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Table 5. Correlation Coefficients between $PaCO_2$ and Other Variables

	r	p
Age	0.198	0.172
BMI	0.113	0.409
AHI	0.146	0.288
Arousal index	0.19	0.321
Mean SaO_2	-0.284	0.088
Minimum SaO_2	-0.140	0.422
ESS	0.430	0.002
%VC	-0.455	0.0009
$FEV_{1.0}$%	-0.422	0.002
PaO_2	-0.433	0.0009
pH	-0.368	0.011

Discussion

We first determined the prevalence of OHS among a large number of patients with moderate to severe OSAS. OHS was only identified in 9% of patients with OSAS. Although the proportion of OHS cases among OSAS cases is unclear, a recent study reported 34 patients with OHS from among 254 OSAS patients (13%) (10). Those results are consistent with the present findings. As the present study was a multicenter study with a large number of subjects, the results might be reliable. Although the prevalence of OHS was not as high as in the present study, other reports have reported that patients with OHS experience impaired quality of life (11), increased medical payments (6), and poor prognosis (5). Clarification of the prevalence and pathophysiology of OHS are thus clinically useful in general medicine.

The present results demonstrate that OHS patients experience a number of disorders compared with typical OSAS patients. OHS is associated with more severe sleep disorder breathing, increased somnolence, higher hematocrit, increased liver dysfunctions, higher total cholesterol, and more impaired pulmonary function. However, these abnormalities may be due to obesity, as when BMI was matched between OHS and OSAS patients, these differences disappeared except for pulmonary function including blood gases. Most abnormalities in OHS could thus be attributable to obesity.

Another key feature of OHS is daytime hypercapnia (chronic hypoventilation). Obesity may not be related with development of daytime hypercapnia alone, as BMI showed no significant correlation with $PaCO_2$ in OHS. What factors contribute to the development of daytime hypercapnia in OHS? Chronic airflow obstruction has been demonstrated to play a major role in the development of daytime hypercapnia in OSAS patients (12). When OSAS patients have chronic airway obstruction, daytime hypercapnia often occurs even in the absence of obesity. This condition is called "overlap syndrome" (13). Subjects in this study generally did not display impaired pulmonary functions. Airway obstruction is thus unlikely to play an important role in the development of daytime hypercapnia in our patients, although $FEV_{1.0}$% was correlated with $PaCO_2$. A significant difference was noted between %VC in OHS and non-OHS patients, and %VC was most closely correlated with $PaCO_2$. In addition, all hypercapnic patients displayed %VC, $FEV_{1.0}$%, and ESS as independent factors in predicting levels of daytime $PaCO_2$ by stepwise multiple regression analysis. These data suggest that daytime $PaCO_2$ in OSAS patients is associated with pulmonary functions, particularly restrictive respiratory capacity, even though these were within normal limits. Akashiba et al (14) recently showed that %VC and oxygen desaturation during sleep play important roles in the development of daytime hypercapnia in Japanese OSAS patients without chronic airway obstruction. Golpe et al (15) also reported that chronic hypercapnia in patients with OSAS is mainly associated with restrictive ventilatory deficit in Caucasian subjects. Although the subjects in these studies were obese OSAS patients, not OHS patients, the present results were consistent with these previous studies. However, why the slight reduction in %VC found in the present study develops with daytime hypercapnia in OHS patients remains uncertain. When patients are markedly obese, a slight reduction in %VC may substantially affect gas exchange due to decreased chest-wall compliance, finally inducing daytime hypercapnia. Since the mechanisms of development of daytime hypercapnia may be quite complex, further investigations are needed to clarify relationships between hypercapnia and reduced vital capacity.

Disorder of central respiratory control is another cause of hypoventilation. Various studies have examined relationships and between hypercapnia and ventilatory responses in patients with OSAS and OHS (16-25). However, results have not always been consistent in these studies. For example, Verbraecken et al (23) observed an increased response to hypercapnia in 14 normocapnic patients with OSAS. In contrast, Garay et al (24) showed a normal response to hypercapnic stimulation in 6 eucapnic patients with OSAS. In both studies, hypercapnic patients with OSAS demonstrated a blunted response to hypercapnia. Lopata and Onal (22) also reported a diminished response to hypercapnia in 15 patients with OSAS. Sin et al (25) investigated hypercapnic ventilatory response in patients with and without OSAS and showed that OSAS was not associated with a blunted ventilatory chemoresponsiveness to carbon dioxide in a relatively large number of subjects. These data suggest the existence of a number of determinants, including age, gender, obesity, obstructive, and restrictive ventilatory impairments in the development of hypercapnia in patients with OSAS or OHS, although disorders of central respiratory control may play a substantial role in the development of daytime hypercapnia. Since ventilatory responses were not examined in this study, we cannot comment on how ventilatory responses contribute

to daytime hypercapnia in patients with OHS. Further investigations are needed to determine relationships between ventilatory responses and daytime hypercapnia in OHS.

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What effect on blood pressure can we expect from continuous positive airway pressure treatment in obstructive sleep apnoea?

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Obstructive sleep apnoea (OSA) is prevalent in 4% of middle-aged men and 2% of middle-aged women [1]. It is caused by the collapse of the pharynx during sleep, which leads to airway occlusion and hypoxia, and is reversed when pharyngeal muscle tone suddenly increases, usually in coincidence with an arousal [2–4]. Sleep apnoeas are repetitive, with severely affected patients having hundreds of respiratory events and arousals every night. Furthermore, sleep apnoeas are associated with sharp, short-lasting blood pressure augmentations at their termination, and with some reduction during their course [5–7]; as an effect, blood pressure during sleep in OSA is highly variable and has slightly higher mean values than during the preceding quiet wakefulness. This is well demonstrated by beat-to-beat measurements, and is different from that occurring in normal subjects, who decrease their blood pressure as they fall asleep [8]. In addition to nocturnal haemodynamic effects, according to epidemiological studies, OSA coexists with systemic hypertension in approximately 50% subjects, and this association is independent of obesity and other risk factors [9–12]. In addition, OSA may be a frequent cause of drug-resistant hypertension [13], and of a 'non-dipping' nocturnal blood pressure behaviour [14]. Studies investigating the potential pathophysiological mechanisms involved in hypertension development in OSA have proposed the involvement of increased sympathetic activity [15], baroreflex impairment [16], endothelial dysfunction [17–18], vascular inflammation [19,20], altered blood rheology [21] and early atherosclerosis development [22–24]. Nocturnal ventilatory treatment by continuous positive airway pressure (CPAP) is the most effectively established treatment for OSA.

In this issue of the journal, Chin *et al.* [25] explore several aspects related to the effects of prolonged CPAP treatment on morning office blood pressure in patients affected by OSA. Although several studies have investigated the effects of OSA treatment on blood pressure, and most of them have shown that blood pressure may be lowered by CPAP treatment, there is still much to clarify.

The time course of blood pressure improvement after CPAP treatment is initiated and the possible difference between CPAP effects on diurnal and nocturnal blood pressure are not clear. The time required for blood pressure to decrease may be different when an individual is asleep or awake. An immediate decrease in nocturnal blood pressure could be expected when CPAP is applied, as a result of elimination of apnoea-associated haemodynamic effects. The time course of blood pressure improvement with OSA treatment when awake is likely to be slower than the time course of blood pressure when asleep. Experimental studies in normal subjects showed that, after short-term exposure to repetitive voluntary apnoeas, sympathetic activity remains high for several minutes, and blood pressure is rapidly reversed to normal as the normal breathing pattern is resumed [26,27]. This suggests that an increase of diurnal blood pressure in patients chronically exposed to apnoeas is not due to a carry-over effect of repetitive apnoeas in the immediately preceding night. However, chronic reduction of nocturnal sympathetic activity by apnoea prevention may be followed by diurnal sympathetic tone reduction with a subsequent decrease in blood pressure. Sympathetic tone [28] and baroreflex gain [16,29,30] change slowly after treatment initiation, whereas diurnal sympathetic activity is not reduced by short-term apnoea treatment [28,31]; similarly baroreflex activity does not improve with acute CPAP application [30]. However, some acute contribution of CPAP in decreasing diurnal blood pressure could also be hypothesized, taking into account that an increased nitric oxide availability is evident after acute OSA treatment [32].

As regards nocturnal blood pressure in OSA, it should be noted that its high variability reduces the reliability of intermittent blood pressure monitoring, particularly when measurement intervals as long as 30 min are used [33]. Among the available studies investigating the effects of CPAP on blood pressure in OSA, only a few were based on beat-by-beat measurements [16,29,30,34–41]. Although the method of investigation may not be the most important source of differences among the results reported in the literature, it may comprise an important contribution to their disagreements.

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Studies concerning the effects of CPAP on diurnal and nocturnal blood pressure have produced different results. The effects of the duration of treatment on blood pressure were found to vary among studies. A few investigations studied the effects for the first few nights of CPAP application: most [34,37,42,43], but not all of them [36,44], observed a decrease in blood pressure. Most other studies investigated the effects of CPAP after weeks or months of treatment. A few studies demonstrated effects that were limited to nocturnal values [45,46], but how the nocturnal blood pressure decrease could be attributed to long-term treatment or to an immediately occurring CPAP effect is not clear. Other studies reported both diurnal and nocturnal blood pressure reduction [34,41,47–50], which could be in agreement with a progressive slow effect of treatment. A final group of studies, in addition to a nocturnal decrease, reported a reduction in blood pressure mainly in the early morning hours [40,51], in agreement with a possible carry-over effect of acute apnoea elimination. Only one study investigated both the acute (1–3 nights) and long-term (4–6 months) effects of CPAP, separately for nocturnal and diurnal values, and found a significant decrease in both of them at the first evaluation and, subsequently, a further but not statistically significant decrease [42].

Some clues about differences between acute and chronic effects of CPAP may be derived by studies concerning the effects of acute CPAP withdrawal after chronic treatment. In one of the few studies not demonstrating any reduction in blood pressure after CPAP, blood pressure was measured before beginning treatment and immediately after its withdrawal [52]. However, more recent studies have compared blood pressure during CPAP application after chronic treatment, and after 1 night [53] or 1 week [48] of CPAP withdrawal, finding only minor differences between the two nights. Moreover, blood pressure reactivity to apnoeas decreased after chronic CPAP treatment [39], whereas an increase in baroreflex gain occurring after chronic CPAP treatment could attenuate apnoea-induced blood pressure variations [16,29]; a similar baroreflex improvement was not observed during acute CPAP application [30]. Therefore, nocturnal blood pressure improvement after chronic CPAP may be caused not only by acute apnoea prevention, but also by the beneficial effects of prolonged treatment.

The study by Chin *et al.* [25] does not clarify the lowest treatment duration associated with a blood pressure reduction because it did not investigate the very acute effects of CPAP. However, it deals with an aspect that has received very little attention to date, as pointed out in a recent meta-analysis [54], namely, the possible long-term persistence of blood pressure reduction with CPAP treatment. In particular, it found that office morning blood pressure recorded after a 1-month treatment is maintained at a constant level for up to approximately 3 years [25], which is a follow-up duration that had not been reached previously.

In addition to the period of treatment, it is important to consider the effects of compliance to treatment. Use of CPAP is variable among patients, and the lowest compliance to treatment necessary to obtain some effect on blood pressure is unknown. In a previous study, a significant CPAP effect on blood pressure reduction was observed only in patients using CPAP more than 5 h per night [49]. According to Chin *et al.* [25], 3 h would be enough for a significant effect, whereas the effect of a lower compliance remains dubious because patients with low compliance were mostly normotensive and, as such, less prone to decreasing their blood pressure [25].

Another important point concerns why some patients undoubtedly decrease their blood pressure in response to CPAP, but others do not. Who are these patients? Apart from few studies demonstrating no differences related to pre-treatment blood pressure level [47,49], almost all studies, including the one by Chin *et al.* [25], agree that a blood pressure decrease is related to its baseline values and occurs only in hypertensives [41,42,55–57]. Besides, some of the different responses could be related to the severity of nocturnal respiratory disorders [49,51] or to genetic factors [58], but this remains almost totally unexplored. An interaction with simultaneous pharmacological antihypertensive treatment is controversial because almost all possible alternatives have been found: from a greater CPAP effect in patients receiving drugs [49], to a similar effect [57], to a lack of effects in patients who are treated pharmacologically [56]. In patients with drug-resistant hypertension, CPAP was found to decrease blood pressure [59]. Chin *et al.* [25] found that the effects of CPAP were evident on both systolic and diastolic pressure in non-pharmacologically treated patients, whereas the effects were only on the diastolic pressure in the other patients [25].

Thus, effects of CPAP on systolic and diastolic blood pressure could differ. In this regard, a controversy remains between those studies that found a CPAP effect for both systolic and diastolic pressure, and those that found an effect on only one of them. To better analyse this point, studies that evaluated both systolic and diastolic pressure separately for diurnal and nocturnal hours are required. Some of them found significant falls after CPAP treatment in both systolic and diastolic blood pressure [34,43], whereas, with only one exception [51], the other studies, including that by Chin *et al.* [25], suggest a prevalent decrease in the systolic pressure during the night, and in the diastolic pressure during the day [35,37,38,45,47,50,55].

Based on the above, apart from the almost common agreement that CPAP treatment may beneficially

influence blood pressure in patients with OSA, the more specific details of the effects of CPAP are far from clear and remain highly controversial. The different designs and quality of studies may partly account for the different results reported. The study by Chin *et al.* [25] adds some data concerning several controversial aspects of the effects of CPAP and, to date, it is the only one to show that the effects of CPAP on blood pressure may persist for as long as 3 years [25]. Future studies should aim to explore more specific aspects of the effects of CPAP. Hopefully, this would allow us to better understand what can be expected from treatment, including identifying those patients who may benefit from treatment, and how treament must be applied to obtain the best results.

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Falls in blood pressure in patients with obstructive sleep apnoea after long-term nasal continuous positive airway pressure treatment

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Objectives Effective treatment of obstructive sleep apnoea (OSA) with nasal continuous positive airway pressure (nCPAP) lowers blood pressure (BP). The long-term effects of nCPAP treatment on BP in OSA patients are not well known. The time period of such treatment sufficient to lower BP in OSA patients is also not known. We investigated compliance with long-term nCPAP therapy and its effects on BP.

Methods This observational study involved 66 OSA patients [59 men, seven women; mean age, 51 (48–54) years; body mass index (BMI), 28.7 (27.7–29.7) kg/m^2; apnoea and hypopnoea, 50.3 (45.6–55.0)/h; 95% confidence intervals]. BP and BMI were measured before the study and at two checkpoints after usage of nCPAP [620 (552–688) and 1071 (1000–1143) days].

Results The different times between the first and second checkpoints for detecting objective compliance were 17 (4–30) min ($P = 0.003$). Diastolic BP decreased by 5.9 (3.1–8.7) mmHg after 600 days nCPAP treatment and by 4.6 (2.0–7.2) mmHg after 1000 days ($P = 0.0006$). Systolic BP and BMI did not change significantly. Usage of nCPAP treatment for a daily average of 3 h was needed to achieve a significant decrease in diastolic BP [7.4 (4.3–10.6) mmHg, $P < 0.0001$]. Diastolic BP of normotensive OSA patients did not change significantly by nCPAP treatment, but that of hypertensive OSA patients decreased significantly within 1 month–3 years of nCPAP treatment whether or not medication was used.

Conclusions In patients with severe OSA, the use of nCPAP for a daily average of 3 h would be sufficient to decrease the diastolic BP of hypertensive OSA patients. *J Hypertens* 24:2091–2099 © 2006 Lippincott Williams & Wilkins.

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Keywords: obstructive sleep apnoea, hypertension, nCPAP, risk factors

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Introduction

In the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure of the National High Blood Pressure Education Program, obstructive sleep apnoea (OSA) was defined as an identifiable cause of hypertension from numerous epidemiologic data [1–3]. The combination of systolic and diastolic hypertension is common in middle-aged hypertensive patients, whereas isolated systolic hypertension is predominately a disease of elderly hypertensive patients [4,5]. The most recent data show that sleep-disordered breathing was associated with systolic/diastolic hypertension in persons aged 40–59 years, but not with isolated systolic hypertension in any age category [5]. It is well known that sustained and effective treatment of OSA with continuous positive airway pressure lowers night-time and daytime blood pressure (BP) in hypertensive patients with severe OSA [6–8]. The duration of nasal continuous positive airway pressure (nCPAP) treatment for OSA patients in these studies ranged from 1 to 3 months [6–8]. The long-term effects of nCPAP treatment on BP in OSA patients are not well known. In addition, the time period of such treatment sufficient to lower BP in OSA patients is not known.

In Japan, according to health insurance rules, patients with OSA who use nCPAP under health insurance must come to the hospital every month. In our hospital, more than 95% of such patients do come to the hospital every month. At that time, we check their body weight and BP. In addition, we objectively evaluate compliance with nCPAP using the built-in compliance software in the nCPAP device. There are little data on long-term (more than 2 or 3 years) compliance with usage of nCPAP

involving more than 50 patients [9,10]. In addition, there are no data on changes in BP in OSA patients who use nCPAP continuously for several years. We hypothesized that the patients with OSA who came to the hospital every month used nCPAP continuously between the two examination points. We investigated long-term compliance and its effects on BP to elucidate the duration of nCPAP that significantly reduces BP because elevation of BP is the most important risk factor for cerebrocardiovascular disease [11].

Methods

Study population

The medical ethics committee at our institution reviewed and approved the study. All participants provided informed consent. The participants were 72 consecutive patients with OSA who used nCPAP therapy continuously for more than 2 years and came to our hospital every month. As medication was changed in six of the 72 patients during the observation time, those six patients were excluded from the study. Sixty-six patients who received the same medical regimen beginning 1 month before the start of this study and throughout the study were investigated. There were 59 men and seven women with a mean age of 51 (48–54) years and body mass index (BMI) of 28.7 (27.7–29.7) kg/m^2. Confidence intervals were 95% values. Tobacco and alcohol consumption did not change during the study. Polysomnography for OSA patients was performed as usual [12,13]. Apnoeas was defined as the complete cessation of airflow, hypopnoea as a clear reduction in airflow or thoracoabdominal excursion lasting for 10 s or more, accompanied by a decrease in oxygen saturation of at least 3%. The number of episodes of apnoea and hypopnoea per hour was defined as the apnoea and hypopnoea index (AHI). The mean AHI of the patients was 50 (46–55). The AHI of each OSA patient was more than 20, because the health insurance system covers nCPAP only if the AHI is greater than 20. The patients underwent manual nCPAP titration and received nCPAP treatment with adequate pressure of 9.8 (9.1–10.4 cmH_2O). nCPAP treatment reduced the patients' AHI to a mean of 3 (2–3) ($P < 0.0001$).

Among the 66 patients with OSA, 47 had hypertension and 11 had diabetes mellitus. Twenty patients with hypertension took medication. Fifteen patients were receiving a calcium inhibitor, four an angiotensin-converting enzyme inhibitor, three an angiotensin II receptor antagonist, four an α-blocker, one a β-blocker, two a diuretic drug, and three a nitrous drug. Some patients were taking multiple drugs.

Study design

After OSA patients had undergone 3 years of nCPAP treatment, we examined their medical charts. We obtained information about each patient's nCPAP therapy every month in the outpatient department of our hospital, such as the patient's subjective perception of usage time, body weight and BP. We gathered data on both objective and subjective compliance with use of the nCPAP machine. The objective compliance with use of the nCPAP machine was based on data that were taken from the regular examination of the machine every 1 or 2 years. Both objective and subjective compliance were defined as the daily average time (hours per day) of usage of the nCPAP apparatus. The former was based on a reading of the time counter in each nCPAP machine, while the latter was based on patient reports; this information was gathered at two time points as close as possible to a yearly interval. Each subjective parameter at two checkpoints was calculated by the mean value over 3 months.

Epworth sleepiness score

The Epworth sleepiness score [14] was obtained before nCPAP therapy in 53 patients with OSA before nCPAP treatment. With the Epworth sleepiness score, individuals score themselves on a scale of 0 (not at all likely to fall asleep) to 3 (very likely to fall asleep) according to how easily they would fall asleep in eight different situations, with possible overall scores of 0–24. The higher the score, the sleepier the individual.

Blood pressure and body weight

Patients' BP and body weight were measured before the study and every month after treatment had begun. The resting BP was measured in the right arm after a 5-min rest using a conventional mercury sphygmomanometer [15]. The first and last Korotkoff sounds were used to determine systolic and diastolic BP, respectively. The average of the second and third of three consecutive measurements was used as the BP value for that month. Weight was measured in light clothes on a portable scale. Each parameter at two checkpoints was calculated by the mean value over 3 months.

Statistical analysis

All statistical analyses were performed using nonparametric tests with statistical software (StatView version 5.0 for Windows; Abacus Concepts, Berkeley, California, USA). Differences between the two groups were compared with the Mann–Whitney U test. Differences between any two conditions in OSA patients were compared with the Wilcoxon signed-rank test. When more than two conditions were compared, a significant difference was tested among all of the conditions by the Friedman test. If a significant difference was found by the Friedman test, the difference between every pair of conditions was retested by the Wilcoxon signed-rank test. Correlations between variables were analysed by the Spearman rank correlation test. As shown in the Results section, the diastolic BP decreased significantly. To determine the average daily usage time of nCPAP treatment that was sufficient to lower BP of the OSA patients,

we compared baseline diastolic BP values with those at the second checkpoint according to various intervals of usage. Data from examination of the records of average daily usage time were evaluated according to usage in 30-min increments as follows: less than 30 min, 30 min, 1 h, 90 min, 2 h, 150 min, 3 h, and so on. We found that a daily average of at least 3 h of nCPAP treatment was necessary to lower the BP of OSA patients. The patients who used a daily average of 3 h or more of nCPAP were defined as the good compliance group, and the patients who used less than 3 h daily of nCPAP were defined as the poor compliance group. A P value less than 0.05 was considered significant. The data are expressed as the mean (95% confidence interval).

Results

Objective and subjective compliance

The time counter was read when the supplier of the nCPAP machine performed the examination mandated by health insurance rules every 1 or 2 years after the beginning of nCPAP treatment. Usage at the first and second checkpoints was 620 (552–688) and 1071 (1000–1143) days, respectively. The duration between the two checkpoints was 439 (405–474) days. Objective compliance decreased from 4.33 (3.81–4.86) to 4.04 (3.52–4.56) h, which amounted to a total of 17 min ($P = 0.003$). Objective compliance at the second checkpoint was correlated with that at the first checkpoint ($r = 0.91$, $P < 0.0001$). Subjective compliance changed from 5.67 (5.27–6.08) to 5.63 (5.27–6.00) h, which was a decrease of only 4 min ($P = 0.26$). Subjective compliance at the second checkpoint was correlated with that at the first checkpoint ($r = 0.86$, $P < 0.0001$). Subjective compliance was significantly greater than objective compliance at both the first and second checkpoints (both $P < 0.0001$) (Table 1).

Blood pressure and body weight

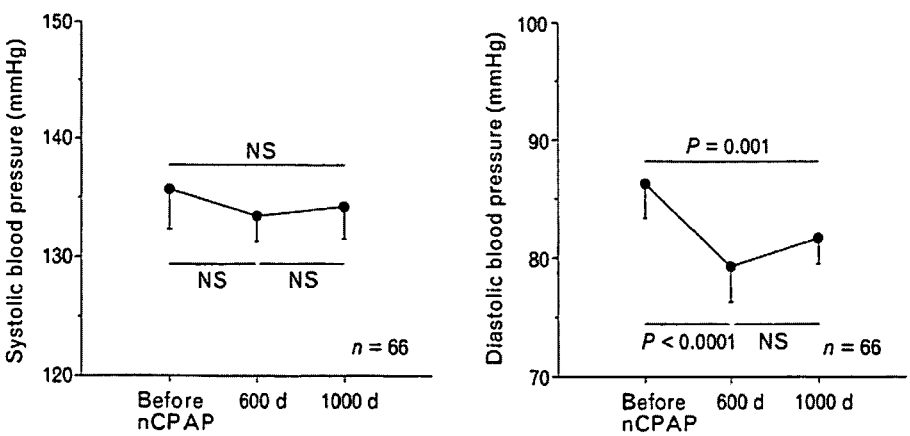
After long-term nCPAP treatment, the diastolic BP in OSA patients significantly decreased while the systolic BP did not (Fig. 1). Diastolic BP decreased by 5.9 (3.1–8.7) mmHg after 600 days of nCPAP treatment and by 4.6 (2.0–7.2) mmHg after 1000 days of nCPAP treatment, but there were no significant changes in systolic BP or body weight (Table 1). The degrees of decrease in diastolic BP were very closely correlated between data at the two checkpoints ($r = 0.78$, $P < 0.0001$). We found that a daily average of at least 3 h of nCPAP treatment was necessary to lower the BP of OSA patients. The diastolic BP improved in 44 of the 66 patients. There were, however, no significant correlations between

Table 1 Several characteristics of 66 patients with obstructive sleep apnoea before and after long-term nasal continuous positive airway pressure (nCPAP) treatment

Variable	Before nCPAP	After 600 days of nCPAP	After 1000 days of nCPAP	*P* value
Body weight (kg)	80.0 (76.7–83.3)	78.2 (75.2–81.2)	78.0 (74.6–81.3)	0.09
Reported usage time (h/day)		5.67 (5.27–6.08)	5.63 (5.27–6.00)	0.26
Actual usage time (h/day)		4.33 (3.81–4.86)	4.04 (3.52–4.56)	0.0027
Systolic blood pressure (mmHg)	135.7 (132.3–139.2)	133.4 (131.3–135.6)	134.2 (131.5–137.0)	0.74
Diastolic blood pressure (mmHg)	86.3 (83.3–89.3)	80.4 (78.6–83.9)	81.7 (79.5–83.9)	0.0006

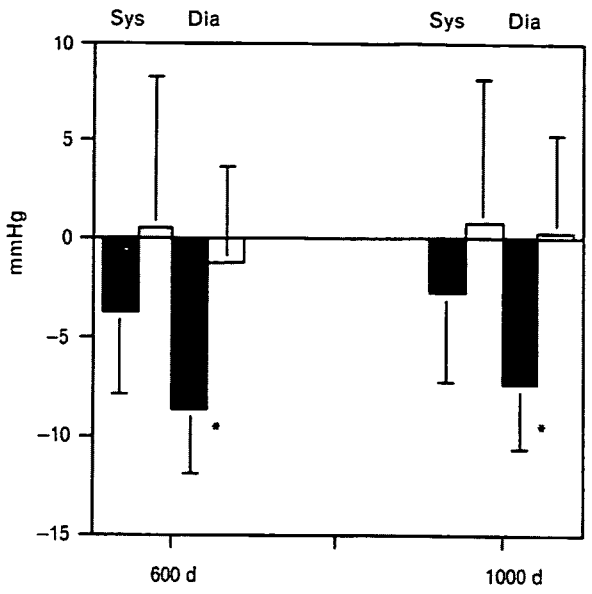
Data presented as mean (95% confidence interval).

Fig. 1



Mean blood pressure values in 66 patients before nasal continuous positive airway pressure (nCPAP) treatment, after 600 and 1000 days of nCPAP treatment. P values are noted when the difference in blood pressure between the baseline and 600 or 1000 days of nCPAP treatment was significant ($P < 0.05$). Bars indicate mean levels with 95% confidence intervals.

Fig. 2



Changes in blood pressure in patients with a daily average of 3 h or more of nasal continuous positive airway pressure (nCPAP) treatment (closed bars, $n = 46$) and less than 3 h of nCPAP treatment (open bars, $n = 20$) after 600 and 1000 days of nCPAP treatment. Sys, systolic blood pressure; Dia, diastolic blood pressure. *indicates significant differences in the diastolic blood pressure. $P < 0.0001$. Bars indicate mean levels with 95% confidence intervals.

the degree of decrease in diastolic BP with the AHI, the lowest arterial O_2 saturation during sleep, the percentage of time spent at less than 90% arterial saturation, or usage time. When the usage times were checked according to 30-min intervals to determine how many hours were needed at least to reduce BP significantly, a significant decrease in diastolic BP [7.4 (4.3–10.6) mmHg, $P < 0.0001$, $n = 46$] was achieved by a daily average of at least 3 h of nCPAP treatment (Fig. 2). Significant and continuous changes in the diastolic BP occurred within 1 month of nCPAP treatment in the good compliance group ($\geq$ 3 h nCPAP) but not in the poor compliance group (< 3 h nCPAP) (Fig. 3). nCPAP was continuously effective on the diastolic BP within 1 month, at 1, 2 (600 days) and 3 years (1000 days) in the good compliance group (Figs 1–3).

Forty-six patients used a daily average of 3 h or more of nCPAP (good compliance group) and 20 patients used less than 3 h daily of nCPAP (poor compliance group) (Table 2). Differences were not significant in age, body weight, AHI or BP before and after nCPAP treatment between the good and poor compliance groups. In addition to usage and reported times, the diastolic BP before treatment was significantly higher in the good compliance group than in the low compliance group (Table 3). After nCPAP treatment, the diastolic BP in the good compliance group was significantly decreased (Fig. 3).

In the good compliance group, 34 patients had hypertension, and the diastolic BP in these patients decreased significantly after nCPAP (Figs 4 and 5). The systolic BP of these 34 hypertensive patients changed significantly at the first checkpoint but did not change significantly overall. Although the systolic BP of 12 normotensive patients in the good compliance group changed significantly within the normal range at the first checkpoint, the systolic BP did not change significantly overall, and the diastolic BP in these patients did not change significantly after nCPAP treatment (Fig. 5). In the poor compliance group ($n = 20$), there was no significant change in either systolic or diastolic BP (Figs 2–4).

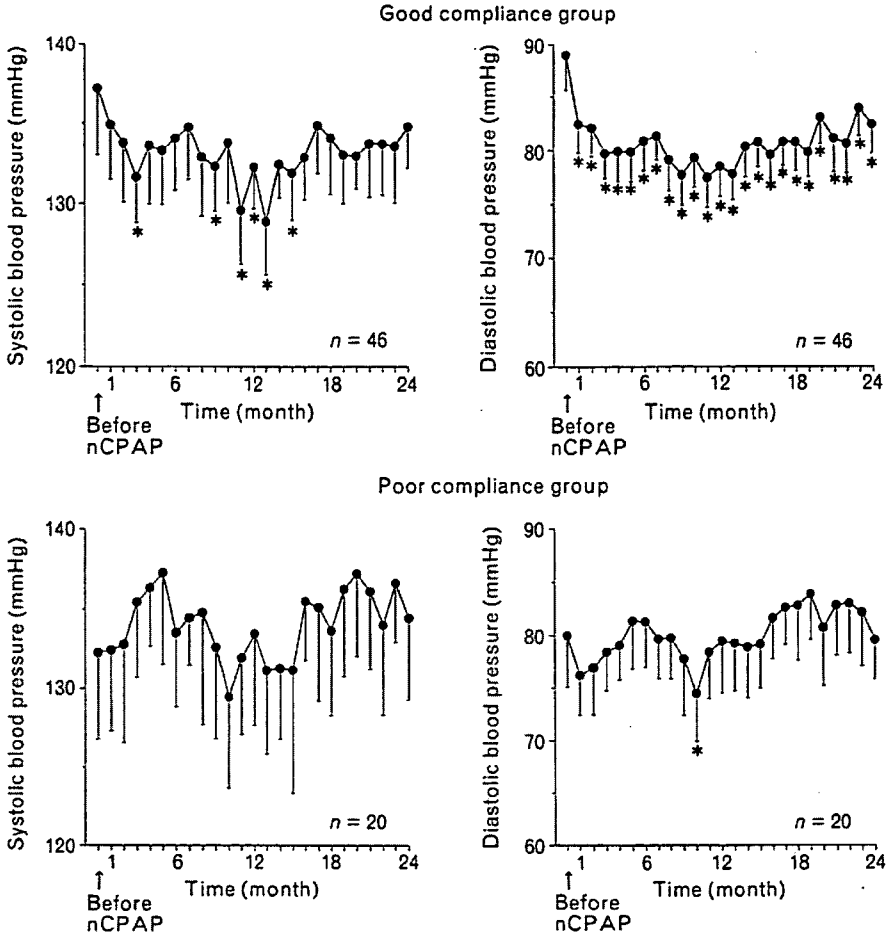
Among the 34 hypertensive patients in the good compliance group, 13 received antihypertensive treatment (treatment group) and the other 21 did not (no treatment group) (Table 2 and Figs 4 and 6). Diastolic BP but not systolic BP decreased significantly after nCPAP treatment in the treatment group ($n = 13$). Their diastolic BP, which had not been lowered by antihypertensive drugs, might be resistant to the drug treatment. Both systolic and diastolic BP decreased significantly after nCPAP treatment in the no treatment group ($n = 21$) (Fig. 6).

Discussion

The present study showed that long-term nCPAP therapy continuously reduced diastolic BP in severe OSA. To achieve a significant effect on diastolic BP, daily average usage of nCPAP for 3 h is needed. With that level of compliance, diastolic BP in hypertensive OSA patients with or without antihypertensive drug treatment decreased significantly, while systolic BP in OSA patients without treatment also decreased significantly. Neither systolic nor diastolic BP in normotensive OSA patients changed significantly overall after nCPAP treatment. Our data on compliance with nCPAP, which is from the longest observation period among such reports on the subject, confirmed findings of previous reports and provided new, previously unreported data, which was a decrease in usage time of 17 min/day over the 2–3 years of nCPAP usage.

Several studies have investigated compliance with nCPAP in patients with OSA. Some showed long-term compliance [9,10,16,17], but they did not report changes in BP. In the present study, 2 or 3 years of nCPAP treatment and a daily average of 3 h of nCPAP treatment — which was nearly compatible with the duration cited in data most frequently referred to (i.e. 4 h of nCPAP 5 days per week) [18,19] — significantly reduced diastolic BP in patients with moderate-to-severe OSA. Six randomized, controlled trials have examined the effect of nCPAP treatment for OSA on systemic arterial BP [6–8,20–23]. Six trials showed convincing falls in BP in sleepy patients with severe OSA [6–8,20–22]. These positive data, however, were derived from trials in which the

Fig. 3



A monthly record of data for mean blood pressure in 46 patients with good compliance [daily average of nasal continuous positive airway pressure (nCPAP) treatment of 3 h or more; good compliance group] and in 20 patients with poor compliance (daily average of nCPAP treatment less than 3 h; poor compliance group) from baseline to 2 years of nCPAP treatment. *indicates significant differences in the blood pressure compared to pre treatment. $P < 0.05-0.0001$. Bars indicate mean levels with 95% confidence intervals.

period of nCPAP usage was within 3 months. From this study, it was shown that long-term (more than 3 years) nCPAP treatment also brought about an effective fall in diastolic BP in patients with severe OSA who use nCPAP for at least a moderate length of time. In the Borgel *et al.* study [24], nCPAP treatment significantly decreased both systolic and diastolic BP of the hypertensive OSA patients without the antihypertensive drug. The usage

Table 2 Characteristics of 66 patients with obstructive sleep apnoea having either good or poor compliance with nasal continuous positive airway pressure (nCPAP)

Variable	Good compliance ($n = 46$)	Poor compliance ($n = 20$)	P value
Age (years)	52.4 (48.9–56.0)	48.7 (41.6–55.8)	0.34
Body mass index (kg/m^2)	28.6 (27.5–29.8)	28.9 (26.9–30.9)	0.95
Apnoea and hypopnoea index (events/h)	50.1 (44.9–55.4)	50.8 (40.4–61.2)	0.81
nCPAP apnoea and hypopnoea index (events/h)	2.5 (1.6–3.5)	2.3 (1.3–3.4)	0.43
Epworth Sleepiness Score	10.8 (9.1–12.4)	9.5 (7.0–12.0)	0.48
Hypertension (+)	34 (74%)	13 (65%)	
Antihypertensive drug	13 (28%)	7 (35%)	
Diabetes mellitus	8 (17%)	3 (15%)	
First reported usage (h/day)	6.22 (5.87–6.66)	4.41 (3.51–5.31)	0.002
Second reported usage (h/day)	6.04 (5.70–6.39)	4.68 (3.86–5.51)	0.005
First usage time (h/day)	5.43 (5.00–5.85)	1.81 (1.32–2.30)	< 0.0001
Second usage time (h/day)	5.16 (4.75–5.57)	1.48 (1.05–1.91)	< 0.0001

Data presented as mean (95% confidence interval) or *n* (%).

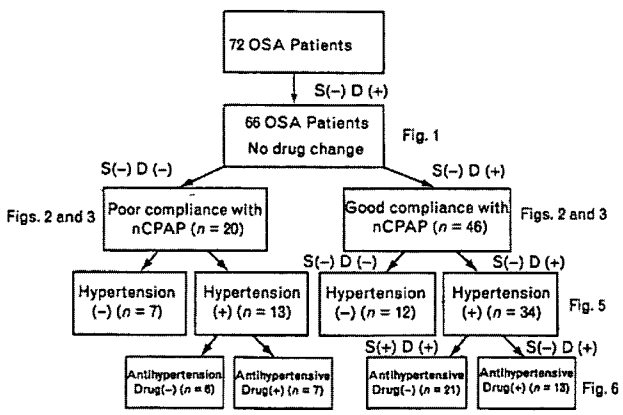
Table 3 Parameters measured in 66 OSA patients with good ($n = 46$) or poor ($n = 20$) compliance

Variable	Good compliance ($n = 46$)	Poor compliance ($n = 20$)	P value
Body weight before nCPAP (kg)	79.3 (75.7–83.0)	81.4 (73.8–89.0)	0.91
Body weight after 600 days nCPAP (kg)	78.3 (74.8–81.7)	77.9 (71.4–84.4)	0.59
Body weight after 1000 days nCPAP (kg)	77.6 (74.3–80.9)	78.6 (71.7–85.5)	0.84
Systolic blood pressure before nCPAP (mmHg)	137.2 (132.9–141.5)	132.3 (126.4–137.7)	0.22
Systolic blood pressure after 600 days nCPAP (mmHg)	133.4 (130.7–136.1)	133.6 (129.5–138.2)	0.98
Systolic blood pressure after 1000 days nCPAP (mmHg)	133.3 (129.9–136.7)	133.9 (128.0–139.7)	0.78
Diastolic blood pressure before nCPAP (mmHg)	89.0 (85.5–92.4)	80.1 (74.8–85.3)	0.02
Diastolic blood pressure before 600 days nCPAP (mmHg)	80.4 (78.0–82.8)	80.4 (77.7–83.0)	0.64
Diastolic blood pressure before 1000 days nCPAP (mmHg)	81.6 (79.1–84.1)	81.9 (76.9–86.9)	0.83

Data presented as mean (95% confidence interval). nCPAP, nasal continuous positive airway pressure.

time of nCPAP, however, was not mentioned in that study [24]. In the present study as well as in the previous report [24], a daily average of 3 h of nCPAP treatment lowered systolic and diastolic BP of hypertensive OSA patients who were not taking medication. In hypertensive OSA patients who were on antihypertensive treatment, however, the diastolic BP but not the systolic BP was lowered by nCPAP. Their diastolic BP did not respond to the antihypertensive drugs but a significant response was achieved through nCPAP treatment. Their diastolic BP might therefore be considered refractory to the antihypertensive drug treatment [25,26]. Davies *et al.* [27] reported that, compared with closely matched control individuals, patients with OSA have increased ambulatory diastolic BP during both day and night and increased systolic BP at night. In that study, the difference in diastolic BP in those with and without OSA was 5.1 mmHg, which was almost the same as the difference in diastolic BP in OSA patients in the good compliance group before and after 1000 days of nCPAP treatment in this study. In a randomized placebo-controlled trial of the effect of nCPAP on BP in persons with OSA, a small decrease in diastolic BP was observed [6]. In other studies, both systolic and diastolic BP decreased significantly after nCPAP treatment [6,8]. The most recent data from the Sleep Heart Health Study [5] shows that sleep-disordered breathing is associated with systolic and diastolic hypertension in persons aged 40–59 years, and no association was found between sleep-disordered breathing and systolic/diastolic hypertension in those over the age of 60 years or between sleep-disordered breathing and isolated systemic hypertension in either age category [5]. The mean age of the patients in this study was 52 (48–55) years. Overall, from previous reports [5–8,20–27], the dominant decrease might occur in diastolic BP in OSA after nCPAP treatment, as in the present study.

Fig. 4

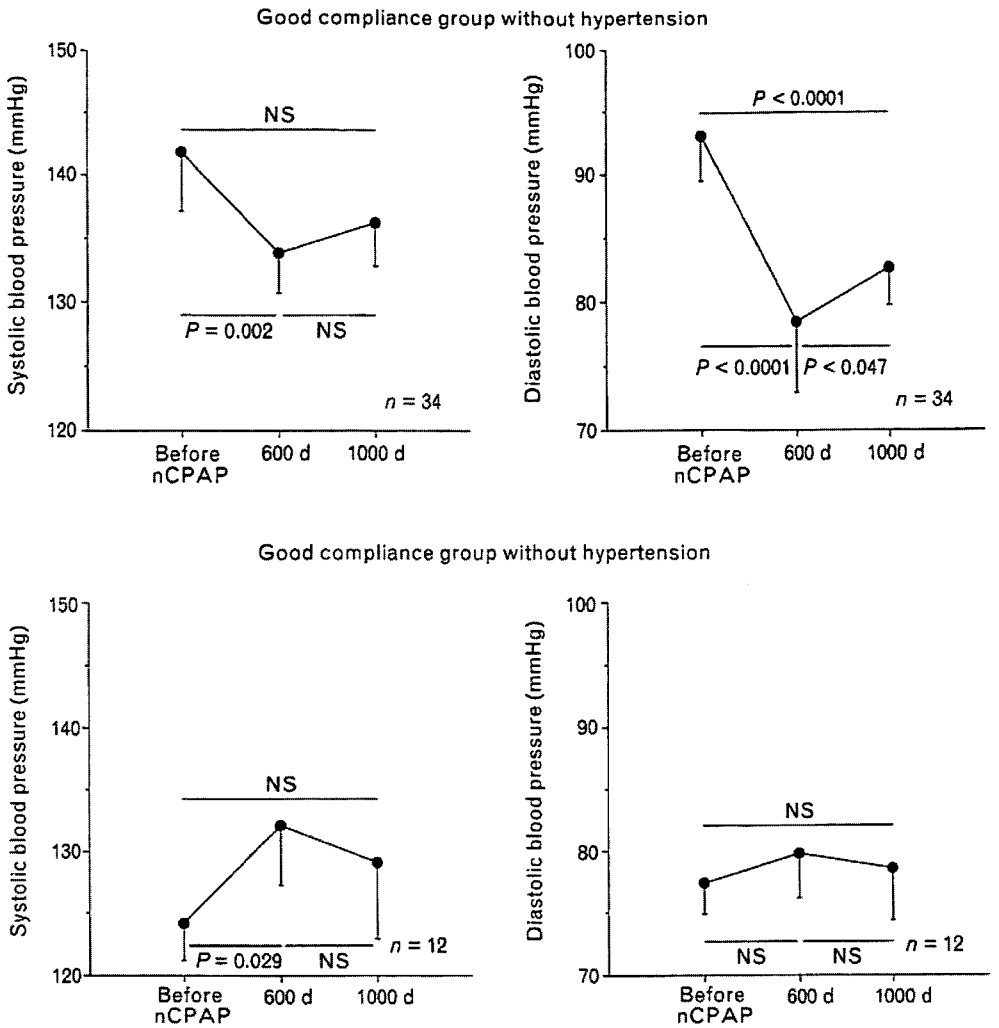


Flow chart of study patients with obstructive sleep apnoea (OSA). Nasal continuous positive airway pressure (nCPAP) treatment significantly lowered the diastolic blood pressure (BP) of hypertensive OSA patients who used nCPAP for a daily average of 3 h or more (Figs 1–3). Use of nCPAP for a daily average of less than 3 h had no significant effects on BP in OSA patients (Figs 2 and 3). nCPAP treatment of 3 h or more significantly lowered both systolic and diastolic BP in hypertensive OSA patients not receiving antihypertensive drugs, and only the diastolic BP in the patients who were receiving antihypertensive drugs (Figs 5 and 6). See text for details. S(−), systolic BP did not decrease significantly; S(+), systolic BP significantly decreased; D(−), diastolic BP did not decrease significantly; D(+), diastolic BP decreased significantly after nCPAP treatment.

In previous reports [6–8,24] it was not shown how much usage time of nCPAP was needed to achieve significant falls in BP. From this study, we found that a daily average of 3 h is needed for such an effect (Figs 2, 3, 5 and 6). The mean age of the compliant patients in this study was 51 years and their diastolic BP fell 7.4 mmHg from the beginning of nCPAP treatment. From another study [11], a diastolic BP fall of 7.4 mmHg would be expected to be associated with stroke risk reduction of about 49% and an ischemic heart disease event risk reduction of about 37%. Two papers recently reported that there was a protective effect of nCPAP therapy against death from cardiovascular disease in patients with severe OSA [28,29]. One of the factors for prevention of cardiovascular diseases in OSA patients may be BP reduction by nCPAP treatment.

An improvement in severity of symptoms in OSA after only 4 h of nCPAP therapy has been reported [18]. Also reported was the fact that a sleep restriction greater than 4 h will increase sleep propensity greatly, and that 4 h of sleep without disturbance may be the minimum

Fig. 5

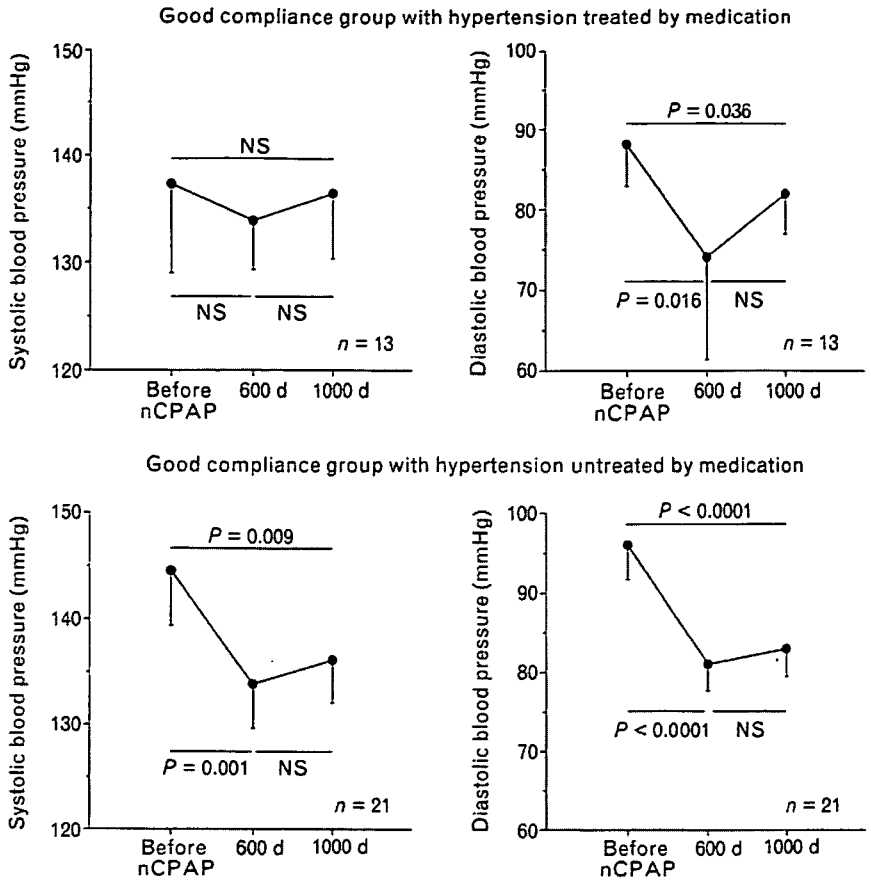


Mean blood pressure values in 34 hypertensive patients with or without antihypertensive treatment and 12 normotensive patients with good compliance [daily average of 3 h or more of nasal continuous positive airway pressure (nCPAP)] before nCPAP treatment, after 600 and 1000 days of nCPAP treatment. Systolic blood pressure (BP) of 34 hypertensive patients in the good compliance group changed significantly at the first checkpoint but did not change significantly overall. Although the systolic BP of 12 normotensive patients with good compliance also changed significantly within the normal range of BP at the first checkpoint, it did not change significantly overall. Diastolic BP of 12 patients without hypertension did not change significantly after nCPAP treatment. Bars indicate mean levels with 95% confidence intervals.

requirement for acceptable daytime performance [30]. In a report of 36 patients, there were two checkpoints, 673 and 1063 days, which were almost the same as in our study, and compliance was 5.2 h during the first period and 5.0 h during the second period [31]. Compliance decreased as in our study, although the difference was not significant, probably because of the small number of patients [31]. Subjective compliance was higher than objective compliance, which is consistent with previous reports [9,19]. Subjective compliance did not significantly decrease between the first and second time points. Patients may therefore decrease usage time without knowing it. OSA patients may titrate their own nCPAP use to provide an acceptable balance between the inconvenience of nCPAP and the benefits of therapy. If lesser usage of nCPAP therapy has almost the same effect on patients, the saving of 17 min in a day may provide an increase in quality of life. Further research is needed on how much awake time OSA patients gain through nCPAP treatment that provides them with good quality sleep.

The limitation of this study may be the method of BP measurement. Ambulatory BP [7] or continuous BP measurement [8] would be better in monitoring changes in BP before and after nCPAP treatment. The BP was calculated by the mean value over 3 months. In addition, the significant decrease in diastolic BP would accurately

Fig. 6



Mean blood pressure values in 21 hypertensive patients taking antihypertensive drugs and in 13 hypertensive patients not taking antihypertension medication with good compliance [daily average of 3 h or more of nasal continuous positive airway pressure (nCPAP)] before nCPAP treatment, after 600 and 1000 days of nCPAP treatment. Systolic blood pressure (BP) did not but diastolic BP did decrease significantly after nCPAP treatment in the treatment group ($n = 13$). Their diastolic BP might be resistant to treatment. Both systolic and diastolic BP decreased significantly after nCPAP treatment in the no treatment group with hypertension ($n = 21$). Bars indicate mean levels with 95% confidence intervals.

reflect the actual situation because the degrees of decreases in diastolic BP were very closely correlated with data from two checkpoints ($r = 0.78$, $P < 0.0001$). The second point was that we did not know the factors that possibly influenced good or low compliance. Patients in the high compliance group had significantly high diastolic hypertension before treatment. An improvement in diastolic BP by nCPAP treatment may therefore be a motivating factor. We should have checked daytime sleepiness and administered a questionnaire about the quality of life after nCPAP treatment because daytime sleepiness or fatigue has significant effects on the acceptance of and the effectiveness of nCPAP treatment, including BP control [20]. In evaluating the effectiveness of nCPAP treatment on the prevention of cardiovascular disease, however, BP data in this study might be valuable.

A daily average of 3 h of nCPAP usage induced a 7.4 mmHg decrease in diastolic BP in OSA patients. Medical personnel should be aware of such an effect so that they may provide intensive support in improving nCPAP use, because in patients in their fifties, as in this study, a diastolic BP fall of 7.4 mmHg would be expected to be associated with stroke mortality risk reduction of about 49%, an ischemic heart disease event mortality risk reduction of about 37% and risk reduction of about 38% from other vascular disorders according to the age-specific relevance of usual BP to vascular mortality [11].

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Forum Original Research Communication

Plasma Thioredoxin, a Novel Oxidative Stress Marker, in Patients with Obstructive Sleep Apnea Before and After Nasal Continuous Positive Airway Pressure

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ABSTRACT

Obstructive sleep apnea (OSA) is associated with increased cardiovascular mortality, and oxidative stress was suggested to play an important role. We hypothesized that the plasma TRX level, a novel oxidative stress marker, is elevated in OSA patients. Plasma TRX and adiponectin levels, which are significantly associated with cardiovascular mortality, were measured in 41 patients with severe OSA before (n 41) and after (n 27) nasal continuous positive airway pressure therapy (nCPAP) for 1 month and in 12 subjects without OSA (non-OSA group). The TRX level was significantly higher (p 0.02) and the adiponectin level was significantly lower (p 0.02) in the OSA group than in the non-OSA group. After 1 month of nCPAP (n 27), the TRX level significantly decreased (p 0.03), and the adiponectin level significantly increased (p 0.03). Among the 14 patients with untreated OSA, the TRX and adiponectin levels did not significantly change over a 1-month interval. Among the 53 (41 OSA 12 non-OSA) subjects, the TRX level was positively correlated with the respiratory disturbance index (p 0.001) and percentage of time with Sao_2 90% (p 0.0002). The adiponectin level, but not the TRX level, was correlated with the BMI (n 53; p 0.02). Plasma TRX may be a unique marker for evaluating oxidative stress and monitoring the effectiveness of nCPAP in OSA patients. *Antioxid. Redox Signal.* 10, 0000–0000.

INTRODUCTION

THIOREDOXIN (TRX) is a small protein that contains a redox-active site and has a variety of biologic functions including cytoprotection against oxidative stress (23). Recent experimental studies showed that TRX is released from cells in response to oxidative stress (31) and plays a protective role against oxidant injury (13). In our previous studies, we found that the plasma/serum level of TRX is elevated in patients with oxidative stress–associated acute and chronic disorders such as viral infection (36), ischemia–reperfusion (21), myocardial infarction (22), chronic heart failure (12), and nonalcoholic steatohepatitis (35). Obstructive sleep apnea (OSA) has been reported to have significant effects on myocardial infarction (17), chronic heart failure (30), and nonalcoholic steatohepatitis (38). However, the blood levels of TRX in patients with OSA have not been investigated.

The mortality rate is increased in untreated patients with OSA, who are at increased risk for cerebrocardiovascular diseases (17). In addition, the prevalence of significant OSA is high (43). Recently, OSA has been associated with inflammation, endothelial dysfunction, and increased oxidative stress

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(34), which are generated by repetitive nocturnal hypoxemia and reoxygenation (Fig. 1). Oxidative damage is involved in the pathogenesis of atherosclerosis and cardiovascular diseases (6), as well as of inflammation (14).

To elucidate the involvement of oxidative stress in OSA, two types of oxidative stress markers have been studied: (a) products of oxidation such as reactive oxygen species, oxidized proteins, lipid oxidation, and DNA degeneration as the end products of oxidative stress; and (b) antioxidant proteins whose gene expression is induced by oxidative stress. An antioxidant protein such as TRX (13, 31) not only has a role as an oxidative stress marker, but also may potentially be protective against oxidative stress. Recently, oxidative stress has been investigated in patients with OSA by measuring the levels of various products of oxidation (3, 5, 15, 32, 41). However, no antioxidant protein has been measured in those reports.

Therefore, it is important and promising to investigate oxidative stress in patients with OSA with a sensitive antioxidant marker, such as plasma TRX, because the plasma TRX level is easy to measure and reflects the cellular response to oxidative stress (12, 22). We hypothesized that the plasma TRX level in OSA patients is elevated and that it is reduced by treatment. We also hypothesized that the plasma TRX level in patients with OSA is associated with inflammation and the pathogenesis of cardiovascular diseases.

Adiponectin is a cytokine produced exclusively by white adipose tissue and appears to play a central role in metabolic syndrome (19) in addition to having antiatherogenic and antiinflammatory effects (39). Adiponectin may play an important role in cardiovascular disorders (28). Therefore, we also measured the plasma adiponectin level in addition to plasma interleukin-6 (IL-6) and serum C-reactive protein (CRP) levels, which are known to be inflammatory markers predictive of cardiovascular diseases (16) and have been reported to be elevated in OSA patients (33, 42). We compared these parameters between the OSA patients and subjects without OSA and investigated the effect of nasal continuous positive airway pressure (nasal CPAP) therapy on these parameters in OSA patients.

METHODS

Subjects

OSA patient group. We enrolled 50 consecutive patients with OSA who were determined to be candidates for nasal CPAP treatment by polysomnography and clinical symptoms. The diagnosis of OSA was established on the basis of clinical symptoms such as excessive daytime sleepiness, unexplained daytime fatigue, choking or gasping during sleep, and an apnea hypopnea index (AHI) of 5 events per hour on polysomnography. Five patients were excluded because they had a history of myocardial infarction, brain infarction, chronic cardiac failure, or colon cancer or had a common cold at the time of the study. Polysomnography was performed in the hospital before CPAP treatment. Patients with an AHI of 20 events per hour were candidates for nasal CPAP.

Hypertension was defined as a diastolic pressure 90 mm Hg, a systolic pressure 140 mm Hg, or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting blood glucose level of 126 mg/dl, increased blood glucose level of 200 mg/dl 2 h after a 75-g oral glucose load, or the use of antidiabetic medication. Hyperlipidemia was defined as a total blood cholesterol level of 220 mg/dl, triglyceride level of 150 mg/dl, or the use of lipid-lowering medication. The OSA patients in this study received the same medical regimen beginning 1 month before the start of this study and throughout the study.

OSA untreated group. When a patient is diagnosed with severe OSA at our hospital, nasal CPAP therapy is started about 1 month later. To investigate whether significant changes in the plasma TRX level occur in OSA patients who have not received CPAP treatment, 15 OSA patients were randomly selected from the 45 patients, and we planned to obtain blood samples from them in the morning twice at about a 1-month interval before nasal CPAP treatment was started. One patient did not return to our clinic for follow-up. Therefore, 14 patients [13

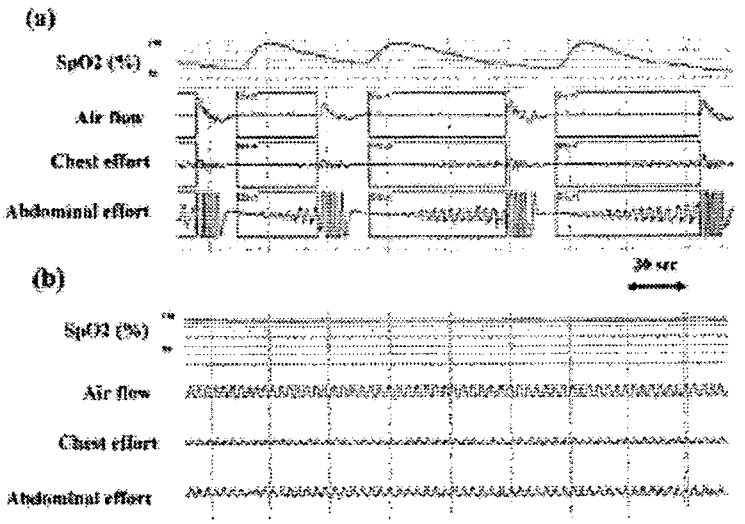

FIG. 1. Polysomnographic data of one of the OSA patients in this study who underwent nasal CPAP therapy (man, 53 years old; body mass index, 29.3 kg/m^2). (a) Polysomnographic data of the OSA patient before nasal CPAP treatment. After cessations of nasal and oral air flow with paradoxic chest and abdominal motions, periodical desaturations were observed. (b) Polysomnographic data of the same OSA patient after nasal CPAP treatment for 3 days. The periodic cessations of air flow and desaturations disappeared. Spo_2, Oxygen saturation measured with pulse oximetry; Ob A., obstructive sleep apnea.

TABLE 1. BASELINE CHARACTERISTICS OF THE OSA SUBJECTS AND NON-OSA SUBJECTS

Variable	*OSA*	*Non-OSA*	p	p*
Number	41	12		
Male/Female (no.)	38/3	11/1	0.96	
Age (yr)	49.8 10.0	46.7 11.2	0.22	
Body mass index (kg/m^2)	29.4 4.2	25.7 4.1	**0.004**	
Respiratory disturbance index (events/h)	48.5 18.2	2.80 1.7	**0.0001**	
Lowest SaO_2 (%)	65.4 15.3	86.3 6.1	**0.0001**	
% of time SaO_2 90% (%)	25.9 2.4	0.50 0.73	**0.0001**	
Current smoking (no.)	11	3	0.92	
Hypertension (no.)	27	6	0.41	
Diabetes mellitus (no.)	10	3	0.97	
Hyperlipidemia (no.)	16	4	0.77	
Thioredoxin (ng/ml)	41.0 24.4	23.9 14.7	**0.02**	**0.04**
Adiponectin (g/ml)	3.84 1.66	5.82 3.09	**0.02**	**0.03**
IL-6 (pg/ml)	1.56 2.49	0.99 0.94	0.77	0.92
CRP (mg/dl)	0.172 0.147	0.087 0.096	**0.02**	0.07

Data are expressed as mean SD.
p*, p value after adjustment for BMI; OSA, obstructive sleep apnea.

men, one woman; age, 52.7 8.3 years; AHI, 49.1 24.1 events/hour; body mass index (BMI), 28.2 3.2 kg/m^2] were included in the OSA-untreated group.

OSA treatment group. To investigate the effect of nasal CPAP treatment, the remaining 30 patients with OSA underwent CPAP titration manually, received CPAP treatment [pressure (mean SD), 9.6 3.1 cm H_2O], and underwent polysomnography on the third night of CPAP therapy. Thereafter, they received nasal CPAP therapy for 1 month at home before revisiting the outpatient clinic. Three patients refused to use nasal CPAP continuously. We checked the use time by reading the time counter in each CPAP machine, and the remaining 27 patients used nasal CPAP for 4 h per night. These 27 patients (25 men, two women; age, 48.3 10.7 years; AHI, 48.2 14.8 events/hour; BMI, 30.1 4.6 kg /m^2) were included in the OSA treatment group. Blood samples were collected in the morning before and 1 month after beginning CPAP use. The BMI after 1 month of nasal CPAP did not significantly differ from that before CPAP therapy was started (p 0.26). Forty-one (14 untreated and 27 treatment) OSA patients were studied (Tables 1 and 2).

Non-OSA volunteer group. Twelve volunteers (11 men, one woman; age, 46.7 11.2 years; BMI, 25.7 4.1 kg/m^2) who did not have OSA were enrolled in the non-OSA group. They were not heavy snorers. In all of the volunteers, the arterial oxygen saturation was continuously monitored during sleep with a pulse oximeter (Pulsox-24; Minolta, Osaka, Japan) over two consecutive nights. The severity of sleep ap-

TABLE 2. BASELINE CHARACTERISTICS OF THE OSA TREATMENT GROUP AND OSA UNTREATED GROUP

Variable	*OSA treatment*	*OSA untreated*	p
Number	27	14	
Male/Female (no.)	25/2	13/1	0.99
Age (yr)	48.3 10.7	52.7 8.29	0.21
Body mass index (kg/m^2)	30.1 4.6	28.2 3.16	0.25
Apnea–hypopnea index (events/h)	48.2 14.8	49.1 24.1	0.83
Lowest arterial O_2 saturation (%)	65.2 16.5	65.8 13.4	0.67
Arterial O_2 90% (% of time)	29.3 22.9	19.3 20.6	0.21
Thioredoxin (ng/ml)	43.6 23.0	35.9 27.1	0.15
Adiponectin (g/ml)	3.55 1.37	4.40 2.04	0.20
IL-6 (pg/ml)	1.68 2.87	1.33 1.59	0.70
CRP (mg/dl)	0.178 0.156	0.161 0.130	0.46
Hypertension (no.)	18	9	0.90
Diabetes mellitus (no.)	6	4	0.74
Hyperlipidemia (no.)	10	6	0.76
Current smoking (no.)	8	3	0.67

Data are expressed as mean SD.
OSA, obstructive sleep apnea.

nea in the volunteers was quantified by the 3% oxygen desaturation index (3%ODI), which was the number of oxygen desaturations of 3% or more below the baseline level per hour during sleep. This index correlates well with the conventional AHI (26). Subjects who had a 3%ODI of 5 were diagnosed as not having OSA. The 3%ODI of the 12 volunteers was 2.8 1.7 (range, 1.74–3.86).

The rates of hypertension, diabetes mellitus, hyperlipidemia, and current smoking habit among the non-OSA group were not significantly different from those among the 41 OSA patients (see Table 1). The BMI was significantly lower in the non-OSA group than in the OSA group. Therefore, the BMI was adjusted in the data analysis afterward. Blood samples were obtained from the non-OSA subjects at 8:00 in the morning after fasting beginning at 20:00 on the previous night.

This study was approved by the medical ethics committee of our university and was in accordance with the recommendations found in the Helsinki Declaration of 1975. All patients and subjects in the study groups provided written informed consent for participation in this study.

Polysomnography

Polysomnography was started at 21:00 and ended at 7:30 the following morning (see Fig. 1). Polysomnography was performed as previously described (4). Surface electrodes were attached by using standard techniques to obtain an electrooculogram, electromyogram of the chin, and 12-lead electroencephalograph. Sleep stages were defined according to the criteria of Rechtschaffen and Kales (29). Ventilation was monitored by inductive plethysmography (Respitrace: Ambulatory Monitoring; Ardsley, NY). Airflow was monitored by thermistors (Nihon Kohden, Tokyo, Japan) that were placed at the nose and the mouth. Arterial oxygen saturation (Sao_2) was monitored continuously with a pulse oximeter (Pulsox-24; Minolta, Osaka, Japan) (see Fig. 1).

Apnea was defined as a complete cessation of airflow at the nose and mouth that lasts for 10s. Hypopnea was defined as a decrease in thoracoabdominal motion of 50% that lasts for 10 sec and associated with a decrease in the baseline Sao_2 of 3% (1). All AHI values were expressed as the number of episodes of apnea and hypopnea per hour over the total sleep time. Lowest Sao_2 during sleep and percentage of time of Sao_2 90% during sleep also were calculated in each patient.

Respiratory disturbance index

The respiratory disturbance index (RDI) (27) was defined as (a) AHI in OSA patients and (b) 3% ODI in the volunteers.

Measurement of plasma/serum factors

Blood samples were drawn at 8:00 in the morning after the subjects had fasted beginning at 20:00 the previous night. Blood samples were centrifuged immediately at 3,000 rpm at 4°C for 10 min. The separated samples were stored at 80°C until assay. The plasma levels of TRX (Redox Bioscience, Kyoto, Japan; intra- and interassay coefficients of variation were 3.7% and 4.8%, respectively) and adiponectin (Otsuka Pharmaceuticals, Tokyo, Japan; intra- and interassay coefficients of variation were 4.1% and 4.7%, respectively) were measured with enzyme-linked immunosorbent assay. The plasma level of IL-6 (R&D Systems, Minneapolis, MN; intra- and interassay coefficients of variation were 7.8 and 4.6%, respectively) was measured with the chemiluminescent enzyme immunoassay. The serum levels of high-sensitivity CRP (Dade Behring, Liederbach, Germany; intra- and interassay coefficients of variation were 1.7% and 4.9%, respectively) were measured by nephelometry.

Data analysis

Data were expressed as mean SD. The data for each parameter did not show a normal distribution. The Mann–Whitney *U* test was used to compare two groups. Differences between two intervals were compared with the Wilcoxon signed-rank test. Correlation analyses were performed with Spearman's correlation coefficients (*Rs*). The BMI was significantly lower in the non-OSA group than in the OSA group. Therefore, multiple linear regression analysis was performed, with plasma TRX level as the dependent variable. Logarithmic transformation was performed on the plasma TRX levels to correct for the abnormal distribution of the values. This transformed variable was used in the model. The independent variables that were entered were BMI and OSA (presence or absence of OSA). Similarly, we performed multiple linear regression analysis with adiponectin, IL-6, and CRP levels as the dependent variables. Statistical analyses were performed by using StatView software for Windows (Version 5.0; Abacus Concepts, Berkeley, CA). A p value of 0.05 was considered to be significant.

RESULTS

Effect of OSA on biomarkers

The plasma TRX level was significantly higher in the 41 OSA subjects before nasal CPAP therapy than in the 12 non-OSA subjects (41.0 24.4 ng/ml *vs.* 23.9 14.7 ng/ml; p 0.02). Conversely, the plasma adiponectin level was significantly lower in the OSA subjects than in the non-OSA subjects (3.84 1.66 g/ml *vs.* 5.82 3.09 g/ml; p 0.02) (see Table 1 and Fig. 2). The serum CRP level was significantly higher in the OSA subjects than in the non-OSA subjects (0.172 0.147 mg/dl *vs.* 0.087 0.096 mg/dl; p 0.02), whereas the plasma IL-6 level did not significantly differ between the two groups (1.56 2.49 pg/ml *vs.* 0.99 0.94 pg/ml; p 0.77) (see Table 1 and Fig. 2).

We divided the 53 subjects into the RDI 40 not-severe OSA group (NS-OSA: n 26) and the 40 RDI very severe OSA group (VS-OSA: n 27). The plasma TRX level was significantly higher in the VS-OSA subjects before nasal CPAP therapy than in the NS-OSA subjects (p 0.002). The serum CRP and plasma IL-6 levels were also significantly higher in the VS-OSA subjects than in the NS-OSA subjects (p 0.05 and p 0.006). Conversely, the plasma adiponectin level was significantly lower in the VS-OSA subjects than in the NS-OSA subjects (p 0.03).

We also divided the subjects into the RDI 20 non-OSA (N-OSA: n 12), 20 RDI 40 moderate OSA (M-OSA: n 14),

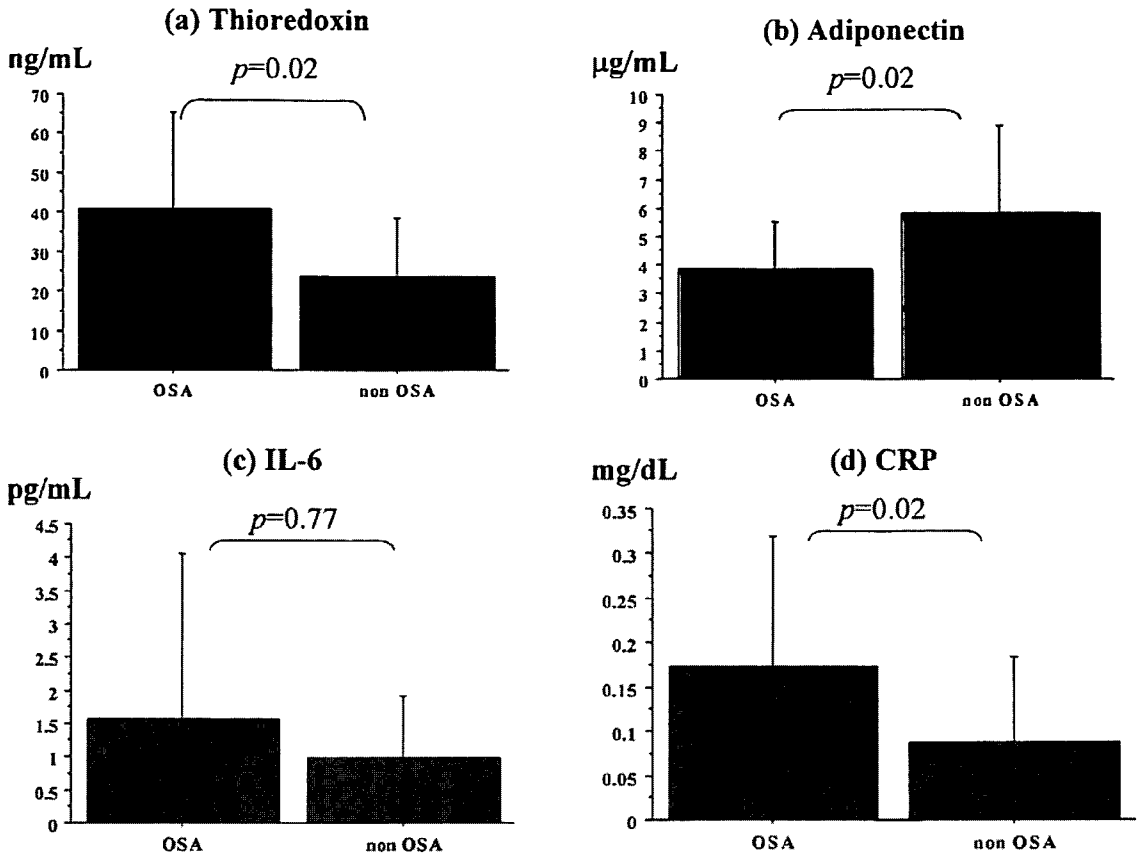

FIG. 2. Comparison of the plasma thioredoxin, adiponectin, IL-6, and serum CRP levels between the OSA group before nasal CPAP therapy and the non-OSA group. The plasma TRX level was significantly greater in the OSA group (n 41) than in the non-OSA group (p 0.02). Conversely, the plasma adiponectin level was significantly lower in the OSA group than in the non-OSA group (p 0.02). The serum CRP level was significantly greater in the OSA group than in the non-OSA group (p 0.02). The plasma IL-6 level did not differ significantly between the OSA and the non-OSA group (p 0.77). OSA, obstructive sleep apnea; IL-6, interleukin 6; CRP, C-reactive protein.

and 40 RDI severe OSA (S-OSA: n 27) groups. The plasma TRX level was significantly higher in the S-OSA subjects before nasal CPAP therapy than in the N-OSA subjects (p 0.004) and in the M-OSA subjects (p 0.02). The plasma TRX level was not significantly different between the M-OSA subjects before nasal CPAP therapy and the N-OSA subjects (p 0.5).

Relations between various parameters before nasal CPAP treatment and plasma TRX

The following correlation analyses were performed by using the baseline laboratory data of the 41 OSA subjects and the laboratory data of the 12 non-OSA subjects. The plasma TRX level was positively correlated with RDI (p 0.001; Rs 0.45) and the percentage of time with Sao_2 90% (p 0.0002; Rs 0.52) (Fig. 3). In addition, the plasma TRX level was positively correlated with the plasma IL-6 (p 0.009; Rs 0.36) and serum CRP levels (p 0.0002; Rs 0.51), and negatively correlated with the plasma adiponectin level (p 0.02; Rs 0.32) (Fig. 4). The adiponectin level was negatively correlated with RDI (p 0.01; Rs 0.35) and with the percentage of time with Sao_2 90% (p 0.04; Rs 0.29) (see Fig. 3). The plasma TRX level was not correlated with BMI (p 0.09; Rs 0.23), whereas the plasma adiponectin level (p 0.02; Rs 0.32) and the serum CRP level (p 0.0009; Rs 0.46) were significantly correlated with BMI (Fig. 5).

Multiple linear regression analysis was performed on the 53 subjects, with plasma TRX level as the dependent variable and BMI and OSA as the independent variables. BMI was not significantly associated with the plasma TRX level (p 0.45). Conversely, OSA was significantly associated with the plasma TRX level (p 0.04). The adjusted correlation coefficient (R) for the model was 0.36. After adjustment for BMI, age, and current smoking habit, the difference in plasma TRX levels between the OSA patients and non-OSA subjects was significant (p 0.04; R 0.38). The RDI was more significantly associated with the TRX level (p 0.02) than with the adiponectin level (p 0.13) independent of BMI (R 0.43). Moreover, after adjustment for BMI, age, current smoking habit, and co-