However, they studied only a small number of subjects, and it is possible that there were alterations in other factors that can influence blood pressure, such as weight and diet, during the 5- to 8-week treatment period. Therefore, it is possible that the significant reductions in blood pressure reflect the direct effect of nasal CPAP in the present study. The results of the present study suggest that the CPAP-induced decrease in nighttime blood pressures caused the decrease in daytime blood pressure. Thus, OSA may contribute to the development of daytime hypertension.

The mechanisms of hypertension in OSA patients are not fully understood. Some studies have shown that sympathetic nervous activity is the major factor in hypertension during sleep (12, 13). Varavdekar et al (19) have recently demonstrated that muscle sympathetic nerve activity (MSNA), measured by peroneal microneurography, is elevated in OSA patients and that MSNA decreases after nasal CPAP treatment. However, the role of catecholamines is controversial. Krieger et al (20) observed no changes in urinary levels of E and NE after nasal CPAP treatment. Fletcher et al (14) and Baruzzi et al (15) reported that the daytime urinary level of NE was higher in OSA patients than in control subjects and that the NE level returned to the control level following tracheostomy or nasal CPAP. In a study by Marrone et al (16), the urinary E level decreased but the NE level remained unchanged during nasal CPAP in patients with OSA. The present results are consistent with the results of the studies by Fletcher et al (14) and Baruzzi et al (15): The daytime and nighttime urinary levels of NE decreased significantly after nasal CPAP. The plasma level of NE also decreased after nasal CPAP, although we measured only the early morning plasma level of NE. These findings suggest that nasal CPAP inhibits the secretion of NE during the daytime and at night in OSA patients. NE induces generalized vasoconstriction and elevated systolic and diastolic blood pressures. An elevated plasma level of NE is generally believed to reflect sympathetic nervous activity. OSA is associated with repeated episodes of hypoxemia and sleep arousal, which result in surges of sympathetic nervous activity and transient elevations in blood pressure. Ehlenz et al (21) and Eisenberg et al (22) reported that the plasma level of NE is increased in OSA patients. However, in a study by Jennum et al (23), the plasma level of E and levels of pancreatic polypeptide decreased in response to nasal CPAP in patients with OSA, while the plasma NE level remained unchanged. The reason for the discrepancy between their results and the present findings is unclear. The pretreatment of plasma E level in their report was 86 ± 7 pg/ml, which is markedly higher than in other reports (21, 24) and in the present study. It is possible that the methods used to measure plasma levels of E and NE contributed to the difference in findings. Jennum et al used a single isotope derivative technique, whereas we used high-performance liquid chromatography which was used in other recent studies (21, 24). We evaluated the changes in catecholamines in both urine and plasma during treatment and observed the same trend in both urine and plasma. Therefore, it is likely that nasal CPAP mainly influenced the NE level but not the E level in patients with OSA. The present findings suggest that nasal CPAP inhibited sympathetic nervous activity during the daytime and at night in OSA patients.

Figure 6. The relationship between CPAP-induced changes in blood pressures and changes in urinary and plasma levels of norepinephrine at nighttime. ∆BP: CPAP-induced change in blood pressure, ∆Norpinephrine: CPAP-induced change in urinary and plasma norepinephrine levels.
and that the decrease in NE secretion may be associated with the reductions in daytime and nighttime blood pressure. Marrone et al (16) have shown that the daytime and nighttime urinary levels of catecholamines are higher in OSA patients than in normal subjects and that only the urinary level of E decreases after nasal CPAP. The reason for the discrepancy between their findings and the present results is unclear, but the differences in the subject’s baseline characteristics may be a contributing factor. Their subjects were all normotensive, while the present study included 9 hypertensive patients and the average blood pressure of our subjects was relatively high. Although we found no direct relationships between the magnitude of the reductions in blood pressure and urinary and plasma levels of NE induced by nasal CPAP, the present findings suggest that sympathetic nervous activity is, at least in part, an important contributor to hypertension in patients with OSA.

References