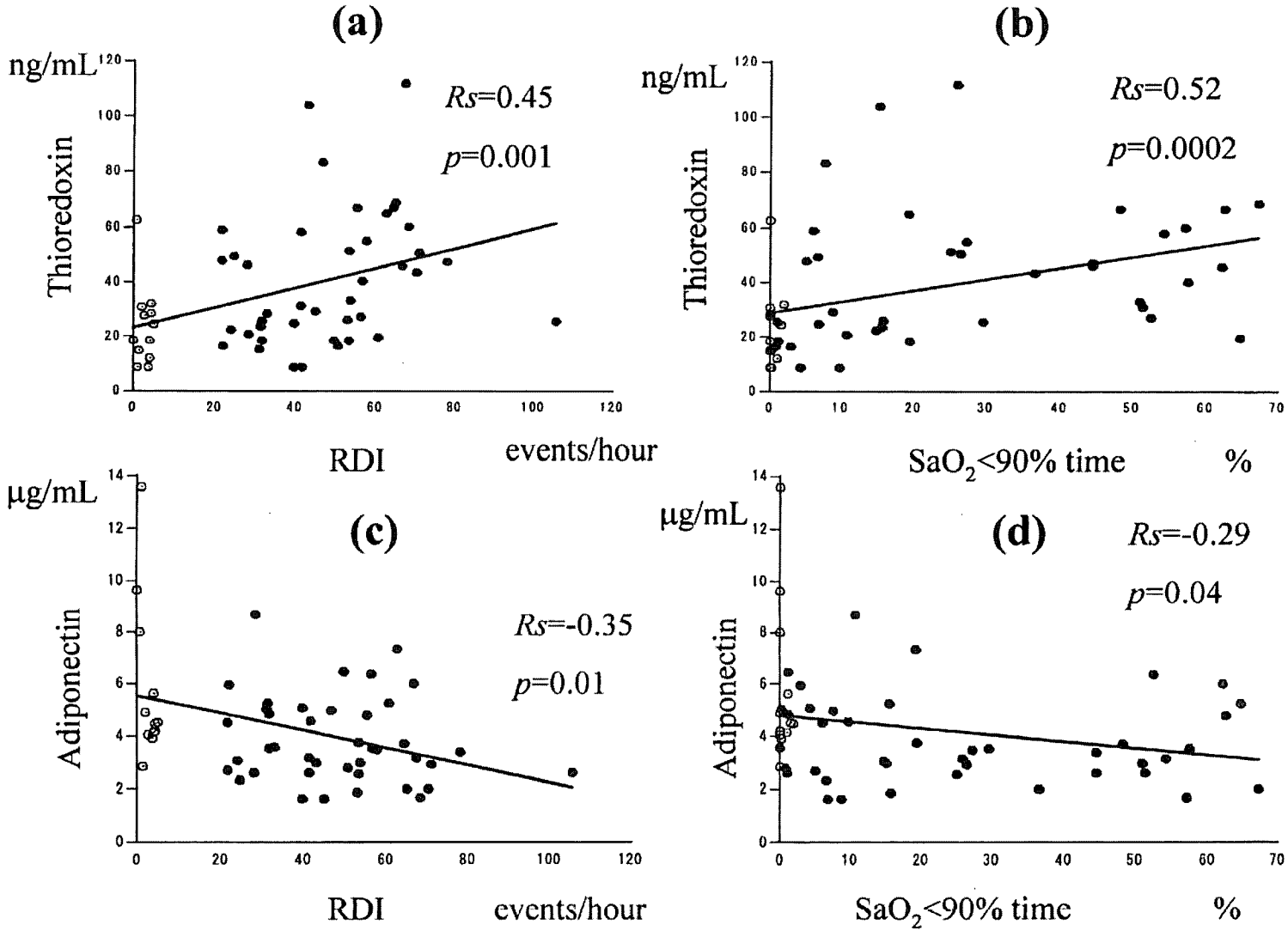

FIG. 3. Correlation analyses between the plasma thioredoxin or adiponectin level and RDI or Sao_2 90% of the time. The correlation analyses included the baseline laboratory data of the OSA subjects (*n* 41) and the laboratory data of the non-OSA subjects (*n* 12). The plasma thioredoxin level was positively correlated with RDI and with Sao_2 90% of the time. The plasma adiponectin level was negatively correlated with RDI and with Sao_2 90% of the time. *Solid circles*, OSA subjects, *n* 41; *open circles*, subjects in the non-OSA group, *n* 12. RDI, respiratory disturbance index; Sao_2, arterial O_2 saturation.

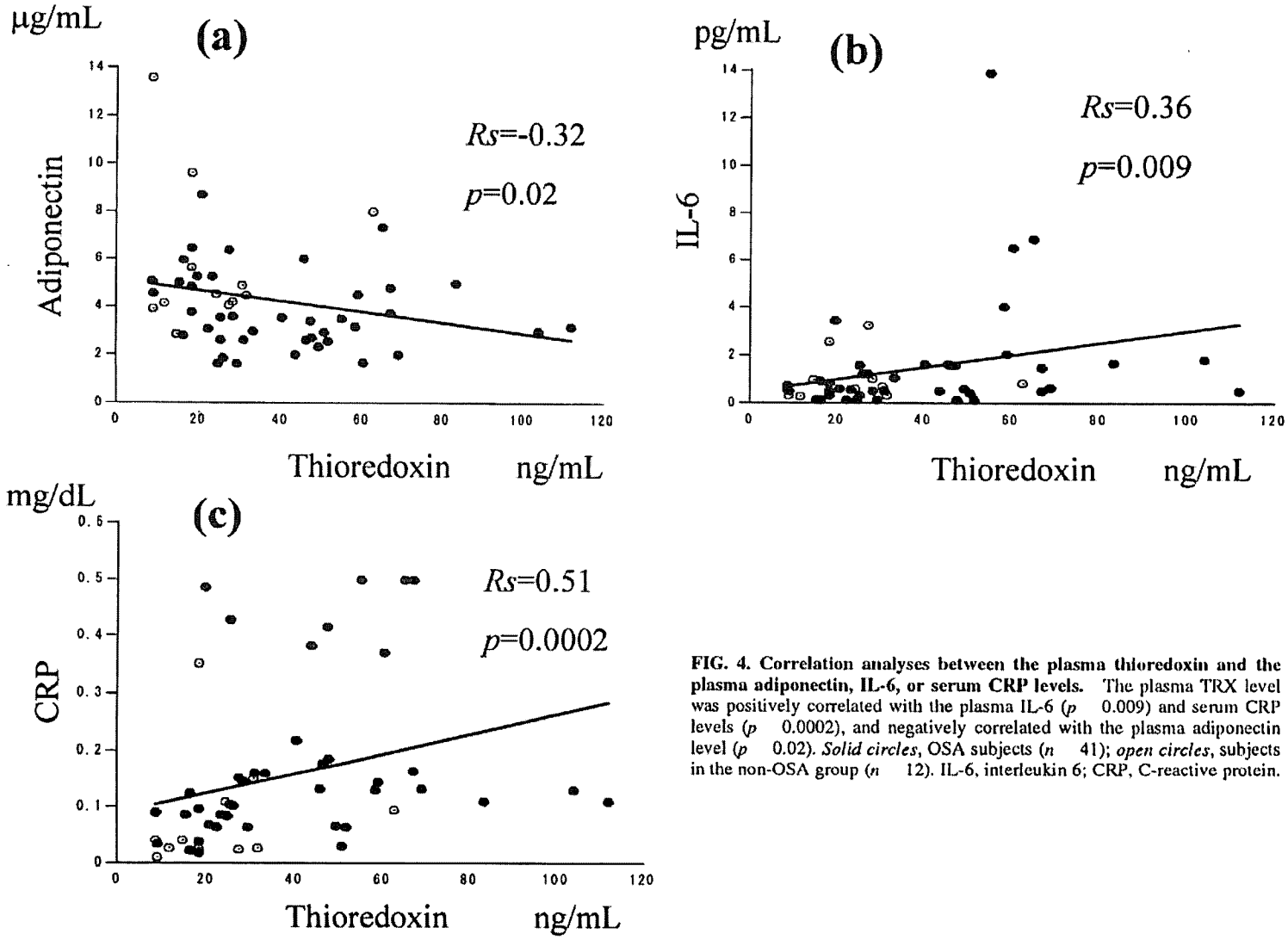

FIG. 4. Correlation analyses between the plasma thioredoxin and the plasma adiponectin, IL-6, or serum CRP levels. The plasma TRX level was positively correlated with the plasma IL-6 (p 0.009) and serum CRP levels (p 0.0002), and negatively correlated with the plasma adiponectin level (p 0.02). *Solid circles*, OSA subjects (n 41); *open circles*, subjects in the non-OSA group (n 12). IL-6, interleukin 6; CRP, C-reactive protein.

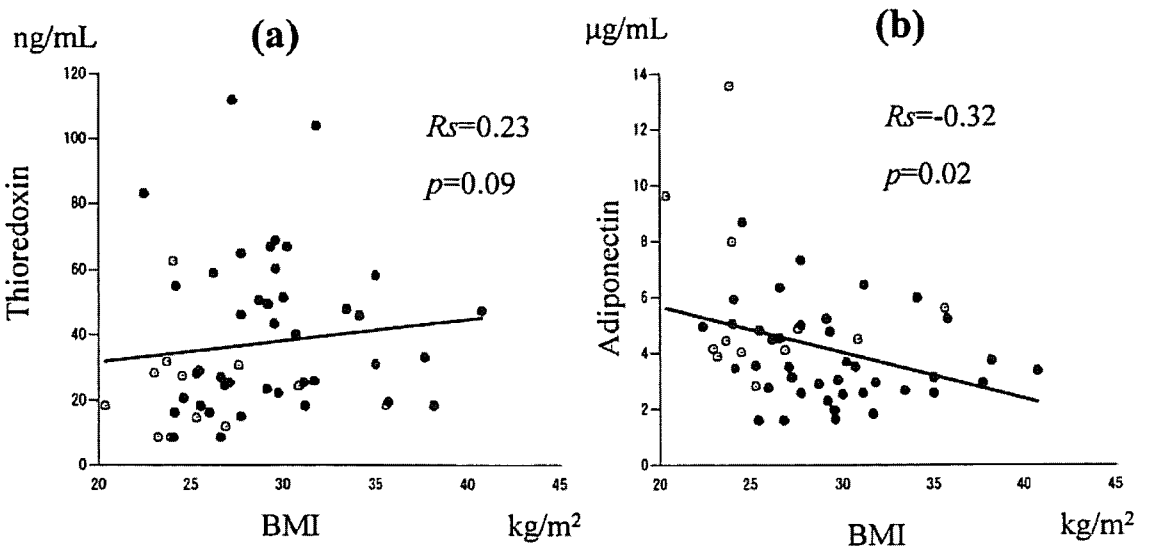

FIG. 5. Correlation analyses between BMI and the plasma thioredoxin or adiponectin level. The plasma adiponectin level, but not the plasma thioredoxin level, was negatively correlated with BMI. *Solid circles*, OSA subjects (n 41); *open circles*, subjects in the non-OSA group (n 12). BMI, body mass index.

morbidities, the difference in plasma TRX level between the OSA patients and non-OSA subjects was still significant (p 0.02; R 0.48). The plasma TRX level was not significantly associated with BMI (p 0.15), whereas it was significantly associated with RDI. (p 0.004; R 0.53).

Effect of nasal CPAP treatment on the biomarkers

In the OSA-treatment group, nasal CPAP for 1 month significantly improved nocturnal hypoxemia/reoxygenation parameters including the RDI (48.2 14.8 events/h to 1.81 1.21 events/h; p 0.0001), lowest nocturnal Sao_2 (65.2 16.5% to 88.1 4.04%; p 0.0001) and the percentage of time with Sao_2 90% (29.3 22.9% to 0.37 0.45% of time; p 0.0001). Although the BMI did not significantly change, the TRX, IL-6, CRP, and adiponectin levels changed significantly after 1 month of nasal CPAP use. The plasma TRX level (43.6 23.0 ng/ml to 33.3 20.8 ng/ml; n 27; p 0.03) significantly decreased after 1 month of nasal CPAP treatment. Conversely, the plasma adiponectin level (3.55 1.37 g/ml to 3.79 1.14 g/ml; p 0.03) significantly increased (Table 3, Fig. 6). The plasma IL-6 (1.68 . 2.87 pg/ml to 0.634 0.619 pg/ml; p 0.0008) and serum CRP levels (0.178 0.156 mg/dl to 0.120 0.120 mg/dl; p 0.01) also significantly decreased (see Table 3 and Fig. 6).

We performed correlation analyses between the "basal" serum TRX level before nasal CPAP treatment and the therapeutic response, such as the change in RDI or Pao_2. The TRX level was not correlated with the change in RDI (p 0.13; Rs 0.30), the change in lowest Sao_2 (p 0.99; Rs 0.003), or the change in the percentage of time with Sao_2 90% (p 0.11; Rs 0.31).

In the OSA-untreated group, the TRX, IL-6, CRP, and adiponectin levels did not significantly differ (all the p values

TABLE 3. CHANGES IN THE LEVELS OF MEDIATORS DURING THE MEASUREMENT INTERVAL IN THE OSA TREATMENT GROUP AND OSA UNTREATED GROUP

Variable		*First blood sample*		*Second blood sample*		p
Thioredoxin (ng/ml)	OSA treated	43.6	23.0	33.3	20.8	**0.03**
	OSA untreated	35.9	27.1	32.5	15.8	0.64
Adiponectin (g/ml)	OSA treated	3.55	1.37	3.79	1.14	**0.03**
	OSA untreated	4.40	2.04	4.30	2.06	0.29
IL-6 (pg/ml)	OSA treated	1.68	2.87	0.63	0.62	**0.0008**
	OSA untreated	1.33	1.59	0.94	0.58	0.78
CRP (mg/dl)	OSA treated	0.178	0.156	0.120	0.117	**0.01**
	OSA untreated	0.161	0.130	0.119	0.091	0.27

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

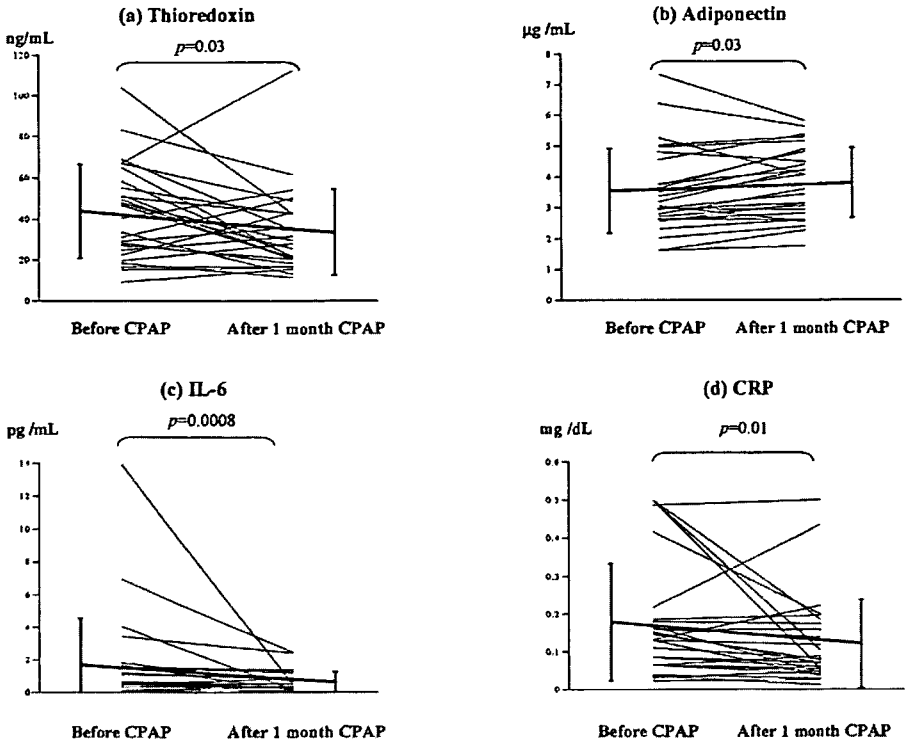

FIG. 6. Changes in the plasma thioredoxin, adiponectin, IL-6, and serum CRP levels after 1 month of nasal CPAP use in the OSA treatment group. Nasal CPAP treatment significantly reduced the plasma thioredoxin level but increased the plasma adiponectin level. Nasal CPAP treatment significantly reduced the plasma IL-6 and serum CRP levels. OSA, obstructive sleep apnea; IL-6, interleukin 6; CRP, C-reactive protein; CPAP, continuous positive airway pressure.

0.27) between the 2 days of measurement (mean interval, 39.4 days) during which nasal CPAP treatment was not provided (see Table 3, Fig. 7).

DISCUSSION

In the OSA patient group (n 41), the plasma TRX level, a marker of oxidative stress, was significantly increased before nasal CPAP treatment, but the plasma level of adiponectin, an adipocytokine, was significantly reduced. The plasma TRX level (n 53: the 41 OSA subjects and the 12 non-OSA subjects) was positively correlated with RDI (p 0.001) and percentage of time with Sao_2 90% (p 0.002). Plasma TRX was strongly related to OSA independent of BMI, age, and current smoking habit (p 0.04; R 0.38). After nasal CPAP treatment, the plasma level of TRX decreased, as did the levels of other cardiovascular parameters, such as serum CRP and plasma IL-6, whereas the plasma level of adiponectin increased.

TRX expression is induced by oxidative stress, and this protein scavenges reactive oxygen radicals directly or together with TRX-dependent peroxiredoxin. Moreover, TRX is released from cells in the presence of oxidative stress, and the plasma/serum TRX levels are good markers of oxidative stress (12, 22). Several studies showed that the TRX level ranges from 10 ng/ml to 30 ng/ml among normal subjects and that it is 40 ng/ml in patients with oxidative stress (20, 21, 35, 36). In the present study, 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). Our results strongly support that OSA patients are subjected to hypoxia-induced oxidative stress every night. Some studies (3, 5) showed that patients with OSA have decreased antioxidant capacity. Indeed, a high concentration of TRX, such as 1,000 ng/ml, would be needed to scavenge reactive oxygen radicals completely and have antiinflammatory effects (24, 25). The mean TRX level of the OSA patients in this study was 41 ng/ml. Therefore, the TRX level in OSA patients may be insufficient to act as an antioxidant protein. Recently, Svatikova *et al.* (37) found that healthy OSA patients without any other comorbidities do not manifest evidence of higher oxidative stress by measuring the levels of oxidized products such as thiobarbituric acid–reactive substances, oxidized low-density lipoprotein, and isoprostanes, contrary to previous reports (3, 5, 15, 32, 41). Oxidative stress in OSA patients may be demonstrated more clearly by measuring the level of an antioxidant protein such as TRX. The plasma TRX level was positively correlated with both RDI and the percentage of time with Sao_2 90%. The plasma TRX level was strongly related to OSA, independent of BMI, age, and current smoking habit. Plasma TRX may be a good marker of oxidative stress in OSA patients and may

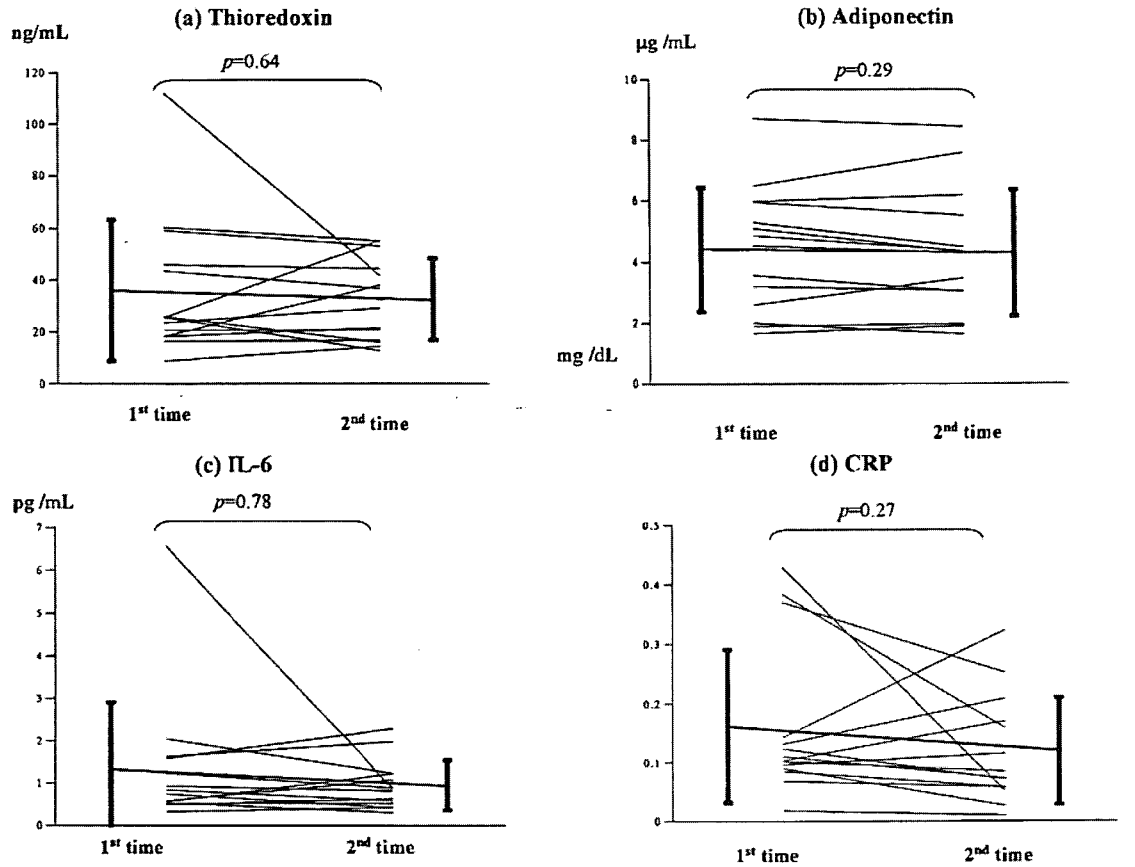

FIG. 7. Changes in the plasma thioredoxin, adiponectin, IL-6, and serum CRP levels between the 2 measurement days (mean interval, 39.4 days) during which nasal CPAP treatment was not provided in the OSA untreated group. The plasma thioredoxin, adiponectin, IL-6, and serum CRP levels did not significantly differ between the two measurement days. OSA, obstructive sleep apnea; IL-6, interleukin 6; CRP, C-reactive protein; CPAP, continuous positive airway pressure.

be a sensitive barometer of the effectiveness of nasal CPAP treatment. Because the number of subjects in our study was small, further studies are needed to investigate the precise role of TRX in OSA.

In this study, the plasma adiponectin level was significantly reduced in the OSA treatment group before nasal CPAP treatment, and it increased after nasal CPAP treatment for 1 month. The plasma adiponectin level was negatively correlated with the plasma TRX level. Adiponectin is an adipocyte-specific cytokine. In clinical studies, a low adiponectin level has been associated with insulin resistance (10), atherosclerosis (18), and cardiovascular diseases (28). Moreover, the increased oxidative stress in patients with obesity has a significant impact on the low adiponectin level (7). OSA is clearly associated with obesity and is also linked to the risk of insulin resistance (11) and cardiovascular diseases (34). However, the linkage between OSA and adiponectin has been equivocal (9, 40). This ambiguity may be due to the complexity of regulation of adiponectin. For example, obesity itself results in a low adiponectin level (2), as well as in our data: the plasma adiponectin level in this study was negatively correlated with BMI (p 0.02; r 0.32).

In addition to plasma TRX and adiponectin levels, we measured the levels of inflammatory markers that have been considered to be elevated in oxidative stress. It has been reported that the levels of inflammatory markers such as CRP and IL-6 were elevated in patients with OSA, and they were reduced by nasal CPAP therapy (33, 42). In our data, the CRP level was significantly elevated, although the IL-6 level was not significantly elevated in the untreated OSA patients. However, when CPAP was administered to OSA patients, the CRP and IL-6 levels significantly decreased. A recent study (8) showed that CRP in OSA patients may be associated with obesity rather than with OSA itself. In our data, the difference in CRP level between the OSA and non-OSA subjects disappeared after adjusting for BMI. The inflammatory pathway can be initiated by oxidative stress (14). Because many confounding factors participate in the inflammatory pathway, it is difficult to show a clear association between OSA and inflammation. However, considering that the plasma TRX level was positively correlated with the plasma IL-6 and serum CRP levels and that CPAP treatment improved the serum CRP and plasma IL-6 levels, oxidative stress may be one mechanism of inflammation in OSA patients. Oxidative stress markers such as TRX are directly as-

sociated with the pathogenesis of OSA and may be more sensitive markers of OSA than inflammatory markers.

This study has some limitations. The first limitation was that a significant difference in BMI was found between the non-OSA group and the OSA patient group. The serum CRP level is increased in patients with obesity, whereas the plasma adiponectin level is decreased (2, 10). In this study, the plasma TRX level was not correlated with BMI. In addition, BMI was not a significant variable in the multiple regression analysis with plasma TRX level as the dependent variable. Therefore, the difference in BMI between the non-OSA group and the OSA patient group would not have significant effects on the plasma TRX level.

Another limitation of this study is that polysomnography was not performed in the non-OSA volunteers. The volunteers were not heavy snorers. It was recently reported that the best agreement between AHI and 3%ODI values was found among individuals with AHI values 15, where the difference between the estimated AHI and 3%ODI values was only -0.4 among 49 subjects (26). Therefore, although sleep-disordered breathing in the non-OSA volunteers in this study was measured by oximetry and not polysomnography, this would not have a significant effect on the overall results.

The last limitation is that the effects of nasal CPAP were not examined in a randomized, placebo-controlled design because of the difficulty in implementing placebo nasal CPAP treatment under the official medical insurance system in Japan. However, in the OSA-untreated group, who did not receive nasal CPAP treatment, the levels of the mediators did not change significantly during the interval between the measurement points. Therefore, we could reveal the effects of nasal CPAP.

In conclusion, we demonstrated that the plasma TRX level was elevated in patients with OSA independent of BMI and comorbidities, but that it is reduced by nasal CPAP. TRX has the potential to be a good marker to evaluate oxidative stress in OSA patients and to monitor the effectiveness of CPAP therapy.

ACKNOWLEDGMENTS

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ABBREVIATIONS

AHI, apnea hypopnea index; BMI, body mass index; CPAP, continuous positive pressure; CRP, C-reactive protein; IL-6, interleukin-6; nCPAP, nasal CPAP; OSA and ObA, obstructive sleep apnea; 3%ODI, 3% oxygen desaturation index; RDI, respiratory disturbance index; Sao_2, arterial oxygen saturation; TRX, thioredoxin.

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Address reprint requests to:
Kazuo Chin
Department of Respiratory Medicine
Kyoto University Graduate School of Medicine
54 Shogoin Kawahara-cho, Sakyo-ku
606-8507 Kyoto, Japan

E-mail: chink@kuhp.kyoto-u.ac.jp

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QU1

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Clinical Characteristics of Obesity-hypoventilation Syndrome in Japan: a Multi-center Study

Tsuneto Akashiba[1], Toshiki Akahoshi[1], Seiji Kawahara[1], Akihito Uematsu[1], Kazuhito Katsura[1], Shigeru Sakurai[2], Akira Murata[3], Hiroki Sakakibara[4], Kazuo Chin[5], Wataru Hida[6] and Hiroshi Nakamura[7]

Abstract

Objective To clarify the prevalence and clinical characteristics of obesity-hypoventilation syndrome (OHS) in a large number of patients with moderate to severe obstructive sleep apnea syndrome (OSAS).

Methods Subjects comprised 611 patients with OSAS registered from 7 sleep centers and clinics and analyzed according to the definitions of the Respiratory Failure Research Group of the Japanese Ministry of Health and Welfare. Baseline characteristics, polysomnographic data during sleep, laboratory blood examinations, excessive daytime sleepiness, pulmonary functions, and arterial blood gases were compared between OHS and non-OHS patients. Determinants of daytime hypercapnia were also examined in OHS patients.

Results OHS was identified in 55 of the 611 patients with OSAS (9%). OHS patients were younger, heavier, and more somnolent than non-OHS patients and displayed more severe OSAS, liver dysfunctions, higher total cholesterol, and impaired pulmonary function. However, these differences were resolved except for pulmonary function after correction for obesity. Daytime hypercapnia was associated with impaired pulmonary function. Percent vital capacity (%VC) was most closely correlated with $PaCO_2$ in OHS.

Conclusion OHS patients display numerous abnormalities due to obesity compared with non-OHS patients. Impaired pulmonary function, particularly %VC, may play an important role in the development of daytime hypercapnia independent of obesity in OHS patients.

Key words: obesity-hypoventilation syndrome, obstructive sleep apnea syndrome, daytime hypercapnia, obesity, pulmonary functions

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Introduction

Obesity-hypoventilation syndrome (OHS) (1) was originally described in 1955 in patients with obesity, daytime hypercapnia and hypoxemia, polycythemia, hypersomnolence and right ventricular failure. This syndrome gained attention among general physicians as the"Pickwickian syndrome"described by Burwell et al (2). Since most patients with OHS display repeated upper airway obstruction during sleep, OHS has been considered as the most severe type of obstructive sleep apnea syndrome (OSAS), although a small number of patients with OHS do not experience sleep apnea (3). The Respiratory Failure Research Group set up by the Japanese Ministry of Health and Welfare (4) recently published a definition of OHS using the following criteria: 1) extreme obesity (body mass index (BMI)$\geq$30 kg/m^2); 2) excessive daytime sleepiness; 3) chronic daytime hypercapnia (arterial

[1] Respiratory Medicine, Nihon University School of Medicine, Tokyo, [2] Department of Internal Medicine, Iwate Medical University, School of Medicine, Morioka, [3] Fourth Department of Internal Medicine, Nippon Medical School, Tokyo, [4] Division of Respiratory, Medicine and Clinical Allergy, Fujita Health University School of Medicine, Toyoake, [5] Respiratory Medicine, Kyoto University School of Medicine, Kyoto, [6] Health Administration Center, Department of Informatics on Pathophysiology, Tohoku University School of Medicine, Sendai and [7] Nakamura Sleep Clinic, Urazoe

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Correspondence to Dr. Tsuneto Akashiba, Respiratory Medicine, Nihon University School of Medicine, 30-1 Oyaguchi Kamimachi, Itabashi-ku, Tokyo 173-8610

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carbon dioxide tension ($PaCO_2$)≥45 mmHg); and 4) severe OSAS (apnea-hypopnea index (AHI)≥30/h or severe oxygen desaturation). As patients with OHS reportedly display a worse prognosis than typical patients with OSAS (5) and use more health-care resources (6), understanding the clinical characteristics of OHS is important for general physicians. The present study therefore aimed to collect a large number of patients with OSAS in whom diagnosis was confirmed by polysomnography (PSG) from 7 sleep centers and clinics in Japan. The prevalence and clinical characteristics of OHS were then analyzed.

Patients and Methods

Patients who were diagnosed with OSAS by PSG and for whom nasal continuous positive airway pressure (CPAP) treatment was indicated in 7 sleep clinics and centers from 2000 to 2001 were registered in this study. Criteria for patient registration were: moderate to severe sleep apnea (AHI >20/h); and nasal CPAP treatment.

A full night of PSG with continuous recordings of electroencephalogram (EEG), electrooculogram (EOG), submental electromyogram (EMG), electrocardiogram (ECG), airflow at the nose and mouth (by thermister recording), movement of the rib cage and abdomen (inductance plethysmography), and oxyhemoglobin saturation (SaO_2) was performed in all patients. Analysis and interpretation of PSG data were performed using standard techniques (7). Apnea was defined as cessation of airflow at the nose and mouth lasting ≥10 s. Hypopnea was defined as decreased airflow, rib cage excursions, or abdominal excursions>50% associated with oxygen desaturation of ≥4% below the preceding baseline value (8). AHI was calculated as the number of apnea and hypopnea episodes per hour of sleep. Mean and minimum SaO_2 values were also calculated from PSG data. Baseline clinical characteristics and laboratory blood examination data were also collected.

Conventional spirometry was measured using a Chestak auto-spirometer (Chest Co., Tokyo, Japan). Percent predicted values were obtained from the literature. Arterial blood samples were drawn from a radial artery with the patient awake and supine. Arterial blood samples were analyzed using an ABL3000 auto-analyzer (Radiometer Co., Tokyo, Japan). Hypercapnia was defined as $PaCO_2$>45 mmHg.

Subjective sleepiness was assessed using the Epworth sleepiness scale (ESS) (9), a well-validated 8-item self-completed questionnaire. Patients were asked to score the likelihood of falling asleep in 8 different situations with different levels of stimulation.

Among the registered patients, those who underwent pulmonary function testing and arterial blood gas analysis were selected for this study. Subjects were divided into OHS and non-OHS patients according to the outlined criteria and baseline characteristics, PSG data, laboratory examination data, pulmonary functions and blood gas data were compared. To correct for the effects of obesity, differences in variables between OSAS patients with OHS and those with BMI>30 kg/m^2 were also compared.

All patients provided written informed consent to participate in this study.

Table 1. Baseline Characteristics in Subjects

Number	611
Sex (M:F)	568:43
Age (years)	48 ±11
BMI (kg/m^2)	29 ±5
AHI (episodes/h)	52 ±26
Arousal index (episodes/h)	48 ±25
Mean SaO_2 (%)	90 ±6
Minimum SaO_2 (%)	67 ±14
PaO_2 (mmHg)	79 ±17
$PaCO_2$ (mmHg)	41 ±6
pH	7.359 ±0.071
ESS	10 ±5

Abbreviations: BMI, body mass index; AHI, apnea-hypopnea index; ESS, Epworth sleepiness scale, ranging from 0 (least sleepy) to 24 (most sleepy).

Statistical analysis

Results are presented as mean ±standard deviation (SD). Group differences were assessed using unpaired t tests. Pearson linear correlations were also determined between certain variables. Correlations between $PaCO_2$ and anthropometric, respiratory and polysomnographic variables were determined by stepwise multiple regression analysis using Statview version 4.0 statistical software (Macintosh, Abacauus Concepts, Inc). Each variable was entered into multiple regression analysis if F value was>4. Values of $p<0.05$ were considered statistically significant.

Results

A total of 611 patients (568 men, 43 women) from 7 sleep centers and clinics underwent pulmonary function testing, arterial blood gas analysis, and PSG, and were included in this study. Baseline characteristics and PSG data are shown in Table 1. Mean age was 48±1 years and mean BMI was 29±5 kg/m^2. Although PSG data revealed that subjects had severe OSAS (mean AHI, 52±26/h), daytime blood gas analyses were within normal limits. OHS was present in 55 of the 611 patients with OSAS (9%). OHS patients were significantly younger and heavier than non-OHS patients and displayed more severe OSAS and more somnolence than non-OHS patients (Table 2). On laboratory blood examinations, hematocrit, GOT, GPT, Al-P, and total cholesterol were all significantly higher in OHS patients than in non-OHS patients. On pulmonary function testing, percent

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Table 2. Baseline Characteristics, Polysomnographic Data and Laboratory Blood Examinations

	OHS	non-OHS	p
Number	55	556	
Sex (M:F)	50:5	518:38	
Age (years)	42 ±10	51 ±13	0.001
BMI (kg/m^2)	37 ±6	27 ±4	0.001
AHI (episodes/h)	72 ±22	50 ±26	0.0001
Mean SaO_2 (%)	86 ±7	90 ±5	0.0001
Minimum SaO_2 (%)	59 ±10	68 ±15	0.0001
ESS	12 ±4	10 ±5	0.013
Hct (%)	46 ±4	45 ±3	0.028
RBC (/μl)	386 ±259	351 ±352	NS
WBC (/μl))	4233 ±3772	3669 ±3677	NS
GOT (IU/l)	38 ±18	29 ±20	0.023
GPT (IU/l)	64 ±41	42 ±36	0.009
LDH (IU/l)	194 ±76	206 ±81	NS
AL-P (IU/l)	252 ±73	196 ±70	0.009
GGTP (IU/l)	65 ±75	59 ±67	NS
TC (mg/dl)	224 ±45	209 ±38	0.034
TG (mg/dl)	218 ±138	204 ±160	NS
FBS (mg/dl)	109 ±43	111 ±33	NS

Abbreviations: OHS, obesity-hypoventilation syndrome; BMI, body mass index; AHI, apnea-hypopnea index; ESS, Epworth sleepiness scale; Hct, hematocrit; RBC, red blood cell; WBC, white blood cell; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; LDH, lactate dehydrogenase; AL-P, alkaline phosphatase; GGTP, γ-glutamyl transpeptidase; TC, total cholesterol; TG, triglyceride; FBS, fasting blood sugar

vital capacity (%VC), forced expiratory volume in one second/forced vital capacity ($FEV_{1.0}$%) and PaO_2 were all significantly lower and $PaCO_2$ was significantly higher in OHS patients than in non-OHS patients (Table 3).

To correct for any effects of obesity, OSAS patients with OHS were compared to markedly obese OSAS patients (BMI $\geq$30 kg/m^2) without hypercapnia (n=117). As shown in Table 4, no significant differences in characteristics were observed between groups except for pulmonary function and blood gases.

As daytime hypercapnia represents a key feature of OHS, correlations between $PaCO_2$ and other variables were examined to determine factors underlying development of hypercapnia in OHS patients. ESS, %VC, $FEV_{1.0}$% and PaO_2 were all significantly correlated with $PaCO_2$ (Table 5). In particular, %VC exhibited the closest correlation with $PaCO_2$ (r=-0.455, p<0.0009). Although multiple stepwise regression analysis in OHS patients showed mean SaO_2 and %VC as independent variables for predicting daytime $PaCO_2$, the correlation was relatively weak (R^2=0.224, p=0.0052). Relationships between $PaCO_2$ and other variables were also investigated in daytime hypercapnic patients, who comprised 126 of the 611 cases. $PaCO_2$ was significantly correlated with ESS, %VC, $FEV_{1.0}$%, PaO_2, and pH. Stepwise multiple regression analysis was performed to identify factors contributing to increased $PaCO_2$ in hypercapnic patients. The results showed that $PaCO_2$ was significantly influenced by ESS, %VC, and $FEV_{1.0}$%. Incorporation of these 3 variables into the model accounted for 47% of the total variance of $PaCO_2$ in hypercapnic patients (R^2=0.477, p<0.0001).

Table 3. Pulmonary Functions and Blood Gas Analysis

	OHS	non-OHS	p
Number	55	556	
%VC (%)	102 ±17	108 ±17	0.024
$FEV_{1.0}$% (%)	76 ±9	80 ±8	0.037
PaO_2 (mmHg)	74 ±8	80 ±17	0.005
$PaCO_2$ (mmHg)	48 ±3	41 ±6	0.0001
pH	7.38 ±0.01	7.35 ±0.07	NS

Abbreviations: VC, vital capacity; $FEV_{1.0}$%, forced expiratory volume in one second/forced vital capacity

Table 4. Comparisons between OHS and Markedly Obese OSAS

	OHS	OSAS	p
Number	55	117	
Age (years)	42 ±10	46 ±12	NS
BMI (kg/m^2)	36 ±6	34 ±3	NS
AHI (episodes/h)	72 ±22	70 ±25	NS
Mean SaO_2 (%)	86 ±7	86 ±7	NS
Minimum SaO_2 (%)	59 ±10	61 ±15	NS
ESS	12 ±4	12 ±5	NS
Hct (%)	46 ±4	47 ±2	NS
GOT (IU/l)	38 ±18	40 ±28	NS
GPT (IU/l)	64 ±41	67 ±53	NS
Al-P (IU/l)	252 ±73	204 ±64	NS
TC (mg/dl)	224 ±45	211 ±46	NS
%VC (%)	102 ±17	106 ±14	0.046
$FEV_{1.0}$% (%)	76 ±9	79 ±8	0.049
PaO_2 (mmHg)	74 ±8	76 ±15	NS
$PaCO_2$ (mmHg)	48 ±3	41 ±2	0.001
pH	7.38 ±0.01	7.40 ±0.02	0.001

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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

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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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First Experience of Using New Adaptive Servo-Ventilation Device for Cheyne-Stokes Respiration With Central Sleep Apnea Among Japanese Patients With Congestive Heart Failure

— Report of 4 Clinical Cases —

Takatoshi Kasai; Koji Narui; Tomotaka Dohi*; Hisashi Takaya; Naotake Yanagisawa**; George Dungan†; Sugao Ishiwata*; Minoru Ohno*; Tetsu Ymaguchi*; Shin-ichi Momomura††

Background Cheyne-Stokes respiration with central sleep apnea (CSR-CSA) in congestive heart failure (CHF) is generally considered a poor prognostic indicator, but treatment of CSR-CSA using an adaptive servo-ventilation (ASV) device has been developed. This is the first evaluation of its use in the management of CSR-CSA in Japanese CHF patients.

Methods and Results Four CHF patients with CSR-CSA that was unresponsive to conventional positive airway pressure (CPAP) underwent 3 nights of polysomnography: baseline, CPAP or bi-level PAP, and on the ASV. The apnea–hypopnea index (AHI) and central-AHI (CAHI) were markedly improved on ASV (AHI 62.7±10.1 to 5.9±2.2/h, p=0.0006, CAHI 54.5±6.7 to 5.6±2.3/h, p=0.007). In addition, the sleep quality improved significantly on ASV, including arousal index (62.0±10.5 to 18.7±6.2/h, p=0.012), percentage of slow-wave sleep (2.6±2.6 to 19.4±4.8 %, p=0.042).

Conclusions ASV markedly improved CSR-CSA in patients with CHF. It is a promising treatment for Japanese patients with CHF. (*Circ J* 2006; **70:** 1148–1154)

Key Words: Adaptive-servo ventilation; Bi-level positive airway pressure; Central sleep apnea; Cheyne-Stokes respiration; Congestive heart failure; Continuous positive airway pressure

Several studies have shown that patients with congestive heart failure (CHF) often suffer from the complication of abnormal periodic breathing during sleep, including Cheyne-Stokes respiration with central sleep apnea (CSR-CSA). Patients with CSR-CSA have a poorer prognosis than CHF patients without CSR-CSA[1-3] To date, CSR-CSA has been treated with positive airway pressure (PAP), including continuous PAP (CPAP) and bi-level PAP[4,5] but although these devices reduce the incidence of apnea, and improve the sleep quality and cardiac function in CHF patients with CSR-CSA, there are some patients who show either no acute improvement or incomplete management of the abnormal breathing pattern[6] To be effective, CPAP requires spontaneous breathing, and it may sometimes not be effective for frank central apnea. In addition, compliance with CPAP is sometimes poor because patients feel uncomfortable when they exhale against the high positive pressures required for appropriate treatment[7] This may have contributed to the results of recent clinical trial, the Canadian Continuous Positive Airway Pressure Trial for Congestive Heart Failure patients with Central Sleep Apnea (CANPAP), which failed to show long-term mortality benefits in CHF patients with CSR-CSA using CPAP[8] Therefore, other alternatives need to be consider when treating CHF patients with CSR-CSA. We previously reported on the efficacy of another PAP device, bi-level PAP, for improving the abnormal breathing pattern or underlying cardiac dysfunction in these patients[9,10] However, in the clinical setting, patients often continue to present with the CSA-CSR breathing pattern. More recently, the adaptive-servo ventilator (ASV), a novel PAP device, has been established as an effective therapeutic alternative to other PAP technologies. The ASV not only manages the sleep disordered breathing, but also may improve cardiac function[11-13] The ASV device was only recently become available for use in Japan, and experience in the Japanese patient population has been unreported. Therefore, we now report the first clinical experience using the ASV device among Japanese CHF patients with CSR-CSA. These subjects continued to have CSR-CSA after using other traditional PAP therapies, including CPAP and bi-level PAP.

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*Sleep Center, *Cardiovascular Center, Toranomon Hospital, **Department of Cardiology, Juntendo University, Tokyo, Japan, †Sleep and Circadian Group, Woolcock Institute of Medical Research, Sydney, NSW, Australia and ††Cardiovascular Division, Jichi Medical School Omiya Medical Center, Saitama, Japan*

Mailing address: Takatoshi Kasai, MD, Sleep Center, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan. E-mail: kasai-t@mx6.nisiq.net

Methods

Subjects

We enrolled patients who have been diagnosed as having

Table 1 Clinical Characteristics of the 4 Patients With CSR-CSA

Case no.	Age (years)	Gender	BMI (kg/m^2)	Etiology of CHF	LVEF (%)	BNP (pg/ml)	NE (pg/ml)	NYHA class	PaO_2 (Torr)	$PaCO_2$ (Torr)	ESS	Medication
1	65	M	29.0	Non IHD	43	189	781	III	76	39	17	ARB, BB, Sp, Diu, Dig
2	77	M	26.0	Non IHD	45	206	448	II	92	36	15	ARB, BB, Diu, Dig, ACEI, BB
3	62	M	29.8	IHD	29	314	678	II	80	36	12	Sp, Diu, Am
4	85	M	19.9	IHD	35	564	570	III	86	39	15	ACEI, BB, Sp, Diu, Am
Mean	72.3		26.2		37.9	318.3	619.3		83.5	37.5	14.8	
SEM	5.3		2.2		3.6	86.5	71.5		3.5	0.9	1.0	

CSR-CSA, cheyne-stokes respiration with central sleep apnea; BMI, body mass index; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; NE, norepinephrine; NYHA, New York Heart Association functional; ESS, epworth sleepiness scale; IHD, ischemic heart disease; ARB, angiotensin II receptor blockers; BB, β-blockers; Sp, spironoractone; Diu, diuretics; Dig, digoxin; ACEI, angiotensin converting enzyme inhibitors; Am, amiodarone; SEM, standard error of the mean.

Table 2 Diagnostic Polysomnography Findings

Case no.	AHI (no./h)			% of TST SO_2 <90%	Lowest SO_2 (%)	ArI (no./h)	Sleep stage (% of TST)		
	Total	Central	Obstructive				1&2	SWS	REM
1	87.3	67.4	19.9	34.7	64	87.8	100	0	0
2	62.6	51.5	11.1	22.8	74	63.5	93.6	0	6.4
3	38.0	37.1	0.9	1.5	77	36.4	70.9	10.5	18.6
4	62.8	62.0	0.8	8.8	81	60.3	93.2	0	6.7
Mean	62.7	54.5	8.2	17.0	74.0	62.0	89.4	2.6	7.9
SEM	10.1	6.7	4.6	7.4	3.6	10.5	6.4	2.6	3.9

AHI, apnea-hypopnea index; TST, total sleep time; SO_2, arterial oxyhemoglobin saturation; ArI, arousal index; SWS, slow wave sleep; REM, rapid eye movement; SEM, standard error of the mean.

CSR-CSA and chronic CHF and were being followed in Toranomon Hospital (Tokyo, Japan). These subjects included patients for whom PAP therapy had already been attempted, but which had failed to resolve the CSR-CSA or the patient had poor compliance with the traditional device (defined as ≤70% of nights used, ≤4 h/night over 1 month of usage). All 4 successful candidates gave informed consent and the trial was performed according to the ethics policies of the institution.

Case 1 had attempted bi-level PAP therapy (BiPAP Synchrony, Respironics, PA, USA) using S/T mode, with the inspiratory PAP (IPAP) set to 12 cmH_2O, expiratory PAP (EPAP) set to 6 cmH_2O, and the back-up respiratory rate set to 16/min. The PAP device did not completely eliminate the respiratory events because this patient required very high pressure support (PS) to sustain ventilation during back-up breathing spanning central apneas. Such high pressure was deemed too uncomfortable, and woke the patient. Thus, the CSR-CSA could not be completely eliminated.

Case 2 had also attempted bi-level PAP therapy (BiPAP Synchrony, Respironics) using S/T mode, IPAP 15 cmH_2O, EPAP 9 cmH_2O, and back-up respiratory rate 15/min. As with the previous subject, the device failed to provide sufficient relief for the CSA-CSR.

Case 3 had been started on CPAP therapy (REMstar Auto, Respironics, PA, USA) at 6 cmH_2O, but it failed to manage the CSR-CSA. This subject was poorly compliant and complained about the uncomfortable sensation of excessive exhalatory pressure.

Case 4 had also been started on CPAP therapy (REMstar Auto, Respironics, 7 cmH_2O) because of both the cost and the difficulty in synchronizing to bi-level PAP therapy. His CSR-CSA was modestly reduced but his compliance was poor, possibly because of the sensation of high exhalatory pressure.

Sleep Study

All participants underwent a nocturnal in-lab attended polysomnography (PSG) using a digital polygraph (Somno Star Alpha Sleep System, Sensor Medics, CA, USA). The standard PSG recorded the central electroencephalograms, bilateral electro-oculograms, submental electromyogram, bilateral anterior tibialis electromyogram, electrocardiogram, chest and abdominal movement recording using respiratory effort bands, body position monitoring, oronasal airflow monitoring using a pressure-sensor, and arterial oxyhemoglobin saturation monitoring using a pulse-oximeter.

The sleep study was scored using standard methodologies. Sleep staging and arousals were scored using 30-s epochs according to Rechtschaffen and Kales[14] and the American Academy of Sleep Medicine criteria[15] Classification of apnea and hypopnea used standard methodologies, as previously described[10] The apnea-hypopnea index (AHI) was defined as the total number of apnea and hypopnea events divided by the total sleep time (TST), and was expressed as the number of events per hour. The arousal index (ArI) was defined as the total number of arousals divided by the TST, and was expressed as the number of events per hour. Sleep stages 1 and 2, slow-wave sleep (SWS) and rapid eye movement (REM) sleep were expressed as a percentage of TST. Each subject underwent 3 PSG recordings: initial baseline diagnostic recording, second recording on the conventional PAP device (either CPAP or bi-level PAP), and then while using the new ASV device.

ASV

In the present study, all subjects used the same type of ASV device (Heart PAP, Respironics, PA, USA). This device is a noninvasive ventilator intended for use in patients with sleep disordered breathing, including CSA-CSR. Therapy is intended to be used by the patient via either a

Table 3 Effect of Treatment on Polysomnography Findings

	At diagnosis	On conventional PAP*	p value**	On ASV	p value**	p value***
AHI (no./h)						
Total	62.7±10.1	17.8±3.3	0.021	5.9±2.2	0.0006	0.047
Central	54.5±6.7	13.5±1.5	0.02	5.6±2.3	0.007	0.053
Obstructive	8.2±4.6	4.3±1.8	0.86	0.3±0.1	0.029	0.084
Arousal index (no./h)	62.0±10.5	22.2±5.3	0.033	18.7±6.2	0.012	0.88
Sleep stage (% of TST)						
SWS	2.6±2.6	11.9±4.1	0.24	19.1±4.8	0.042	0.33
REM	7.9±3.9	14.7±1.4	0.60	18.4±4.4	0.21	0.69

*Conventional positive airway pressure (PAP), continuous PAP or bi-level PAP.
** vs diagnosis, ***conventional PAP vs ASV.
PAP, positive airway pressure; ASV, adaptive servo-ventilation. Other abbreviations see in Table 2.

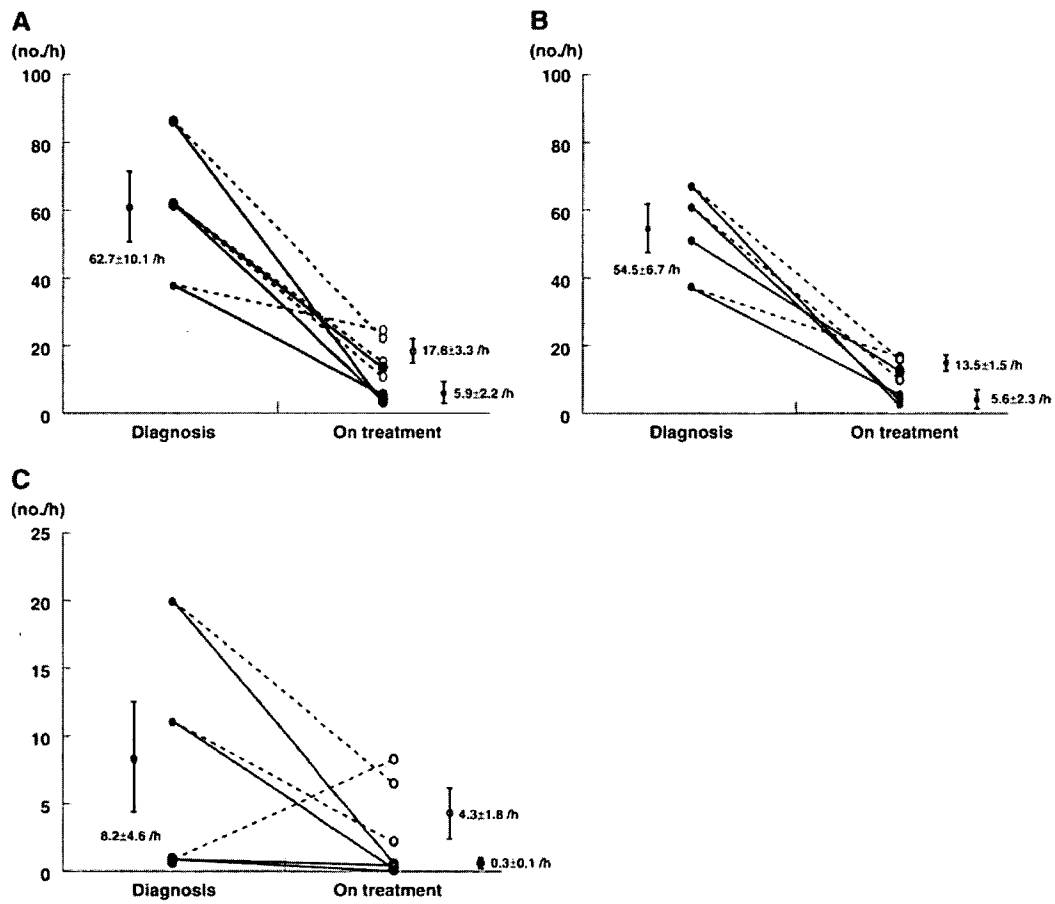

Fig 1. Effect of treatment on the apnea–hypopnea index (AHI). (A) Total AHI. Significant reductions in the total AHI with both conventional positive airway pressure (PAP), including continuous PAP and bi-level PAP (p=0.02), and adaptive servo-ventilation (ASV) (p=0.0006) were observed. There were significant differences between the AHI on conventional PAP and on ASV (17.8±3.3 vs 5.9±2.2/h, p=0.047). (B) Central AHI (CAHI): significant reductions of the CAHI with both conventional PAP (p=0.02) and ASV (p=0.007) were observed. There was a tendency for the CAHI to reduce more on ASV than on conventional PAP (13.5±1.5 vs 5.6±2.3/h, p=0.053). (C) Obstructive AHI (OAHI): significant reductions in the OAHI were observed only on ASV (p=0.029). Data are presented individually: (●) diagnosis and on ASV, (○) treatment with conventional PAP. Mean and standard error of the mean are also presented.

nasal or full-face mask in the home or clinical setting. Although the ASV has several modes of therapy available, only the auto mode was used in this study.

Under normal operation of the ASV, the management of any obstructive component of sleep disordered breathing is performed using a previously titrated CPAP or bi-level pressure setting. The clinician sets the EPAP and minimum IPAP ($IPAP_{min}$) levels to maintain airway patency by management of any obstructive sleep disordered breathing. This is typically performed during a traditional in-laboratory monitored titration PSG study. If clinically appropriate, EPAP and $IPAP_{min}$ can be set to the same value, offering the patient a baseline therapy of CPAP. A maximum IPAP ($IPAP_{max}$) is set according to clinical presentation, and is typically set 15 cmH_2O greater than $IPAP_{min}$.

When a CSR-CSA event begins, the PS, the difference

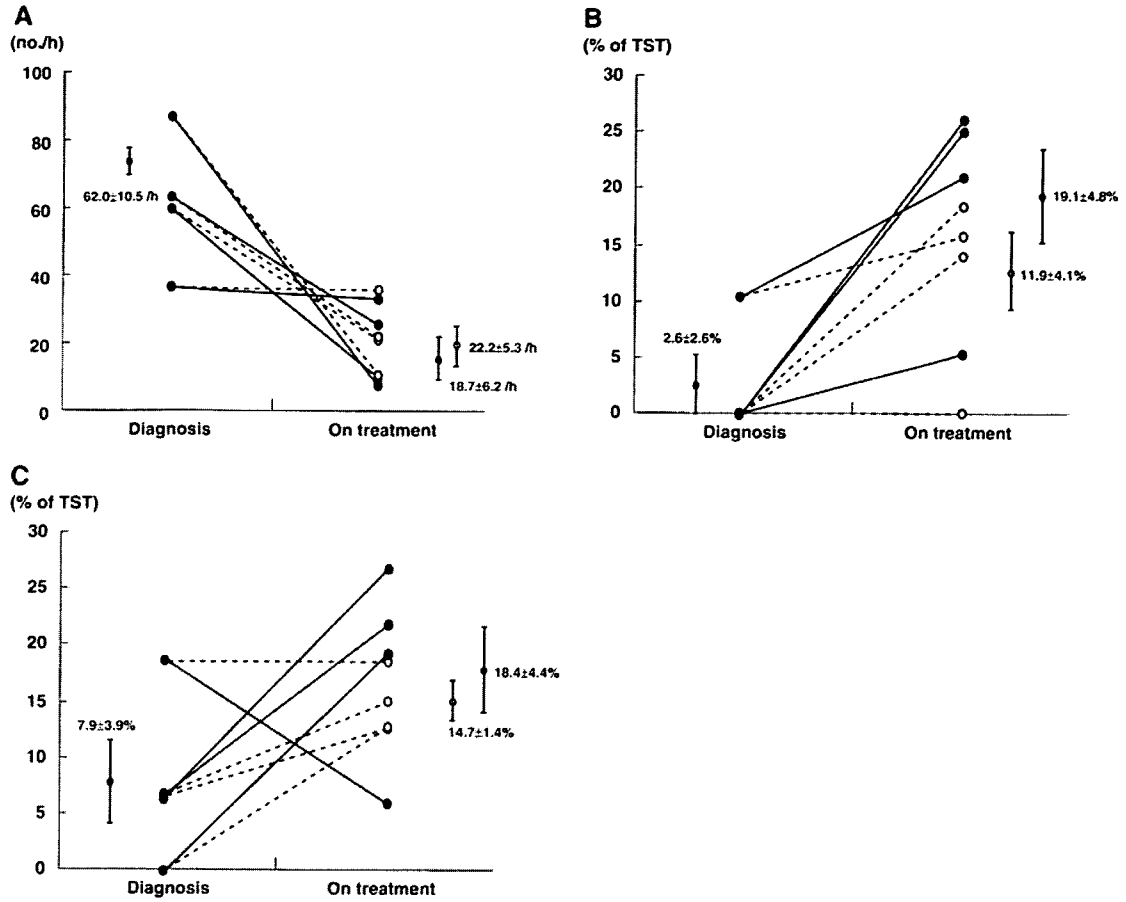

Fig 2. Effect of treatment on sleep quality. (A) Arousal index (ArI): significant reductions in the ArI with both conventional positive airway pressure (PAP), including continuous PAP and bi-level PAP (p=0.033), and adaptive servo-ventilation (ASV) (p=0.012) were observed. There was a greater reduction in the Ar I on ASV (22.2±5.3 vs 18.7±6.2/h, p=0.88), although it was not statistically significant. (B) Slow wave sleep (SWS): significant increases in the percentage of SWS was observed only with the ASV (p=0.042). (C) Rapid eye movement (REM) sleep: increases in the percentage of REM sleep with both conventional PAP (p=0.60) and ASV (p=0.21) were observed, although it was not statistically significant. Data are presented individually: (●) diagnosis and on ASV, (○) treatment with conventional PAP. Mean and standard error of the mean are also presented. TST, total sleep time.

between the IPAP and the EPAP pressures, increases and the gradually increasing PS provides augmented ventilation in an attempt to achieve a target peak flow. As the patient's spontaneous respiratory effort improves, the PS provided by the ASV gradually decreases, which helps prevent extension of hyperventilation during the typical hyperpnea following the CSR 'waning' period. The serial application of this additional ventilatory support is intended to normalize patient ventilation and eliminate the persistent CSR-CSA phenomenon. Should frank apnea events occur, the ASV will attempt to ventilate the patient according to an internal algorithm, providing ventilatory support using back-up breaths delivered during the apnea event

In the present study, the setting of the ASV device was determined before the sleep study as follows.

(a) The initial EPAP level was determined by the previously set pressure on other devices (the CPAP level or the EPAP level for bi-level PAP).

(b) If the patient has been on bi-level PAP initially, the $IPAP_{min}$ was set to the previous IPAP level to eliminate any obstructive flow limitation.

(c) For this study, the $IPAP_{max}$ was set to between 10 and 20 cmH_2O above the baseline maintenance pressures.

Table 4 Individual Settings for the Adaptive Servo-Ventilation Device

Case no.	*$IPAP_{max}$*	*$IPAP_{min}$*	*EPAP*
1	*16*	*11*	*6*
2	*20*	*14*	*9*
3	*16*	*6*	*6*
4	*17*	*7*	*7*

$IPAP_{max}$, maximum inspiratory positive airway pressure; $IPAP_{min}$, minimum inspiratory positive airway pressure; EPAP, expiratory positive airway pressure.

A maximum pressure of greater than 20 cmH_2O was avoided, in order to lessen the chance of direct pressure-related compromise in cardiac output, as well as the chance that excessive PS would awaken the patients. The overriding objective during the study was to minimize the intrathoracic pressure to which the patient was exposed during the course of the therapy.

Measurements

In the current study changes between the diagnostic study and the subsequent studies under therapy were measured. Parameters of interest included total AHI, central AHI

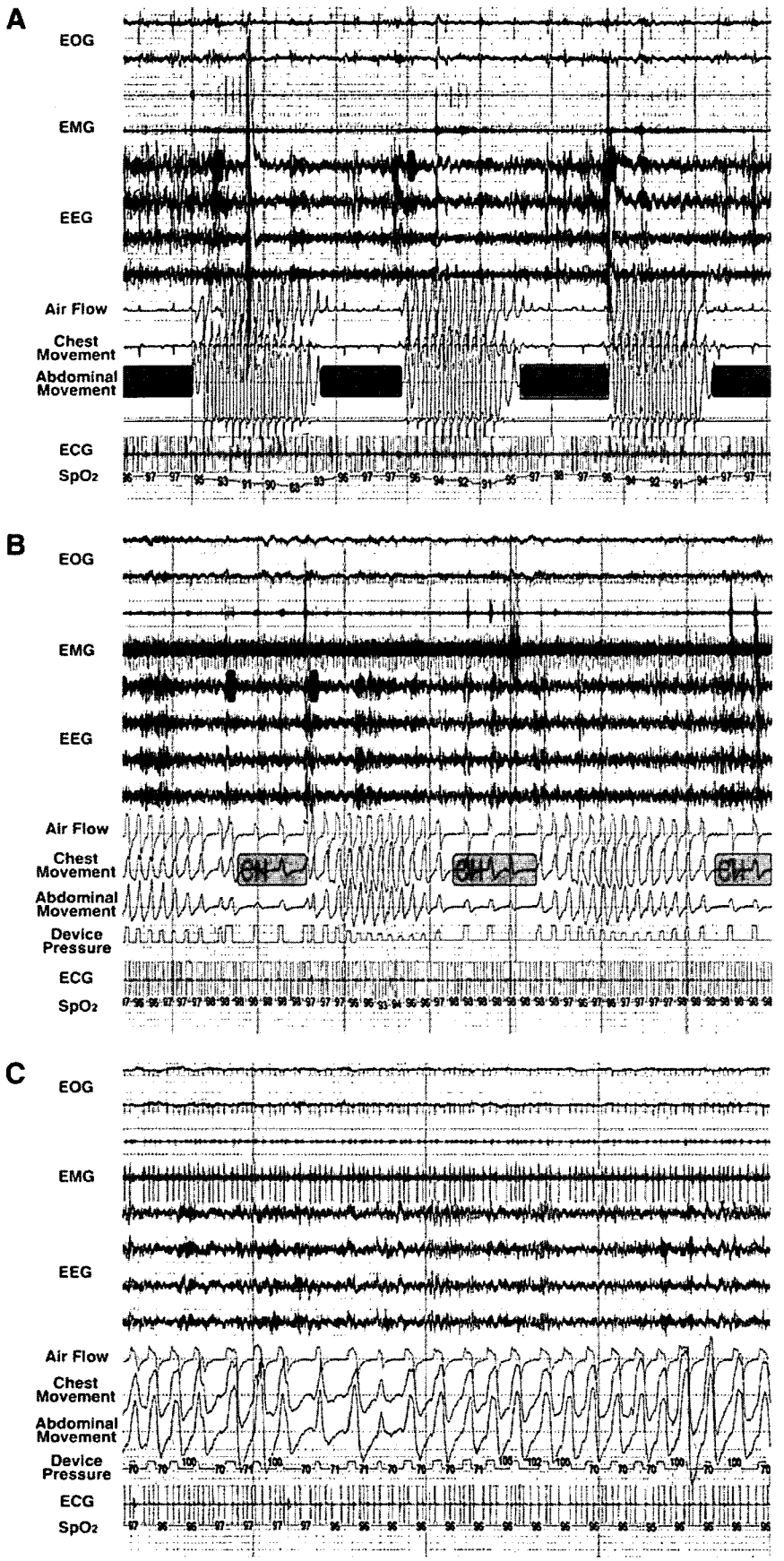

Fig 3. Representative raw wave form on polysomnography (PSG) from 1 patient. (A) Typical Cheyne-Stokes respiration with central sleep apnea (CSR-CSA) on the diagnostic PSG; note 4 central apneas and subsequent hyperventilation. (B) Improvement of CSR-CSA with adaptive servo-ventilation (ASV) on PSG; note the back-up ventilation during a central apnea with maximum inspiratory positive airway pressure and the reduction toward the minimum inspiratory positive airway pressure ($IPAP_{min}$) during the hyperventilation phase. (C) Spontaneous breathing with the ASV on PSG; note the adaptation of the ASV with $IPAP_{min}$ on spontaneous inspiration and expiratory PAP on spontaneous expiration. EOG, electro-oculogram; EMG, submental electromyogram; EEG, electroencephalogram; ECG, electrocardiogram; SpO_2, oxyhemoglobin saturation.

(CAHI), obstructive AHI (OAHI), ArI, percentage of SWS and REM sleep. Differences between various therapy nights were also evaluated to assess differences involving the use of the ASV in the management of CSR-CSA.

Statistical Analysis

All values are mean ± standard error of the mean (SEM). The comparisons of each PSG parameter between the diagnostic sleep study and the subsequent study with either the conventional PAP devices (CPAP or bi-level PAP) or the ASV, and between the second study and third study were performed using the exact nonparametric permutation test, in which the permutation sample size was 10,000. In this analysis, data were rank transformed because of the small number of subjects assessed. Additionally, the comparison of each PSG parameter between the second study on conventional PAP and the third study on ASV was performed with the exact nonparametric permutation test, as well. P values of less than 0.05 were considered to indicate a statistically significant difference.

Results

Four patients agreed to participate in the trial of the ASV. There were no adverse events during overnight use of the device, nor were there complaints from the patients about 1-night use of the ASV. The characteristics and drug use of all 4 patients are shown in Table 1. Patients were older-aged males who had symptomatic chronic CHF with moderately or severely impaired left ventricular ejection fraction. Most of them were obese except for Case 4 whose body mass index was only 19 kg/m^2. They had been treated with conventional medication for chronic CHF, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and/or β-blockers.

The diagnostic PSG findings of each patient are shown in Table 2. Patients revealed moderate to severe sleep apnea that predominantly consisted of CSR-CSA. All had severely disturbed sleep. All patients underwent their second PSG on their previous CPAP or bi-level PAP pressure settings.

The changes in each PSG parameter between the diagnostic study and the second study on conventional PAP device or the third on ASV are summarized in Table 3 and changes in the parameters of each patient are shown in Figs 1 and 2. The setting of the ASV during the third sleep study in each patient is shown in Table 4. The ASV markedly improved the total AHI (62.7±10.1/h to 5.9±2.2/h, p=0.0006), CAHI (54.5±6.7/h to 5.6±2.3/h, p=0.007) and OAHI (8.2±4.6/h to 0.3±0.1/h, p=0.029). These levels of AHI are consistent with normal and furthermore, the improvement in AHI was significantly greater on the ASV than on conventional PAP (17.8±3.3/h on conventional PAP vs 5.9±2.2/h, p=0.047). Moreover, the ASV significantly improved sleep quality, with a reduction in the ArI (62.0±10.5/h to 18.7±6.2/h, p=0.012) and an increase in the proportion of SWS (2.6±2.6% to 19.4±4.8%, p=0.042). The REM sleep increased, although it is not statistically significant (7.9±3.9% to 18.4±4.4%, p=0.21). Representative wave forms in the diagnostic and third PSG are shown in Fig 3. There was a tendency to reduce the CAHI more on the ASV than on conventional PAP (13.5±1.5/h on conventional PAP vs 5.6±2.3/h on ASV, p=0.053). The improvement in the OAHI and SWS was observed only on ASV. Although the improvements in ArI and REM sleep with the ASV were greater than those on conventional PAP therapy, the differences between the therapies were not significant.

The acute response to the ASV by all patients was better. In fact, although there are more than 3 awakenings in each case during the second PSG on conventional PAP, but none during the third PSG on ASV, except for 1 awakening in case 4, under the condition of no differences in TST between the 2 occasions. In addition, there were no complaints about uncomfortable sensations from either case 3 or 4, even though the same level of exhilatory pressure was used for ASV and CPAP. Cases 1 and 2 continued to use the ASV device with good compliance, but cases 3 and 4 discontinued their use, not because of poor compliance but for cost reasons.

Discussion

The present study showed the CSR-CSA in CHF patients significantly improved when using the new ASV device. The ASV has 2 novel therapeutic algorithms. The primary algorithm is a pressure control system that normalizes patient ventilation levels by adjusting the inspiratory pressure and the secondary algorithm is an automatic timed back-up system that allows the patient to take natural pauses in inspiration while still providing PS assistance during true apneas. The pressure control system closely monitors the peak inspiratory flow of the patient and compares it to an internal target calculated as the patient's average normal breathing pattern (peak flow). PS is dynamically adjusted breath to breath as necessary to ensure that the patients' actual inspiratory flow matches the target. The automatic timed back-up system tracks the patient's spontaneous breath rate and time of inspiration. Based on these data, a back-up breath is automatically delivered to the patient during an apnea event.

The residual CSR-CSA of the 4 patients was not resolved completely with conventional PAP therapy (bi-level PAP or CPAP), which is an important finding because in Japan many heart failure patients with sleep disordered breathing do not use either CPAP or bi-level PAP therapy. In those who do, the CSR-CSA is not completely managed either because of the intrinsic limitations of the therapy or patient compliance issues. The ASV may provide improved management of these cases now that it has been approved for clinical use in Japan.

The recent report of the Canadian trial of Continuous Positive Airway Pressure for management of CSR-CSA in a heart failure population (CANPAP) failed to show long-term mortality, hospitalization, and transplant-free survival benefit with CPAP. Thus, conventional CPAP should be used cautiously to treat current CHF patients with CSR-CSA[8] and other alternative treatments may need to be considered to improve the poor outcome among patients with CHF.[1-3]

Many questions remain unanswered in the CANPAP trial; however the method of applying pressure to the patient (often without titration) certainly raises the question of untoward consequences of hemodynamic compromise secondary to higher intrathoracic pressures in these patients. In our study, the ASV was set to provide the absolute minimum pressure necessary to support the airway to prevent obstructive sleep disordered breathing. Higher pressures were only used during episodes of CSR-CSA hypopnea or apnea, with a rapid return to baseline pressure.

We previously reported the efficacy of bi-level PAP for

CSR-CSA in CHF patients[10] but the ASV was not yet available at the time of that study. The current study included 2 subjects for whom the use of conventional bi-level therapy was impractical and who were better managed using the ASV. In general, the combination of OSA and CSR-CSA often occurs in CHF patients and the ability of the ASV to manage both obstructive and CSR-CSA means that more patients can be managed by this therapy. Javaheri reported that 49% of CHF patients had significant sleep disordered breathing, 37% of them having CSR-CSA combined with OSA, and 12% of them having OSA as well as CSR-CSA.[16] CPAP has been established as the therapy for OSA, even in the CHF patients,[17] but is sometimes ineffective for ceasing a central apnea event.[18] Bi-level PAP is effective for both OSA and CSR-CSA, but in practice, such patients tend to require the IPAP level be set to lower values, because of the perceived difficulty with higher PS, and such reduction in IPAP often leads to insufficient management of the CSR-CSA. The ASV is able to resolve this problem of bi-level PAP, because the IPAP level is automatically and appropriately adapted.

There have been similar improvements reported in sleep quality, expressed by ArI, percentages of SWS and REM sleep.[11] The improvement in sleep quality may affect the perception of sleepiness and this, coupled with the device's algorithmic tendency to minimize applied pressures, may further improve the long-term compliance with therapy in such patients.

The present study showed only an acute improvement in CSR-CSA and there were no data about chronic use of this device. Further, only sleep specific outputs were evaluated and improvement in cardiac functions and quality of life have not been demonstrated. Several clinical studies in Western countries have shown the efficacy of chronic use of similar ASV devices on cardiac function and quality of life.[12,13] Therefore, further investigations of chronic use and assessment of cardiac function are also needed in Japanese CHF patients.

Conclusion

The CSR-CSA among 4 Japanese patients with CHF, which was uncontrolled using conventional PAP therapies, was adequately and immediately controlled using the ASV device. These early and encouraging findings suggest that the long-term application of this novel therapy in the Japanese CHF population must be evaluated in subsequent prospective studies.

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ORIGINAL ARTICLE

Demographic characteristics of 3,659 Japanese patients with obstructive sleep apnea–hypopnea syndrome diagnosed by full polysomnography: associations with apnea–hypopnea index

Fumi Ohdaira · Kazutoshi Nakamura · Hideaki Nakayama · Makoto Satoh · Tetsuro Ohdaira · Masami Nakamata · Masaki Kohno · Akira Iwashima · Akira Onda · Yoshiaki Kobayashi · Katsuya Fujimori · Toshio Kiguchi · Shuji Izumi · Tadaharu Kobayashi · Hideo Shinoda · Sugata Takahashi · Fumitake Gejyo · Masaharu Yamamoto

Abstract Information on obstructive sleep apnea–hypopnea syndrome (OSAHS) in Japan has been limited. The purposes of this clinical study were to evaluate the demographic characteristics of Japanese OSAHS patients and to assess how demographic factors are associated with OSAHS severity. We analyzed 3,659 OSAHS patients who underwent polysomnographic evaluation between January 2000 and December 2004 at 11 hospitals in Niigata

F. Ohdaira · K. Nakamura (✉) · M. Yamamoto
Department of Community Preventive Medicine, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Niigata 951-8510, Japan
e-mail: kazun@med.niigata-u.ac.jp

H. Nakayama · F. Gejyo
Division of Respiratory Medicine, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Niigata 951-8510, Japan

M. Satoh
Department of Sleep Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

M. Satoh
Division of Medicine, Joetsu General Hospital, Niigata, Japan

T. Ohdaira
Division of Respiratory Medicine, Nishi-Niigata Chuo National Hospital, Niigata, Japan

M. Nakamata
Division of Respiratory Medicine, Niigata Rinko Hospital, Niigata, Japan

M. Kohno
Nippon Dental University Niigata Hospital, Niigata, Japan

A. Iwashima
Division of Respiratory Medicine, Center of Respiratory Disease, Nagaoka Chuou General Hospital, Niigata, Japan

A. Onda
Department of Psychiatry, Koseiren-Kariwagun General Hospital, Niigata, Japan

Y. Kobayashi
Sado General Hospital, Niigata, Japan

K. Fujimori
Department of Internal Medicine, Niigata Prefectural Kamo Hospital, Niigata, Japan

T. Kiguchi
Tachikawa General Hospital, Niigata, Japan

S. Izumi
Department of Otolaryngology, Kido Hospital, Niigata, Japan