Ⅱ　研究成果の刊行に関する一覧表

執筆者氏名	論文題名	雑誌名
Tatsumi K, et al.	Vascular endothelial growth factor in obstructive sleep apnea syndrome.	*Jpn J Clin Physiol* 36: 89-94, 2006.
Tatsumi K, et al.	Obstructive sleep apnea syndrome is associated with some components of metabolic syndrome.	*Chest* 131: 1387-92, 2007
Tatsumi K, et al.	Decreased lipoprotein lipase in obstructive sleep apnea syndrome.	*Circ J* 71: 1293-1298, 2007
Tatsumi K, et al.	Daytime hypercapnia in obstructive sleep apnea syndrome.	*Chest* 132:1832-1838, 2007
Chin K, et al.	Falls in blood pressure in patients with obstructive sleep apnoea after long-term nasal continuous positive airway pressure treatment.	*Journal of Hypertension* 24; 2091-2099, 2006
Chin K, et al.	Effect of nCPAP therapy on heart rate in patients with obstructive sleep apnoea-hypopnoea.	*Quarterly Journal of Medicine* 99: 545-553, 2006
Chin K, et al.	Clinical characteristics of obesity-hypoventilation syndrome in Japan: a Multi-center study.	*Inter Med* 2006; 45:1121-1125
Chin K, et al.	Plasma thioredoxin, a novel oxidative stress marker, in patients with obstructive sleep apnea before and after nasal continuous positive airway pressure.	*Antioxidants & Redox Signaling 10: 205-216, 2008*
Chin K, et al.	Acylated ghrelin level in patients with obstructive sleep apnoea before and after nasal CPAP treatment.	*Respirology* (in press)
Chin K, et al.	Sleep-disordered breathing in the usual lifestyle setting as detected with home monitoring in a Japanese male working population.	*Sleep* (in press)
Chin K, et al.	Noninvasive ventilation for pediatric patients under 1 year of age after cardiac surgery.	*J Thoracic Cardiovascular Surgery* 134: 260-261, 2007
Sato M, et al.	Demographic characteristics of 3659 Japanese patients with obstructive sleep apnea-hypopnea syndrome diagnosed by full polysomnography: associations with apnea-hypopnea index.	*Sleep and Breathing 11: 93-101, 2007*
Sato M, et al.	Association of sleep-disordered breathing and ventricular arrhythmias in patients without heart failure.	*Am J Cardiol 101:2008 (in press)*
Narui K, et al.	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 -	*Circulation J* 70:1148-1154, 2006

Ⅲ　研究成果の刊行物・別冊

Obstructive Sleep Apnea Syndrome Is Associated With Some Components of Metabolic Syndrome*

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Background: **Obesity, hypertension, dyslipidemia, and hyperglycemia are prevalent in obstructive sleep apnea syndrome (OSAS). Metabolic syndrome, however, is defined by visceral fat obesity plus at least two of these factors. However, whether OSAS contributes to the development of metabolic syndrome has not been defined. We investigated whether the components of metabolic syndrome were associated with OSAS in nonobese patients.**

Methods: **We investigated the occurrence of hypertension, dyslipidemia, and hyperglycemia in 42 men with OSAS and 52 men without OSAS matched for age, body mass index (BMI), and visceral fat accumulation.**

Results: **Although serum levels of triglycerides, high-density lipoprotein cholesterol, and diastolic BP did not differ significantly between the two groups, fasting blood glucose (111 ± 6 mg/dL vs 93 ± 3 mg/dL) [mean ± SE] and the percentage of hypertensive patients (45% vs 15%) were significantly higher in the group with OSAS. In addition, a significantly higher percentage of patients with OSAS (19% vs 4%) had at least two of the following: hypertension, hyperglycemia, and dyslipidemia. Logistic regression analysis showed that the apnea-hypopnea index value was the predictor of number of metabolic syndrome parameters such as hypertension, hyperglycemia, and dyslipidemia, while BMI and lowest arterial oxygen saturation during sleep did not.**

Conclusion: **Independent of visceral fat obesity, OSAS was associated with hypertension, dyslipidemia, and hyperglycemia. It is possible that OSAS may predispose even nonobese patients to the development of metabolic syndrome.** ***(CHEST 2007; 131:1387–1392)***

Key words: atherosclerosis; hypertension; hypoxia; insulin resistance; sleep apnea

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; FPC = fasting plasma glucose; HDL-C = high-density lipoprotein cholesterol; HOMA-R = homeostasis model assessment method; OSAS = obstructive sleep apnea syndrome; Sa_{O_2} = arterial oxygen saturation; SFA = subcutaneous fat accumulation; TC = total cholesterol; VFA = visceral fat accumulation

The group of patients with multiple risk factors for cardiovascular diseases related to arteriosclerotic plaques has been highlighted. This group includes those with metabolic syndrome, which has been defined by multiple organizations.[1–3] In the pathogenesis of metabolic syndrome, insulin resistance and visceral obesity seem to be key factors.[1–3] The criteria defining metabolic syndrome include visceral obesity because studies[4,5] have revealed that visceral

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fat produces a great amount of cytokines and hormones such as tumor necrosis factor-α, interleukin-6, and leptin, which may be associated with the development of atherosclerosis. Insulin resistance is thought to play a part in the pathogenesis of metabolic syndrome, although the precise relationship between insulin resistance and visceral obesity has not been defined.[6]

Obstructive sleep apnea syndrome (OSAS) is a prevalent disorder particularly among middle-aged, obese men. Several features of OSAS suggest that sleep apnea is a manifestation of metabolic syndrome.[7–9] Indeed, there is a strong association of OSAS with obesity, male gender, hypertension,[10,11] and diabetes,[8,12] which are also found in patients with metabolic syndrome. Visceral fat accumulation (VFA) correlates with the severity of OSAS[13] and is a key factor for the development of metabolic syndrome.[1–3]

Although obesity, hypertension, and diabetes are frequently present in patients with OSAS, whether OSAS directly contributes to the development of metabolic syndrome has not been defined. OSAS may be associated with a number of cardiovascular risk factors such as hypertension,[10,11] insulin resistance,[8,12] and dyslipidemia[14,15] independent of obesity. The purpose of this study was to investigate whether some components (hypertension, hyperglycemia, and dyslipidemia) of metabolic syndrome were present in nonobese patients with OSAS. Only men were enrolled into the study because of avoiding the confounding effects of gender and insufficient number of women (approximately one eighth of men) for statistical analysis.

Materials and Methods

Subjects

From April 2002 to March 2006, 1,205 consecutive male patients with clinical symptoms of sleep apnea were examined by polysomnography and classified into two groups by their apnea-hypopnea index (AHI) [AHI ≥ 5/h, n = 1,153; AHI < 5/h, n = 52]. Presenting symptoms were either snoring or daytime sleepiness or both. The subjects were all Japanese.

The diagnostic criteria for metabolic syndrome in Japan[16] include a VFA ≥ 100 cm^2. First, we selected patients with a body mass index (BMI) ≤ 30 kg/m^2 for both groups. When matching patients with and without OSAS for BMI, VFA tends to be higher in those with OSAS. Therefore, we selected patients with OSAS whose VFA was < 90 cm^2 and patients without OSAS whose VFA was < 100 cm^2. In the end, we selected 42 patients with OSAS and 52 without OSAS, matched for age, BMI, and VFA.

None of the patients had heart failure or other respiratory problems such as COPD at the time of polysomnography. They were asked to complete a questionnaire on sleep symptoms, medical history, and medications. OSAS was established on the basis of clinical and polysomnography criteria. AHI was calculated as the sum of sleep-disordered breathing. In addition to clinical symptoms, an AHI > 5/h was also used as a selection criterion of OSAS.

Pulmonary function tests were performed to determine FVC and FEV_1 using a standard spirometer (Fudac-60; Fukuda Denshi; Tokyo, Japan). Patients with obstructive airway disease (FEV_1/FVC < 70%) were excluded. Arterial blood for the analysis of gases during room air breathing was drawn with the patient in the supine position, and Pa_{O_2} and Pa_{CO_2} were measured in a blood gas analyzer (Model ABL3000; Radiometer; Tokyo, Japan). The study protocol was approved by the Research Ethics Committee of Chiba University School of Medicine, and all patients gave their informed consent prior to the study.

Polysomnography

Polysomnography (P Series Sleep System; Compumedics; Melbourne, Australia) was performed overnight between 9:00 PM and 6:00 AM. Polysomnography consisted of continuous polygraphic recording from surface leads for EEG, electrooculography, electromyography, ECG, thermistors for nasal and oral airflow, thoracic and abdominal impedance belts for respiratory effort, pulse oximetry for oxyhemoglobin level, and tracheal microphone for snoring and sensor to assess changing of the position during sleep. Polysomnography records were staged manually according to standard criteria.[17,18] The severity of OSAS was determined by the AHI and mean and lowest arterial oxygen saturation (Sa_{O_2}) during sleep.

On the morning after the sleep study, BP was measured twice on waking up between 7:00 AM and 8:00 AM with the subjects in the seated position after a 5-min rest. Venous blood was obtained in the fasting state at 7:00 AM after polysomnography to measure triglycerides, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), and fasting insulin. Insulin resistance was estimated using the homeostasis model assessment method (HOMA-R) and calculated with the following formula: fasting serum insulin (μU/mL) × FPG (mg/dL)/405.

Radiologic Assessment

VFA and subcutaneous fat accumulation (SFA) were assessed by CT (TSX-101A/4E; Toshiba; Tokyo, Japan) and commercially available software (Fat Scan; N2 System; Ashiya, Japan) for personal computer. The areas of SFA and VFA were measured in a single cross-sectional scan at the level of the umbilicus. A CT range of – 150 to – 50 Hounsfield units was used to encompass all fat. VFA was measured by drawing a line within the muscular wall surrounding the abdominal cavity. The area after subtraction of the VFA from the total fat area was defined as SFA,[19] and the visceral/subcutaneous fat ratio was calculated (Fig 1).

Definition of the Metabolic Abnormalities

The definition of metabolic abnormalities was based on the published criteria of metabolic syndrome for the Japanese population.[16] Dyslipidemia was defined as serum triglycerides ≥ 150 mg/dL and/or HDL-C ≤ 40 mg/dL; hypertension as either systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg; and hyperglycemia as FPG ≥ 110 mg/dL. Patients with a previous diagnosis of dyslipidemia, hypertension, or diabetes mellitus, and were receiving drugs for any of these conditions were also included in this category.

Statistical Analysis

Results are expressed as mean ± SE. All clinical parameters are summarized by descriptive statistics. Continuous clinical

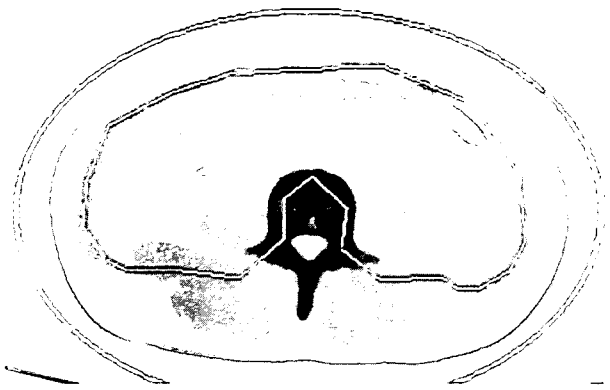

FIGURE 1. CT scan at the level of the umbilicus. First, the total fat area was calculated. Second, the intraperitoneal space (VFA) was defined by tracing its contour on the scan image. Third, subtraction of the VFA area from the total fat area was defined as the SFA. In this patient, VFA was 61.7 cm^2 and SFA was 52.9 cm^2.

parameters in patients with and without OSAS were compared using Mann-Whitney test, and categorical parameters using χ^2 test. Logistic regression analysis was applied to predict the number of metabolic syndrome parameters such as hypertension, hyperglycemia, and dyslipidemia using the values of AHI, lowest SaO_2 during sleep, and BMI as potential predictors; $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 summarizes the characteristics of the subjects. Two patients each in both groups were receiving antihypertensive drugs. Three patients in the OSAS group and two patients in the non-OSAS group had diabetes; of them, two patients in the OSAS group and one patient in the non-OSAS group were receiving an oral hypoglycemic agent, while the others were receiving diet therapy.

Systolic BP was higher in the OSAS group, while diastolic BP did not differ between the two groups. However, the percentage of hypertensive patients was significantly higher in the OSAS group (45% vs 15%; $p < 0.01$) [Table 2].

No significant differences were observed between the two groups regarding serum levels of triglycerides, TC, or HDL-C. However, the percentage of patients with dyslipidemia (serum triglycerides $\geq$ 150 mg/dL and/or HDL-C $\leq$ 40 mg/dL) was significantly higher in the OSAS group (48% vs 25%; $p < 0.05$) [Table 2].

FPG was higher in the OSAS group, and the percentage of subjects with hyperglycemia (FPG $\geq$ 110 mg/dL) was also significantly higher in the OSAS group (33% vs 10%; $p < 0.01$) [Table 2]. The calculated HOMA-R was significantly higher in the OSAS group as well ($p < 0.05$) [Table 2].

Nineteen percent of patients in the OSAS group, compared with only 4% in the non-OSAS group, had at least two of the following: hypertension, hyperglycemia, and dyslipidemia (Table 2). Logistic regression analysis showed that AHI value was the predictor ($p = 0.0001$) of the number of metabolic syndrome parameters such as hypertension, hyperglycemia and dyslipidemia, while BMI ($p = 0.10$) and lowest SaO_2 during sleep ($p = 0.85$) did not.

DISCUSSION

This cross-sectional analysis involved a selected group of male patients with and without OSAS matched for age, BMI, and VFA. Since they were matched for abdominal obesity, we compared them for the other components of metabolic syndrome. The main finding of this study was that 19% of the men with OSAS, compared with only 4% of those without it, had at least two of the following: hyper-

Table 1—*Characteristics of Patients With and Without OSAS

Characteristics	OSAS (n = 42)	Non-OSAS (n = 52)	p Value
Male/female gender	42/0	52/0	NS
Age, yr	51.8 ± 2.4	46.5 ± 2.2	NS
BMI, kg/m^2	22.7 ± 0.6	23.9 ± 0.4	NS
VFA, cm^2	62.0 ± 3.2	58.4 ± 3.8	NS
SFA, cm^2	82.4 ± 7.0	92.8 ± 8.8	NS
Visceral/subcutaneous fat ratio	0.89 ± 0.05	0.76 ± 0.05	< 0.05
AHI, /h	32.2 ± 3.1	2.4 ± 0.2	< 0.01
Average SaO_2, %	94.4 ± 0.4	96.3 ± 0.2	< 0.01
Lowest SaO_2, %	81.9 ± 1.3	87.4 ± 0.7	< 0.01
Vital capacity, % of predicted	107.9 ± 3.3	104.3 ± 2.7	NS
FEV_1, % of predicted	83.1 ± 1.4	85.2 ± 1.2	NS
PaO_2, mm Hg	88.2 ± 1.5	88.6 ± 1.7	NS
$PaCO_2$, mm Hg	43.0 ± 0.6	42.9 ± 0.5	NS

*Data are presented as mean ± SE. NS = not significant.

Table 2—*Metabolic Characteristics of Patients With and Without OSAS**

Characteristics	OSAS (n = 42)	Non-OSAS (n = 52)	p Value
Systolic BP, mm Hg	131 ± 3	125 ± 1	< 0.05
Diastolic BP, mm Hg	77 ± 2	77 ± 1	NS
Subjects with high BP	19/42 (45.2)	8/52 (15.4)	< 0.01
Serum triglycerides (range), mg/dL†	126 (35–271)	117 (40–244)	NS
Serum TC, mg/dL	182 ± 5	189 ± 4	NS
Serum HDL-C, mg/dL	50 ± 2	55 ± 2	NS
Subjects with dyslipidemia	20/42 (47.6)	13/52 (25.0)	< 0.05
FPG, mg/dL	111 ± 6	93 ± 3	< 0.05
Subjects with hyperglycemia	14/42 (33.3)	5/52 (9.6)	< 0.01
HOMA-R	3.7 ± 0.4	2.5 ± 0.2	< 0.05
Subjects with at least two of the following: hypertension, hyperglycemia, and dyslipidemia	8/42 (19.0)	2/52 (3.8%)	< 0.05

*Data are presented as mean ± SE or No./total (%) unless otherwise indicated. See Table 1 for expansion of abbreviation.
†Data are presented as median (range).

tension, hyperglycemia, and dyslipidemia. It is possible that even in nonobese OSAS subjects might be predisposed to metabolic syndrome. In addition, the logistic regression analysis, in which AHI value was the predictor of number of metabolic syndrome parameters such as hypertension, hyperglycemia, and dyslipidemia, while BMI and lowest SaO_2 during sleep were not, may support our results.

Obesity and VFA are known to be risk factors for the development of OSAS.[13,20] Especially, VFA increases the risk for obesity-related disorders such as vascular-related diseases.[1–4] OSAS itself is a risk for VFA,[13] which increases insulin resistance,[8,12] an important factor involved in the pathogenesis of metabolic syndrome. In an abdominal CT scan, a VFA > 100 cm^2 is a diagnostic feature of metabolic syndrome.[1–3,16] The subjects with OSAS in the present study did not meet this criterion of metabolic syndrome, since the VFA (62.0 ± 3.2 cm^2) was ≤ 90 cm^2. If OSAS was a risk factor for metabolic syndrome, any factor related to the pathophysiology of OSAS, such as intermittent hypoxia, increased oxygen-radical production, and membrane lipid peroxidation, would contribute to the development of metabolic syndrome.

Hypoxia is known to increase hypoxia-inducible factor 1 gene transcription and messenger RNA stabilization, while intermittent hypoxia also up-regulates hypoxia-inducible factor 1 expression.[21] In experimental animals, intermittent hypoxia resulted in an increase of FPG and serum leptin levels. Microarray messenger RNA analysis of adipose tissue revealed that leptin was the only up-regulated gene affecting glucose uptake.[22] Leptin may play an important role in mitigating the metabolic disturbances that accompany intermittent hypoxia.

Obesity, especially the presence of VFA, could worsen metabolic abnormalities such as insulin resistance; while insulin resistance, a putative background of the metabolic syndrome, could be associated with OSAS.[8,12] Since continuous positive airway pressure treatment improves insulin sensitivity in patients with OSAS within a few days before any possible changes in body weight or lifestyle, OSAS itself appears to predispose to insulin resistance.[23] The severity of OSAS may affect insulin resistance to a greater extent in nonobese patients with OSAS.[23] These results indicate that OSAS *per se* may be associated with insulin resistance, although concomitant obesity or VFA are predominant risk factors for insulin resistance. Increased production of tumor necrosis factor-α[24] and increased sympathetic drive[25,26] may partly explain changes of glucose homeostasis in OSAS. In the present study, both FPG and calculated HOMA-R were higher in the OSAS group. Thus, intermittent hypoxia is likely to aggravate the insulin resistance associated with significant VFA in patients with OSAS.

This study confirmed the association of OSAS with hypertension,[10,11] even though the subjects of the present study were not obese. The percentage of subjects with a systolic BP ≥ 130 mm Hg and/or a diastolic BP ≥ 85 mm Hg was significantly higher in the OSAS group. OSAS may contribute to hypertension in obese individuals through increased sympathetic activation,[25,26] leptin, aldosterone, fatty acids and oxidative stress, and insulin resistance.[27] Insulin resistance predisposes patients with OSAS to hypertension, although several factors can lead to hypertension regardless of obesity.

The percentage of subjects who met the criteria of dyslipidemia (serum triglycerides ≥ 150 mg/dL and/or HDL-C ≤ 40 mg/dL) was significantly higher in the OSAS group. Disorders of lipid metabolism are known to play a part in atherosclerotic changes of vascular walls. The association between OSAS and

lipid metabolism was addressed in the Sleep Heart Health Study.[15] However, serum triglycerides, TC, and HDL-C did not differ significantly between the OSAS and non-OSAS groups in this study, suggesting that the severity of intermittent hypoxia (lowest Sao_2, 81.9 ± 1.3% in the OSAS group, vs 87.4 ± 0.7% in the non-OSAS group) may not have been too severe to affect lipid metabolism.

OSAS may be independently associated with an increased prevalence of metabolic syndrome, although subjects with OSAS in previous studies[7–9] were more obese compared with control subjects. In previous research[9] regarding the prevalence of metabolic syndrome in Japanese patients with OSAS, it was found that metabolic syndrome was more common in patients with OSAS than in control subjects (50% vs 22%). Our present subjects were not obese according to the standard for white people, and did not meet the criteria of the metabolic syndrome. However, the percentage of subjects with high FBG levels or hypertension was significantly higher in the OSAS group. In addition, the percentage of patients presenting at least two metabolic abnormalities was also significantly higher in the OSAS group. These results suggest that even nonobese patients with OSAS may be prone to metabolic syndrome.

This was a cross-sectional descriptive study and did not provide direct evidence that patients with OSAS are at an increased risk for cardiovascular mortality. It has not been defined whether OSAS directly enhances the factors that comprise the metabolic syndrome. OSAS and metabolic syndrome may share a common pathomechanism other than visceral obesity. An interventional study using continuous positive airway pressure may clarify this question. Due to absence of women in this study, our conclusions cannot be extrapolated to other cohorts. In addition, the results of this study cannot be extrapolated to other ethnic groups. This study was intended to analyze all consecutive male patients with clinical symptoms of sleep apnea who were examined using polysomnography. A limitation of our study is that our strict selection criteria allowed us to evaluate only a small number of patients.

In conclusion, the percentage of patients presenting at least two metabolic abnormalities (among hypertension, dyslipidemia, and hyperglycemia) was significantly higher in the OSAS group than in the non-OSAS group matched for age, BMI, and VFA. Early intervention may help to decrease the cardiovascular morbidity and mortality associated with OSAS and metabolic syndrome.

References

1 World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: Part I. Diagnosis and classification of diabetes mellitus. Geneva, Switzerland: World Health Organization, 1999

2 Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. JAMA 2001; 285:2486–2497

3 Alberti KG, Zimmet P, Shaw J. Metabolic syndrome: a new world-wide definition; a consensus statement from the International Diabetes Federation. Diabet Med 2006; 23:469–480

4 Masuzaki H, Paterson J, Shinyama H, et al. A transgenic model of visceral obesity and the metabolic syndrome. Science 2001; 294:2166–2170

5 Matsuzawa Y. Pathophysiology and molecular mechanisms of visceral fat syndrome: the Japanese experience. Diabetes Metab Rev 1997; 13:3–13

6 Hanley AJG, Karter AJ, Festa A, et al. Factor analysis of metabolic syndrome using directly measured insulin sensitivity: the insulin resistance atherosclerosis study. Diabetes 2002; 51:2642–2647

7 Coughlin SR, Mawdsley L, Mugarza JA, et al. Obstructive sleep apnea is independently associated with an increased prevalence of metabolic syndrome. Eur Heart J 2004; 25:735–741

8 Ip MS, Lam B, Ng MMT, et al. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002; 165:670–676

9 Sasanabe R, Banno K, Otake K, et al. Metabolic syndrome in Japanese patients with obstructive sleep apnea syndrome. Hypertens Res 2006; 29:315–322

10 Peppard PE, Young T, Mari PM, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000; 342:1378–1384

11 Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. JAMA 2000; 283:1829–1836

12 Punjabi NM, Sorkin JD, Katzel LI, et al. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 2002; 165:677–682

13 Chin K, Shimizu K, Nakamura T, et al. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. Circulation 1999; 100:706–712

14 Börgel J, Sanner BM, Bittlinsky A, et al. Obstructive sleep apnoea and its therapy influence high-density lipoprotein cholesterol serum levels. Eur Respir J 2006; 27:121–127

15 Newman AB, Nieto FJ, Guidry U, et al. Relation of sleep-disordered breathing to cardiovascular disease risk factor: the Sleep Heart Health Study. Am J Epidemiol 2001; 154:50–59

16 Committee on Evaluation of Diagnostic Standards for Metabolic Syndrome. Definition and diagnostic standards for metabolic syndrome [in Japanese]. Nippon Naika Gakkai Zasshi 2005; 94:794–809

17 Rechtschaffen A, Kales AA, eds. A manual of standardized terminology, techniques and scoring for sleep stages of human subjects. Washington, DC: Government Printing Office, 1968; National Institutes of Health Publication 204

18 The Report of an American Academy of Sleep Medicine task force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999; 22:667–689

19 Yoshizumi T, Nakamura T, Yamane M, et al. Abdominal fat: standardized technique for measurement at CT. Radiology 1999; 211:283–286
20 Grunstein RR, Wilcox I, Yang TS, et al. Snoring and sleep apnea in men: association with central obesity and hypertension. Int J Obes 1993; 17:533–540
21 Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathway by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 2005; 112:2660–2667
22 Polotsky VY, Li J, Punjabi NM, et al. Intermittent hypoxia increases insulin resistance in genetically obese mice. J Physiol 2003; 552:253–264
23 Harsch IA, Schahin SP, Radespiel-Tröger M, et al. Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2004; 169:156–162
24 Uysal K, Wiesbrock SM, Marino MW, et al. Protection from obesity-induced insulin resistance in mice lacking TNF-α function. Nature 1997; 389:610–614
25 Somers VK, Dyken ME, Clary MP, et al. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995; 96:1897–1904
26 Peled N, Greenberg A, Pillar G, et al. Contributions of hypoxia and respiratory disturbance index to sympathetic activation and blood pressure in obstructive sleep apnea syndrome. Am J Hypertens 1998; 11:1284–1289
27 Ferrannini E, Buzzigoli G, Bonadonna R, et al. Insulin resistance in essential hypertension. N Engl J Med 1987; 317:350–357

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Decreased Lipoprotein Lipase in Obstructive Sleep Apnea Syndrome

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Background Lipoprotein lipase (LPL) might play a major role in lipid metabolism by hydrolyzing triglyceride-rich lipoproteins. Decreased LPL activity can trigger early inflammatory responses central to atherosclerosis. However, whether repeated apnea-related hypoxemia influences lipid metabolism in patients with obstructive sleep apnea syndrome (OSAS) remain undefined. This investigation determined whether circulating LPL was influenced by repeated apnea-related hypoxemia, and the effect of nasal continuous positive airway pressure (CPAP) therapy on LPL concentrations in OSAS patients.

Methods and Results The participants of the study were 155 men with OSAS and 39 men without OSAS. Circulating LPL concentrations decreased with the severity of OSAS. They correlated negatively with serum triglyceride, and the linear regression lines between LPL concentrations and triglyceride in OSAS patients were shifted downward compared with those in non-OSAS patients, suggesting that any pathophysiological factor might decrease LPL activity in OSAS patients. Some OSAS patients were subjected to CPAP therapy for 3 months. CPAP therapy increased LPL concentrations and decreased C-reactive protein (CRP) concentrations.

Conclusions The present study suggests that repeated apnea-related hypoxemia might affect lipid metabolism and augment inflammatory responses, and CPAP therapy could be effective to decrease inflammatory responses and ameliorate lipid metabolism in patients with OSAS. (*Circ J* 2007; **71**: 1293–1298)

Key Words: Atherosclerosis; Inflammation; Lipid metabolism; Sleep apnea

Increased concentrations of triglyceride (TG)-rich lipoproteins provoke lipid accumulation in the artery wall, triggering early inflammatory responses central to atherosclerosis[1] Lipoprotein lipase (LPL) might play a major role in lipid metabolism by hydrolyzing TG-rich lipoproteins and releasing fatty acids[2] Peroxisome proliferators-activated receptor (PPAR)-α might be activated by fatty acids to induce the transcription of genes involved in the oxidation of fatty acids. Then, LPL could act on circulating lipoproteins to generate PPAR-α ligands. PPAR-α activation might exert cardiovascular protective effects in hypertension or other forms of cardiovascular disease[3]

There is a continuous dissociation of LPL from the endothelium to blood[4] Therefore, blood levels of LPL might be associated with the pathogenesis of cardiovascular diseases[5] including the complications of obstructive sleep apnea syndrome (OSAS). However, the roles of LPL in inflammatory responses, atherosclerosis and cardiovascular complications in patients with OSAS remain undefined. Assuming that the pathophysiology of OSAS manifests a systemic inflammatory response, repeated hypoxemia and recovery to normoxemia could affect LPL activity.

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Serum levels of TG and body mass index (BMI) have been reported to correlate negatively with the blood concentrations of LPL[5–7] We hypothesized that the pathophysiological conditions, related to the severity of OSAS, might affect the blood concentrations of LPL[3–5] The purpose of the present study was to examine whether the blood concentrations of LPL are influenced by repeated apnea-related hypoxemia in patients with OSAS and to determine whether nasal continuous positive airway pressure (CPAP) therapy ameliorate the levels of LPL.

Methods

Subjects

A consecutive male population with clinical symptoms of sleep apnea (n=260), who were examined by polysomnography (PSG) from August 2003 to October 2004, was first divided into 2 groups according to their apnea-hypopnea index (AHI) (AHI ≥5: n=214, AHI <5: n=46). The patients were recruited from the sleep clinic where they had been referred for further investigation regarding snoring or possible OSAS. Presenting symptoms were either snoring or daytime sleepiness or both. The subjects were all Japanese, and no other ethnic group was included to avoid the effects of ethnic difference.

Patients with heart failure, or other respiratory problems, including chronic obstructive pulmonary disease were excluded from the study. Subjects with kidney disease and hormonal disease were also excluded. Subjects on medication known to affect insulin action, including the treatments for diabetes mellitus, or plasma lipoprotein concentrations,

Table 1 Clinical Characteristics of OSAS and Non-OSAS Patients

	OSAS (n=155)	*Non-OSAS (n=39)*	*p value*
Age (years)	49.8±1.1	47.7±2.2	*NS*
%FVC	96.8±1.5	96.3±2.6	*NS*
$FEV_{1.0}$%	83.0±0.7	85.8±0.9	*<0.05*
PaO_2 (mmHg)	87.2±1.1	91.9±1.3	*<0.01*
$PaCO_2$ (mmHg)	42.3±0.4	42.5±0.5	*NS*
BMI (kg/m^2)	28.9±0.4	25.6±0.6	*<0.01*
VFA/SFA	0.97±0.02	1.04±0.04	*NS*
VFA (cm^2)	194±6	134±9	*<0.01*
SFA (cm^2)	207±10	146±12	*NS*
AHI (events/h)	36.7±2.1	1.8±0.2	*<0.01*
Mean SaO_2 (%)	90.0±0.5	96.1±0.3	*<0.01*
Lowest SaO_2 (%)	77.7±1.0	88.7±0.5	*<0.01*
Triglycerides (mg/dl)	201±6	163±12	*<0.01*
Total cholesterol (mg/dl)	203±3	200±6	*NS*
HDL-C (mg/dl)	43±1	51±3	*<0.01*
FPG (mg/dl)	116±2	105±3	*<0.01*
Insulin (μU/ml)	11.6±0.4	7.6±0.5	*<0.01*
HOMA index	3.4±0.1	2.0±0.2	*<0.01*
LPL (ng/ml)	43.1±1.3	58.4±4.3	*<0.01*
CRP (ng/ml)	1.525±115	721±115	*<0.01*

Values are means±SEM.

OSAS, obstructive sleep apnea syndrome; BMI, body mass index; VFA, visceral fat accumulation; SFA, subcutaneous fat accumulation; AHI, apnea-hypopnea index; mean SaO_2, mean value of SaO_2 during sleep (%); lowest SaO_2, the lowest value of SaO_2 during sleep (%); HDL-C, high-density lipoprotein-cholestrol; FPG, fasting plasma glucose; HOMA, homeostasis model assessment; LPL, lipoprotein lipase; CRP, C-reactive protein.

including antihypertensive drugs and the treatments for hyperlipidemia were also excluded. The subjects without medication for diabetes mellitus, hypertension and hyperlipidemia, were included in the current study. They were asked to complete a questionnaire on sleep symptoms, medical history and medications. OSAS was established on the basis of clinical and polysomnographic criteria. AHI was calculated as the summary measurement of sleep-disordered breathing. In addition to clinical symptoms, an AHI of more than 5 events per hour was also used as a selection criterion of OSAS. In the end we obtained 155 patients with OSAS and 39 without OSAS.

The study protocol was approved by the Research Ethics Committee of Chiba University School of Medicine, and all patients gave their informed consent before study commencement.

PSG

Overnight PSG (Compumedics, Melbourne, Australia) was performed between 21.00–06.00. The PSG consisted of continuous polygraphic recording from surface leads for electroencephalography, electrooculography, electromyography, electrocardiography, thermistors for nasal and oral airflow, thoracic and abdominal impedance belts for respiratory effort, pulse oximetry for oxyhemoglobin concentration, tracheal microphone for snoring and sensor for the position during sleep. PSG records were staged manually according to standard criteria[8,9] Severity of OSAS was determined by the AHI and lowest oxygen saturation (SaO_2) during sleep (lowest SaO_2).

Laboratory Tests

Venous blood was obtained in the fasting state at 07.00 after overnight PSG to measure TG, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), serum insulin, high-sensitivity C-reactive protein (CRP) and LPL. Pre-heparin serum LPL mass was measured by a sandwich enzyme-linked immunosorbent assay (Daiichi Pure Chemicals, Tokyo, Japan) with a specific-monoclonal antibody against bovine milk LPL[5–7] Insulin resistance was estimated using the homeostasis model assessment ratio (HOMA-R) [fasting serum insulin (mU/L)×FPG (mmol/L)/22.5].

Radiological Assessment

Visceral fat accumulation (VFA) and subcutaneous fat accumulation (SFA) were assessed by computed tomography (CT) (TSX-101A/4E Toshiba, Tokyo) and the commercially available software Fat Scan (N2 System, Co Ltd, Ashiya, Japan), for personal computers. The areas of SFA and VFA were measured in a single cross-sectional scan at the level of the umbilicus. A CT range of −150 to −50 Hounsfield units was used to encompass all fat. VFA was measured by drawing a line within the muscular wall surrounding the abdominal cavity. The area after subtraction of the VFA from the total fat area was defined as SFA and the VFA/SFA ratio was calculated[10]

CPAP Treatment

The effects of CPAP were examined in a group of treatment-tolerated consecutive OSAS patients, who were examined by PSG from April 2004 to October 2004. Thirty-six OSAS patients with an AHI of 20 events/h could tolerate CPAP treatment, and were successfully treated for 3 months. CPAP titration was performed with the AutoSet® (ResMed, Sydney, Australia), and treatment was continued with AutoSet®. Adequate CPAP tolerance was considered when the system counter indicated that the patient was using the device for at least 4 h at night during at least 70% of the follow-up nights. Three months after the initiation of CPAP therapy, venous blood was obtained in the fasting state at 08.00 to measure concentrations of CRP and LPL.

Statistics

The results were expressed as mean values ± standard errors. The Mann–Whitney U-test was used to compare age, BMI, serum parameters, sleep parameters and CT parameters between patients with and without OSAS. Proportions were compared by the chi-squared test. Linear regression analysis was performed to examine the association between 2 parameters. Analysis of covariance was used to compare the influence of BMI, TG, HDL-C, FPG, VFA, SFA and CRP on LPL concentrations between OSAS and non-OSAS patients with post hoc test as Bonferroni/Dunn. The significance of differences before and after CPAP therapy was determined by Student's t-test and p-values less than 0.05 were considered to be statistically significant.

Results

Clinical Characteristics of OSAS Patients

Baseline characteristics of the study population are shown in Table 1. None of the patients had obstructive airway disease ($FEV_{1.0}$/FVC <70%). $FEV_{1.0}$% and PaO_2 were higher in the non-OSAS group, whereas %FVC and $PaCO_2$ did not differ between the 2 groups. BMI, VFA and SFA were higher in the OSAS group, although V/S ratio did not differ significantly between OSAS and non-OSAS patients. Mean and lowest SaO_2 during sleep were significantly lower, and AHI was higher in the OSAS group.

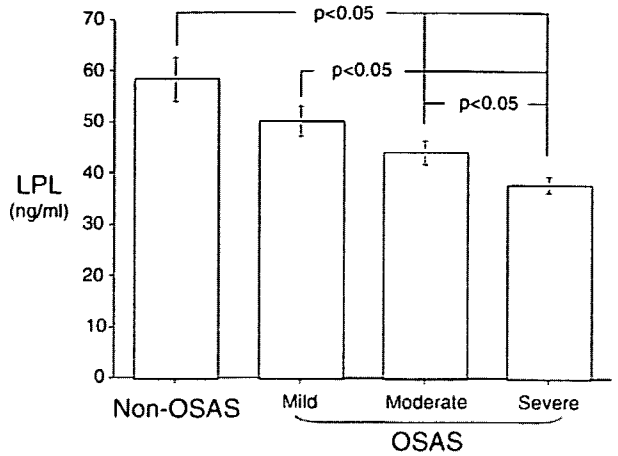

Fig 1. Serum concentrations of lipoprotein lipase (LPL) in patients with mild, moderate and severe obstructive sleep apnea syndrome (OSAS). LPL concentrations in severe OSAS group are significantly lower compared with those in mild and moderate OSAS group. Values are mean±standard errors.

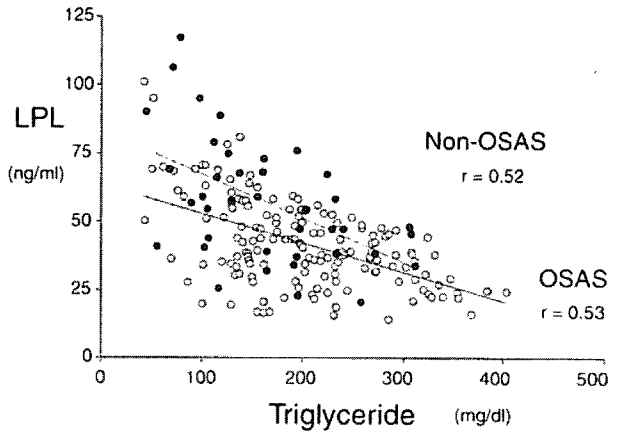

Fig 2. Relationship between serum concentrations of triglycerides (TG) and lipoprotein lipase (LPL) in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS. The solid and dashed regression lines describe the relationship between serum LPL concentrations and TG in OSAS and non-OSAS patients, respectively. The regression line between serum concentrations of LPL and TG was located downward in patients with OSAS compared with that in patients with non-OSAS ($p<0.0001$ by analysis of covariance).

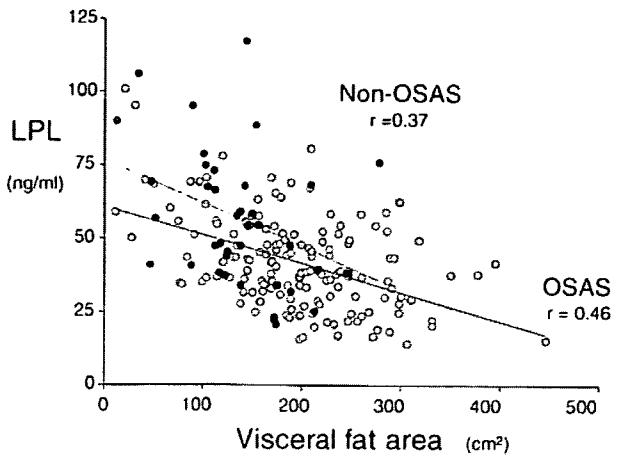

Fig 3. Relationship between visceral fat area (VFA) and serum concentrations of lipoprotein lipase (LPL) in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS. The solid and dashed regression lines describe the relationship between serum LPL concentrations and VFA in OSAS and non-OSAS patients, respectively. The regression line between serum concentrations of LPL and VFA was located downward in patients with OSAS compared with that in patients with non-OSAS ($p<0.0001$ by analysis of covariance).

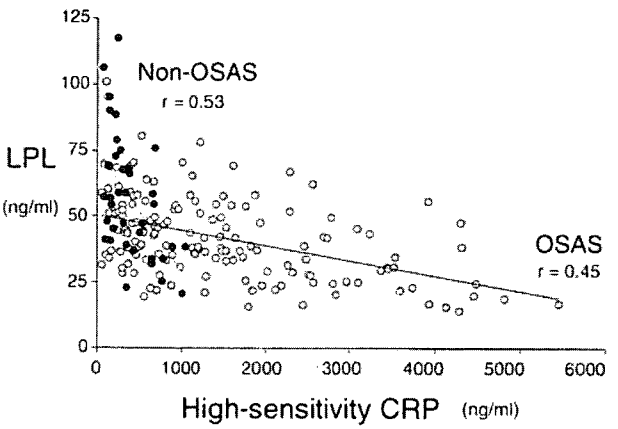

Fig 4. Relationship between serum concentrations of lipoprotein lipase (LPL) and C-reactive protein (CRP) in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS. The solid and dashed regression lines describe the relationship between serum LPL concentrations and CRP in OSAS and non-OSAS patients, respectively.

Serum TG, FPG, insulin, CRP and HOMA-R were higher, whereas HDL-C and LPL were lower in the OSAS group, although TC was similar in the 2 groups.

LPL in OSAS Patients

OSAS patients had lower LPL concentrations than non-OSAS patients. OSAS patients were divided based on their AHI values into those with severe OSAS (n=67, AHI >40), those with moderate OSAS (n=44, AHI: 15–40) and those with mild OSAS (n=44, AHI: 5–14.9). This system was chosen because leaving 3 groups of about the same size usually maximizes the statistical power of any comparison. LPL concentrations were lower in severe OSAS group compared with those in moderate or mild OSAS group. Moderate OSAS group had lower LPL concentrations than non-OSAS group. No significant difference was observed in LPL concentrations between mild OSAS and non-OSAS group (Fig 1). LPL concentrations negatively correlated with AHI in whole SAS group ($r=0.32$, $p<0.01$). These suggest that LPL concentrations decrease especially in patients with frequent episodes of apnea.

LPL concentrations negatively correlated with BMI, VFA, SFA, TG, insulin and HOMA-R in OSAS patients. Circulating LPL concentrations positively correlated with HDL-C. OSAS patients had lower LPL concentrations than non-OSAS patients (Table 1) even when compared relative to TG, VFA, SFA and BMI. For example, the linear regression line between LPL concentrations and TG in OSAS patients was shifted downward compared with that in non-OSAS patients ($p<0.01$) (Fig 2). Likewise, the linear regression lines between LPL concentrations and VFA (Fig 3), SFA and BMI in OSAS patients were shifted downward compared with those in non-OSAS patients ($p<0.01$), suggesting that any pathophysiological factor might

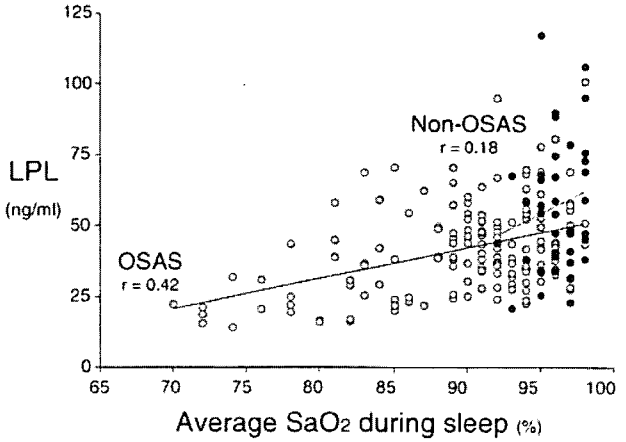

Fig 5. Relationship between average SaO_2 during sleep and serum concentrations of lipoprotein lipase (LPL) in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS. The solid and dashed regression lines describe the relationship between serum LPL concentrations and average SaO_2 during sleep in OSAS and non-OSAS patients, respectively.

decrease LPL activity in OSAS patients.

LPL concentrations correlated negatively with CRP in both OSAS and non-OSAS patients (Fig 4), suggesting that decreased LPL activity might be associated with systemic inflammatory responses.

LPL concentrations correlated positively with average SaO_2 during sleep in OSAS patients (Fig 5), suggesting that LPL activity might decrease with apnea-related repeated hypoxemia.

The factors which influence the LPL concentrations in OSAS patients were examined. A significant correlation was observed between serum LPL concentrations and sleep average SaO_2, sleep lowest SaO_2, AHI, BMI, VFA, SFA, TG, HDL-C, insulin, HOMA-R or CRP (Table 2), indicating that any metabolic or inflammatory factor might influence the serum concentrations of LPL.

Next, multiple regression analysis was performed to predict the LPL concentrations, using the values of TG, amount of VFA, BMI, HOMA-R, the average SaO_2 during sleep and AHI as potential predictors. The results of multiple regression analysis showed that the primary factors influencing LPL concentrations were TG ($p<0.0001$), the average SaO_2 during sleep ($p=0.003$) and amount of VFA ($p=0.037$), whereas AHI ($p=0.062$), HOMA-R ($p=0.34$) and BMI ($p=0.97$) did not significantly affect LPL concentrations.

Table 2 Correlation Coefficients of Several Parameters With the Concentrations of Serum LPL

Variables	*OSAS (n=155)*	*Non-OSAS (n=39)*	*Total (n=194)*
BMI	*0.41**	*0.48**	*0.30**
VFA	*0.46**	*0.37**	*0.44**
SFA	*0.31**	*0.58**	*0.28**
AHI	*0.25**	*0.04*	*0.48**
Sleep average SaO_2	*0.42**	*0.25*	*0.59**
Sleep lowest SaO_2	*0.24**	*0.12*	*0.37**
Triglycerides	*0.53**	*0.12*	*0.37**
HDL-C	*0.46**	*0.12*	*0.37**
FPG	*0.06*	*0.14*	*0.18*
Insulin	*0.28**	*0.19*	*0.30**
HOMA-R	*0.23**	*0.20*	*0.29**
CRP	*0.46**	*0.12*	*0.37**

*$p<0.05$.
HOMA-R, HOMA ratio. Other abbreviations see in Table 1.

Effect of CPAP Therapy on CRP and LPL Concentrations

In 36 patients with moderate to severe OSAS, BMI did not change significantly during the 3 months of CPAP therapy. Treatment with CPAP significantly decreased AHI (57.5±3.9 to 1.4±0.1, $p<0.01$) and increased sleep lowest SaO_2 (70.5±1.8 to 91.5±0.4, $p<0.01$). In addition, CPAP significantly decreased the concentrations of CRP (1,774±278 to 999±210, $p<0.01$), and increased the concentrations of LPL (44.4±2.0 to 49.1±2.2, $p<0.01$) (Fig 6).

Discussion

The purpose of the present study was to investigate whether repeated apnea-related hypoxemia influences lipid metabolism, thereby systemic inflammatory responses in patients with OSAS. Increased concentrations of TG-rich lipoproteins as a result of decreased LPL activity might eventuate in lipid accumulation in the arteries wall, triggering early inflammatory responses and thereby the occurrence of cardiovascular diseases in OSAS.

In the present study circulating LPL concentrations were lower and CRP concentrations were higher in OSAS patients compared with those in non-OSAS patients, and LPL concentrations were lower in severe than in mild OSAS

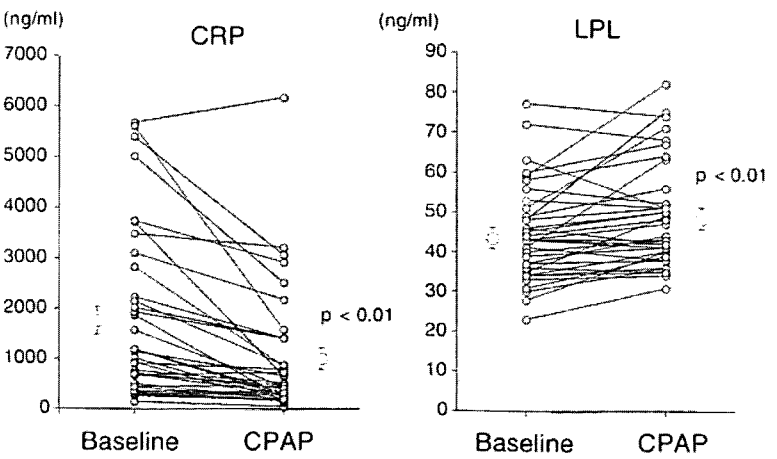

Fig 6. Effects of nasal continuous positive airway pressure (CPAP) on blood concentrations of high-sensitivity C-reactive protein (CRP) and lipoprotein lipase (LPL) in patients with obstructive sleep apnea syndrome (OSAS) (n=36). CRP decreased and LPL increased 3 months after treatment with nasal CPAP. Large open circle with bar represents mean±standard errors.

group. In addition, nasal CPAP therapy increased LPL and decreased CRP concentrations in OSAS patients. These results suggest that repeated apnea-related hypoxemia might affect lipid metabolism and augment inflammatory responses, although direct link between LPL activity and systemic inflammatory responses has not been determined.

Inflammatory responses play important roles in atherosclerosis[11] and CRP is a non-specific marker of inflammation[12,13] Circulating concentrations of CRP are elevated in patients with OSAS[14] as a result of OSAS itself and concomitant diseases, such as obesity and hyperlipidemia[15] Circulating concentrations of CRP represent a strong independent predictor of the risk of suffering a myocardial infarction, stroke or vascular death in persons without overt signs or symptoms of a cardiovascular disease[12] The inverse relationship between circulating LPL concentrations and CRP suggests that decreased LPL activity might accentuate vascular inflammatory responses, or that vascular inflammatory responses could decrease LPL concentrations in patients with OSAS. However, the cause and effect relationship between circulating LPL concentrations and CRP has not been clearly defined.

LPL plays a central role in lipoprotein metabolism by hydrolyzing both dietary and endogenous TG[2] The negative correlation of blood LPL concentrations with TG concentrations and positive correlation with HDL-C concentrations are essentially consistent with previous studies[5,16] Although the meaning and mechanisms of these relationships have not been clarified, these relationships suggest that circulating concentrations of LPL reflect to some extent the amount of LPL activity[5-7]

OSAS patients are frequently associated with obesity, and OSAS and obesity might synergistically contribute to the development of cardiovascular complications, such as hypertension and ischemic heart disease. In the present study, LPL concentrations were lower in OSAS patients compared with those in non-OSAS patients. In addition, circulating LPL concentrations correlated negatively with BMI, VFA and SFA, and the linear regression line between LPL concentrations and BMI in OSAS patients was shifted downward compared with that in non-OSAS patients, suggesting that any pathophysiological factor might decrease LPL concentrations in OSAS patients. One plausible explanation is the atherogenic effects of hypoxia through decreased LPL activity in patients with OSAS[17,18] Hypoxia modulates the expression of several endothelial genes, including those for vascular endothelial growth factor and endothelin[19,20] Therefore, it might be that repeated apnea-related hypoxemia is one of the causes to decrease LPL concentrations. It has been clarified that intermittent hypoxia influence the pathogenesis of atherosclerosis rather than sustained hypoxia[21] That AHI was related to LPL concentrations might suggest that repeated apnea-related desaturation is an important determinant of LPL concentrations.

One important mechanism by which OSAS might promote cardiovascular diseases is intermittent hypoxia, in which patients are subjected to repeated episodes of brief oxygen desaturation, followed by reoxygenation[22,23] Such cycles of hypoxia/reoxygenation might result in the generation of reactive oxygen species. Reactive oxygen species and redox events are also involved in the regulation of signal transduction for oxygen-sensing mechanisms[24,25] and could be involved in the regulation of the LPL production, although the mechanisms of decreased LPL concentrations in OSAS patients have not been determined in the present study. Serum LPL mass might have significant relationships with insulin resistance[26] In the present study, HOMA-R, one of the markers representing insulin resistance, was higher in OSAS patients and LPL concentrations negatively correlated with HOMA-R, suggesting that insulin resistance might be partly associated with blood LPL concentrations. However, the multiple regression analysis showed that the primary factors influencing LPL concentrations were TG, the average SaO_2 during sleep and amount of VFA, whereas HOMA-R did not significantly affect LPL concentrations.

A limitation of the present study is that no women were included. The balance between the LPL activity of visceral adipocytes and that of less pathogenic subcutaneous fat deposits has a major influence on the development of visceral obesity, and appears to be favorably influenced by restoration of sex hormones in both men and women[27] suggesting that gender might influence LPL activity. Therefore, in the present study, only men were recruited to avoid the confounding effects of gender on LPL concentrations, although LPL concentrations might not be affected by aging and gender[5] In addition, the subjects were limited to Japanese male in the present study, and therefore the results of this study might not be extrapolated to other groups of OSAS patients.

Three months of treatment with CPAP reduced CRP and increased LPL concentrations in patients with OSAS, confirming that CPAP therapy ameliorates inflammatory responses[14,28] A limitation of the present study was that we did not measure the time course of CRP and LPL changes during the usage of CPAP. Whether the relief of hypoxemia for a relatively short term affects LPL or CPR production or release has not been defined. Another limitation of this study was that the effects of CPAP on CRP and LPL levels were not examined according to a randomized, placebo-controlled design because of the difficulties of placebo CPAP measurements.

In conclusion, we found that decreased LPL concentrations could be associated with inflammatory responses in patients with OSAS. Increased concentrations of TG-rich lipoproteins as a result of decreased LPL activity might result in lipid accumulation in arteries wall, triggering early inflammatory responses and thereby the occurrence of cardiovascular diseases in OSAS. Three months of CPAP therapy may be effective to decrease inflammatory responses.

Acknowledgements

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References

1. Zilversmit DB. Atherogenic nature of triglycerides, postprandial lipidemia, and triglyceride-rich remnant lipoproteins. *Clin Chem* 1995; **41**: 153–158.
2. Ziouzenkova O, Perrey S, Asatryan L, Hwang J, MacNaul KL, Moller DE, et al. Lipolysis of triglyceride-rich lipoproteins generates PPAR ligands: Evidence for an anti-inflammatory role for lipoprotein lipase. *PNAS* 2003; **100**: 2730–2735.
3. Schiffrin EL, Amiri F, Benkirane K, Iglarz M, Diep QN. Peroxisome proliferator-activated receptors: Vascular and cardiac effects in hypertension. *Hypertension* 2003; **42**: 664–668.
4. Camps L, Reina M, Llobera M, Vilaro S, Olivecrona T. Lipoprotein lipase: Cellular origin and functional distribution. *Am J Physiol*

1990; **258:** C673–C681.
5. Watanabe H, Miyashita Y, Murano T, Hiroh Y, Itoh Y, Shirai K. Preheparin serum lipoprotein lipase mass level: The effects of age, gender, and types of hyperlipidemias. *Atherosclerosis* 1999; **145:** 45–50.
6. Kobayashi J, Tashiro J, Murano S, Morisaki N, Saito Y. Lipoprotein lipase mass and activity in post-heparin plasma from subjects with intra-abdominal visceral fat accumulation. *Clin Endocrinol* 1998; **48:** 515–520.
7. Kobayashi J, Saito K, Fukamachi I, Taira K, Takahashi K, Bujo H, et al. Pre-heparin lipoprotein lipase mass: Correlation with intra-abdominal visceral fat accumulation. *Horm Metab Res* 2001; **33:** 412–416.
8. Rechtschaffen A, Kales AA, editors. A manual of standardized terminology, techniques and scoring for sleep stages of human subjects. Washington, D.C.: Government Printing Office. NIH Publication No. 204, 1968.
9. The Report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999; **22:** 667–689.
10. Yoshizumi T, Nakamura T, Yamane M, Islam AH, Menju M, Yamasaki K, et al. Abdominal fat: Standardized technique for measurement at CT. *Radiology* 1999; **211:** 283–286.
11. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; **105:** 1135–1143.
12. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease: FRISC Study Group: Fragmin during instability in coronary artery disease. *N Engl J Med* 2000; **343:** 1139–1147.
13. Burke AP, Tracy RP, Kolodgie F, Malcom GT, Zieske A, Kutys R, et al. Elevated C-reactive protein values and atherosclerosis in sudden coronary death: Association with different pathologies. *Circulation* 2002; **105:** 2019–2023.
14. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation* 2002; **105:** 2462–2464.
15. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; **347:** 1557–1565.
16. Tornvall P, Olivercrona G, Karpe F, Hamsten A, Olivecrona T. Lipoprotein lipase mass and activity in plasma and their increase after heparin injection. *Arterioscler Thromb Vasc Biol* 1995; **15:** 1086–1093.
17. Kjeldsen K, Wanstrup J, Astrup P. Enhancing influence of arterial hypoxia on the development of atheromatosis in cholesterol-fed rabbits. *J Atherosclerosis* 1968; **8:** 835–845.
18. Heilin P, Lorenzen IB. Arteriosclerosis in rabbit aorta induced by systemic hypoxia: Boichemical and morphological studies. *Angiology* 1969; **20:** 1–12.
19. Guillemin K, Krasnow MA. The hypoxic response: Huffing and HIFing. *Cell* 1997; **89:** 9–12.
20. Schulz R, Hummel C, Heinemann S, Seeger W, Grimminger F. Serum levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea and severe nighttime hypoxia. *Am J Respir Crit Care Med* 2002; **165:** 67–70.
21. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med* 2005; **172:** 613–618.
22. Suzuki YJ, Jain V, Park AM, Day RM. Oxidative stress and oxidant signaling in obstructive sleep apnea and associated cardiovascular diseases. *Free Radic Biol Med* 2006; **40:** 1683–1692.
23. Hayashi M, Fujimoto K, Urushibata K, Imamura H, Kinoshita O, Kubo K. Nocturnal oxygen desaturation as a predictive risk factor for coronary restenosis after coronary intervention. *Circ J* 2005; **69:** 1320–1326.
24. Alam I, Lewis K, Stephens JW, Baxter JN. Obesity, metabolic syndrome and sleep apnoea: All pro-inflammatory states. *Obes Rev* 2007; **8:** 119–127.
25. Lavie L, Vishnevsky A, Lavie P. Evidence for lipid peroxidation in obstructive sleep apnea. *Sleep* 2004; **27:** 123–128.
26. Kobayashi J, Nohara A, Kawashiri MA, Inazu A, Koizumi J, Nakajima K, et al. Serum lipoprotein lipase mass: Clinical significance of its measurement. *Clin Chim Acta* 2007; **378:** 7–12.
27. McCarty MF. Modulation of adipocyte lipoprotein lipase expression as a strategy for preventing or treating visceral obesity. *Med Hypotheses* 2001; **57:** 192–200.
28. Ohike Y, Kozaki K, Iijima K, Eto M, Kojima T, Ohga E, et al. Amelioration of vascular endothelial dysfunction in obstructive sleep apnea syndrome by nasal continuous positive airway pressure–possible involvement of nitric oxide and asymmetric NG, NG-dimethylarginine. *Circ J* 2005; **69:** 221–226.

CHEST Original Research

SLEEP MEDICINE

Daytime Hypercapnia in Obstructive Sleep Apnea Syndrome*

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Background: **The pathogenesis of daytime hypercapnia ($PaCO_2$ ≥ 45 mm Hg) may be directly linked to the existence of obstructive sleep apnea syndrome (OSAS) *per se*, although only some patients with OSAS exhibit daytime hypercapnia.**

Objective: **To investigate the prevalence of daytime hypercapnia in patients with OSAS; the association of daytime hypercapnia and obesity, obstructive airflow limitation, restrictive lung impairment, and severity of sleep apnea; and the response to continuous positive airway pressure (CPAP) therapy in a subset of subjects.**

Methods: **The study involved 1,227 patients with OSAS who visited a sleep clinic and were examined using polysomnography. As for the response to CPAP therapy, the patients were considered good responders if their daytime $PaCO_2$ decreased ≥ 5 mm Hg and poor responders if it decreased < 5 mm Hg.**

Results: **Fourteen percent (168 of 1,227 patients) exhibited daytime hypercapnia. These patients had significantly higher body mass index (BMI) and apnea-hypopnea index (AHI) values compared with normocapnic patients, while percentage of predicted vital capacity (%VC) and FEV_1/FVC ratio did not differ between the two groups. Logistic regression analysis showed that only AHI was a predictor of daytime hypercapnia ($p < 0.0001$), while BMI ($p = 0.051$) and %VC ($p = 0.062$) were borderline predictors of daytime hypercapnia. Daytime hypercapnia was corrected in some patients (51%, 19 of 37 patients) with severe OSAS after 3 months of CPAP therapy.**

Conclusion: **The pathogenesis of daytime hypercapnia may be directly linked to sleep apnea in a subgroup of patients with OSAS.** ***(CHEST 2007; 132:1832–1838)***

Key words: continuous positive airway pressure; hypercapnia; hypoventilation; obesity; sleep apnea

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; FEV_1% = FEV_1/FVC ratio; OSA = obstructive sleep apnea; OSAS = obstructive sleep apnea syndrome; OHS = obesity hypoventilation syndrome; $P(A\text{-}a)O_2$ = alveolar-arterial oxygen pressure difference; SaO_2 = arterial oxygen saturation; %VC = percentage of predicted vital capacity

Obstructive sleep apnea (OSA) is characterized by intermittent closure of the pharyngeal airway during sleep, resulting in episodic hypoxemia and sleep disruption. To date, no single pathophysiologic mechanism has been identified. It is possible that the cause of OSA is multifactorial. Some patients with OSA syndrome (OSAS) exhibit daytime hypercapnia. The prevalence of daytime hypercapnia in these patients varies from 11 to 43% according to previous reports.[1–5] Mechanical impairment of the respiratory system due to obesity[5,6] and COPD[3,4] are known causes of daytime hypercapnia in patients with OSAS. It is generally accepted that there is no direct association of OSAS with hypercapnia.[7] However, in these patients daytime $PaCO_2$ may be an end product of complex factors including severity of sleep apnea; obesity; daytime PaO_2; chemosensitivity; respiratory mechanics, including chronic airflow limitation; respiratory muscle strength; metabolic rate; daytime symptoms of sleepiness; endocrine modulation; cardiac function; face, nose, and cranial bony structure (cephalometry); and others. Thus, daytime hypercapnia may exist without obesity and/or airflow limitation.

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The hypothesis of the present study was that the levels of daytime $PaCO_2$ in patients with OSAS are partly influenced by the degree of OSAS, as expressed by the apnea-hypopnea index (AHI). Since continuous positive airway pressure (CPAP) therapy can reverse CO_2 retention in some patients with hypercapnic OSAS,[8] the pathogenesis of daytime hypercapnia may be directly linked to the existence of OSAS *per se*, although only some patients with OSAS exhibit daytime hypercapnia.

The prevalence of OSAS in Asian countries has recently been reported[9–11]; however, no such epidemiologic studies have been performed in Japan. Obesity appears to be a common and important risk factor for sleep-disordered breathing in previous studies done in Western countries. However, the evaluation of daytime hypercapnia in patients with OSAS has been limited in Asian countries.[12] Ethnic differences between Asian and Western populations might influence the pathogenesis of OSAS, which might limit the relevance of this study, but at the same time emphasize the heterogeneity of OSAS. Therefore, the aim of the present study was first to assess the prevalence of daytime hypercapnia in a large group of patients who visited a sleep clinic; then to evaluate a possible association between daytime hypercapnia and obesity, obstructive airflow limitation, restrictive lung impairment, and severity of sleep apnea; and finally to examine the response to CPAP therapy in a subgroup of patients.

Materials and Methods

Subjects

The subjects of this study were 1,407 consecutive patients with clinical symptoms of sleep apnea who sought treatment from January 2002 to December 2005 and were examined using polysomnography. The patients were recruited from the sleep clinic where they had been referred for further investigation regarding snoring or possible OSAS. Presenting symptoms were either snoring or daytime sleepiness or both. The subjects were all Japanese.

Patients who exhibited Cheyne-Stokes breathing with central sleep apnea (n = 4), those receiving cardiac drugs (digitalis and β-blockers) due to heart failure (n = 2), and patients with restrictive diseases such as kyphoscoliosis (n = 2) and diffuse interstitial fibrosis (n = 2) were excluded from this study. OSAS was established on the basis of clinical and polysomnographic criteria. AHI was calculated as the sum of sleep-disordered breathing events. In addition to clinical symptoms, an AHI > 5 events per hour was also used as a selection criterion of OSAS. The patients (n = 1,399) were distributed into two groups according to AHI (AHI ≥ 5/h, n = 1,227; AHI < 5/h, n = 172). Patients with hypercapnic OSAS who satisfied the criteria of obesity hypoventilation syndrome (OHS) were included in this study if their body mass index (BMI) was ≥ 30 kg/m^2, which indicated obesity.

Pulmonary function tests were performed to determine vital capacity, FEV_1, and FVC using a standard spirometer (Fudac-60; Fukuda Denshi; Tokyo, Japan). Arterial blood was drawn with the patient resting in the supine position between 9:00 AM and 10:00 AM the morning after the sleep study to measure PaO_2 and $PaCO_2$ during room air breathing in a blood gas analyzer (Model ABL555; Radiometer; Tokyo, Japan). The supine position was selected when arterial blood was obtained because polysomnography was started with the patient in that position. Hypercapnia was defined as $PaCO_2 \geq 45$ mm Hg, and normocapnia was defined as $PaCO_2 < 45$ mm Hg. The ideal alveolar gas equation was used to calculate alveolar Po_2 so that the alveolar-arterial oxygen pressure difference ($P[A\text{-}a]O_2$) could be calculated. The study protocol was approved by the Research Ethics Committee of Chiba University School of Medicine, and all patients gave their informed consent prior to the study.

Polysomnography

Overnight polysomnography (P Series or E Series Polygrapher; Compumedics; Melbourne, Australia) was performed between 9:00 PM and 6:00 AM. Polysomnography consisted of continuous polygraphic recording from surface leads for EEG; electrooculography; electromyography; ECG; thermistors for nasal and oral airflow; thoracic and abdominal impedance belts for respiratory effort; pulse oximetry for oxyhemoglobin level; tracheal microphone for snoring; and sensor for the position during sleep. Respiratory events were basically scored according to American Academy of Sleep Medicine criteria: apnea was defined as complete cessation of airflow lasting ≥ 10 s; hypopnea was defined as a ≥ 50% reduction of airflow from baseline for 10 s that was associated with an oxygen desaturation > 3% or an arousal. Polysomnograms were staged manually according to standard criteria.[13,14] Severity of OSAS was determined based on the AHI, and lowest and average values of arterial oxygen saturation (Sao_2) during sleep.

CPAP Treatment

Arterial blood gas analysis was re-evaluated 3 months after the initiation of CPAP therapy (AutoSet; ResMed; Sydney, Australia). The subjects were consecutive hypercapnic OSAS patients (n = 55) examined using polysomnography from January to December 2005 with AHI values > 40/h. Thirty-seven patients could tolerate CPAP treatment and were successfully treated for 3 months with CPAP. CPAP tolerance was considered adequate when the system counter indicated that the patient was using the

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device for at least 4 h at night during at least 70% of the follow-up nights. Nonadherence to CPAP therapy was observed in 18 patients.

Statistical Analysis

The results are expressed as mean ± SE. All clinical parameters are summarized by descriptive statistics. The Mann-Whitney *U* test was used to compare age, BMI, pulmonary functions, and sleep parameters between two groups of patients. Proportions were compared using the χ^2 test. Linear regression analysis was performed to examine the association between two parameters. The patients were distributed into five groups according to BMI (18.5 to 25 kg/m^2, 25 to 30 kg/m^2, 30 to 35 kg/m^2, 35 to 40 kg/m^2, and > 40 kg/m^2), percentage of predicted vital capacity (%VC) [70%, 70 to 80%, 80 to 90%, 90 to 100%, and > 100%]; FEV_1/FVC ratio (FEV_1%) [≤ 60%, 60 to 70%, 70 to 80%, 80 to 90%, and > 90%]; and AHI (5 to 15/h, 15 to 30/h, 30 to 45/h, 45 to 60/h, and > 60/h). Groups 1 to 4 were defined according to AHI levels. Levels of BMI were classified according to World Health Organization criteria.[15] Analysis of variance was used to compare levels among the groups. This was followed by a *post hoc* Bonferroni multiple-comparison test. Logistic regression analysis was applied to predict daytime hypercapnia using the category classification of BMI, %VC, FEV_1%, and AHI as potential predictors. AHI was a parameter for the degree of sleep apnea, BMI for obesity, %VC for obesity-related impairment of lung function, and FEV_1% for obstructive impairment of lung function; p values < 0.05 were considered statistically significant.

Results

Patients With OSAS vs Without OSAS

The male to female ratio in patients with OSAS was approximately 8, while it was approximately 3 in non-OSAS patients ($p < 0.01$, χ^2 test). Mean age was higher in the OSAS group. FEV_1% and PaO_2 values were lower, while BMI and P(A-a)O_2 values were higher in the OSAS group. $PaCO_2$ values were not statistically different between two groups (Table 1).

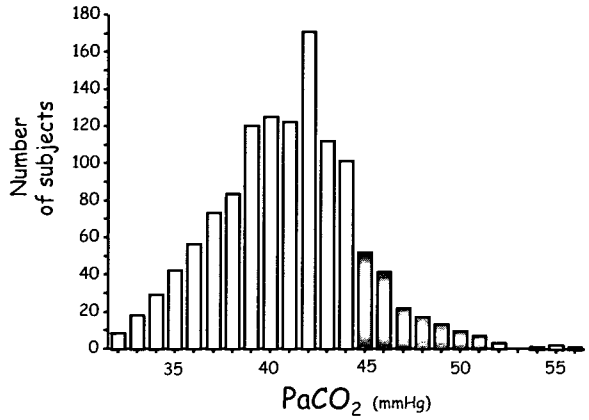

FIGURE 1. Distribution of patients according to $PaCO_2$. Open and closed bar show patients without and with hypercapnia, respectively.

Patients With Hypercapnia vs Normocapnia

Fourteen percent (168 of 1,227 patients) of those with OSAS showed daytime hypercapnia ($PaCO_2$ ≥ 45 mm Hg) [Fig 1]. Fourteen percent of men and 8% of women (no significant difference in gender) exhibited daytime hypercapnia. %VC was slightly lower in hypercapnic patients compared with normocapnic patients, while FEV_1% was similar between the two groups. PaO_2 was significantly lower in hypercapnic patients. P(A-a)O_2 values were similar between the two groups. BMI and AHI were significantly higher in hypercapnic patients (Table 2).

Predictive Factors for Daytime Hypercapnia

Age and gender distribution differed between the OSAS group and the non-OSAS group (Table 1). However, no gender difference in $PaCO_2$ levels was observed in either group. In addition, no significant

Table 1—*Characteristics of Patients With OSAS vs Without OSAS

Variables	AHI ≥ 5/h (n = 1,227)	AHI < 5/h (n = 172)	p Value
Men/women, No.	1,091/136	130/42	< 0.01
Age, yr	49.9 ± 0.8	45.3 ± 1.1	< 0.01
%VC	100.7 ± 0.5	100.2 ± 1.5	NS
FEV_1%	82.3 ± 0.2	84.5 ± 0.5	< 0.01
PaO_2, mm Hg	80.8 ± 0.3	87.8 ± 0.7	< 0.01
$PaCO_2$, mm Hg	41.3 ± 0.1	40.8 ± 0.2	NS
P(A-a)O_2, mm Hg	11.1 ± 0.7	17.6 ± 0.3	< 0.01
AHI, events/h	42.0 ± 0.8	2.2 ± 0.1	< 0.01
Lowest SaO_2, %	74.5 ± 0.3	88.4 ± 0.4	< 0.01
Average SaO_2, %	90.9 ± 0.2	96.5 ± 0.1	< 0.01
BMI, kg/m^2	28.6 ± 0.2	25.0 ± 0.4	< 0.01

*Data are presented as mean ± SE unless otherwise indicated. NS = not significant.

Table 2—*Characteristics of Patients With Hypercapnia vs Normocapnia

Variables	$PaCO_2$ < 45 mm Hg (n = 1,059)	$PaCO_2$ ≥ 45 mm Hg (n = 168)	p Value
Men/women, No.	935/124	156/12	NS
Age, yr	50.0 ± 0.4	49.3 ± 1.0	NS
%VC	100.8 ± 0.5	97.5 ± 1.5	< 0.05
FEV_1/FVC, %	82.9 ± 0.2	82.5 ± 0.5	NS
PaO_2, mm Hg	81.9 ± 0.3	73.9 ± 0.8	< 0.01
$PaCO_2$, mm Hg	40.4 ± 0.1	47.4 ± 0.2	< 0.01
P(A-a)O_2, mm Hg	17.7 ± 0.4	16.9 ± 0.7	NS
AHI, events/h	39.3 ± 0.8	58.8 ± 2.0	< 0.01
Lowest SaO_2, %	75.6 ± 0.3	67.5 ± 1.0	< 0.01
Average SaO_2, %	91.5 ± 0.2	86.9 ± 0.6	< 0.01
BMI, kg/m^2	28.2 ± 0.2	31.1 ± 0.6	< 0.01

*Data are presented as mean ± SE unless otherwise indicated. See Table 1 for expansion of abbreviation.

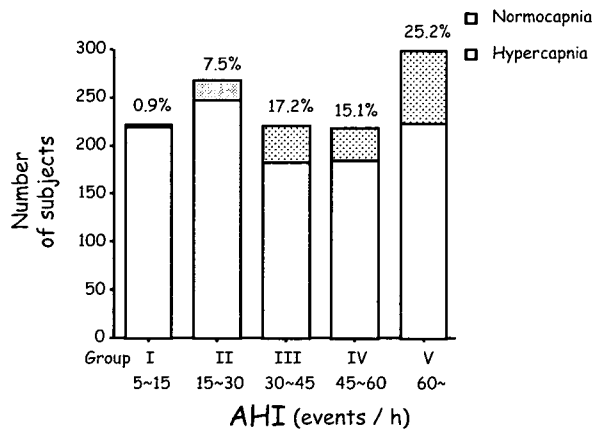

FIGURE 2. Prevalence of daytime hypercapnia in patients with OSAS distributed according to AHI.

correlation was observed between age and $PaCO_2$ levels in patients with OSAS.

Hypoxemia (PaO_2) is a predictive factor for daytime hypercapnia when alveolar hypoventilation is the main cause of hypercapnia. In the present population, alveolar PO_2 was a definite predictive factor for hypercapnia because $P(A\text{-}a)O_2$ values were similar in the two groups. Therefore, the predictive values of BMI, $FEV_1\%$, %VC, and/or AHI for daytime hypercapnia were examined. Univariate analysis showed that $PaCO_2$ significantly correlated with AHI, BMI, and %VC, while $PaCO_2$ did not correlate with $FEV_1\%$. The prevalence of daytime hypercapnia differed according to BMI, %VC, and AHI (Fig 2) but not according to $FEV_1\%$. The logistic regression analysis for prediction of daytime hypercapnia showed that only AHI values were predictors for the presence of daytime hypercapnia, while BMI and %VC were borderline predictors and $FEV_1\%$ was not a predictor (Table 3).

Table 3—*Univariate Analysis of $Paco_2$ Values and Multivariate Analysis of Potential Predictors of Daytime Hypercapnia ($Paco_2 \geq 45$ mm Hg)

	Univariate		Multivariate	
Variables	*r* Value	p Value	p Value	Relative Risk (95% CI)
AHI, events/h	0.21	< 0.0001	< 0.0001	
5 to 15				1.00
15 to 30				4.72 (1.59–14.01)
30 to 45				11.74 (4.08–33.77)
45 to 60				10.27 (3.53–29.86)
> 60				16.26 (5.69–46.4)
BMI	0.16	< 0.0001	0.051	
%VC	−0.06	0.03	0.062	
$FEV_1\%$	0.03	0.38	0.558	

*CI = confidence interval.

Because only AHI values were predictive for the presence of daytime hypercapnia, anthropometric, blood gas, and sleep study data were analyzed in patients with OSAS distributed according to AHI (Table 4). $PaCO_2$ in group 5 was the highest ($p < 0.05$) among the five groups. $PaCO_2$ in group 4 was significantly higher than that in group 1 (Fig 3). BMI in group 5 was the highest ($p < 0.05$) among the five groups. BMI in group 4 was significantly ($p < 0.05$) higher than that in groups I and II, and BMI in group 3 was significantly ($p < 0.05$) higher than that in group 1 (Fig 4).

In the present study, we used logistic regression analysis to predict daytime hypercapnia. However, when we used multiple regression analysis, the results were similar to those obtained using AHI as the only statistically significant variable to predict hypercapnia.

Responses of $Paco_2$ to CPAP Therapy

Based on the response of $PaCO_2$ to CPAP therapy, patients were distributed into good responders (n = 19) showing a decrease of $PaCO_2$ by 5 mm Hg; poor responders (n = 18) showing a decrease of < 5 mm Hg after 3 months on CPAP therapy; and nonadherents (n = 18) [Table 5]. Sex distribution, age, pulmonary function (%VC, $FEV_1\%$), arterial blood gas analyses (PaO_2, $PaCO_2$), and AHI did not differ significantly between good and poor responders. BMI was lower in good responders than in poor responders. The degree of sleep desaturation was more severe in poor responders than in good responders. BMI decreased significantly after 3 months of CPAP therapy in good and poor responders ($p < 0.05$). Nonadherents to CPAP therapy were older, not obese, and had milder degree of hypercapnia and sleep apnea (Table 5).

DISCUSSION

The present study showed that 13.7% (168 of 1,227 patients) of a relative large group of patients with OSAS examined using polysomnography had daytime hypercapnia. Patients with daytime hypercapnia had significantly higher BMI and AHI, and lower PaO_2 and %VC values compared with normocapnic patients, while $FEV_1\%$ did not differ between the two groups. Logistic regression analysis showed that only AHI was a predictor of daytime hypercapnia, although this index was not independent of BMI. Obesity partly contributed to the presence of daytime hypercapnia in our patients, suggesting that BMI acts as a modifier. In some patients with OSAS, daytime hypercapnia responded to CPAP therapy for 3 months. These data suggest that the pathogenesis of daytime hypercapnia might be directly linked to OSAS *per se* in a subset of patients with OSAS.

Table 4—*Anthropometric, Blood Gas, and Sleep Study Data of OSAS Patients Distributed According to AHI**

Variables	Group 1, AHI ≥ 5 to < 15/h (n = 222)	Group 2, AHI ≥ 15 to < 30/h (n = 268)	Group 3, AHI ≥ 30 to < 45/h (n = 221)	Group 4, AHI ≥ 45 to < 60/h (n = 218)	Group 5, AHI ≥ 60/h (n = 298)
Men/women, No.	184/38	229/39	207/14	204/14	267/31
Age, yr	50.6 ± 0.9	50.8 ± 0.8	51.6 ± 0.8	50.9 ± 0.9	46.6 ± 0.7†
%VC, %	107.4 ± 1.1	106.6 ± 1.1	107.4 ± 1.2	106.0 ± 1.3	101.7 ± 1.0†
FEV_1%, %	83.5 ± 0.4	82.7 ± 0.4	81.9 ± 0.4	82.6 ± 0.4	83.1 ± 0.3
PaO_2, mm Hg	86.2 ± 0.6	82.5 ± 0.6†	81.8 ± 0.6†	80.1 ± 0.7†	74.8 ± 0.6†
$PaCO_2$, mm Hg	40.4 ± 0.2	40.7 ± 0.2	41.2 ± 0.3	41.4 ± 0.3†	42.6 ± 0.2†
$P(A\text{-}a)O_2$, mm Hg	13.3 ± 0.6	16.5 ± 0.6†	16.6 ± 0.6†	18.2 ± 0.7†	22.0 ± 0.6†
BMI, kg/m^2	25.5 ± 0.3	27.1 ± 0.3†	27.6 ± 0.3†	28.6 ± 0.4†	32.9 ± 0.4†

*Data are presented as mean ± SE unless otherwise indicated.
†$p < 0.05$ vs group 1.

The pathogenesis of OSAS and/or hypoventilation (daytime hypercapnia) may differ between Western and Asian populations including Japan because different genetic factors may contribute to the development of these disorders.[16] In the present study, mean AHI in the normocapnic and hypercapnic OSAS groups was 28.2/h and 31.1/h, respectively, which was lower than that found in previous reports[1–8] from Western countries. In addition, the level of hypercapnia was relatively mild (mean, 47.4 mm Hg) in our cohort, and the proportion of patients with a $PaCO_2 \geq 50$ mm Hg was only 13.7% (23 of 168 hypercapnic patients) [Fig 5]. Therefore, it is unclear whether the results of this study could be explored to white patients.

Daytime hypercapnia was corrected in approximately half of our patients treated with CPAP. A limitation of this result was that the patients who tolerated this therapy were not representative of the entire hypercapnic OSAS group because their AHI and BMI values were higher than those observed in the whole group of hypercapnic patients. Another limitation was that we did not measure the time course of $PaCO_2$ changes during the usage of auto-CPAP. However, our result was similar to that reported by Rapoport et al,[8] who found that four patients became eucapnic within 2 weeks of CPAP therapy, while four others remained hypercapnic, although the subjects were morbid obese. Rapoport et al[8] proposed that two separate mechanisms exist for hypercapnia in OSAS. The pathogenetic mechanisms of daytime hypercapnia in patients with OSAS who responded to CPAP therapy may be a balance between ventilation while awake and hypoventilation due to repetitive sleep apnea; thus, the effects of sleep apnea on daytime hypercapnia could be abolished by CPAP therapy. Han et al[17] reported that $PaCO_2$ had fallen to < 45 mm Hg and hypoxic and hypercapnic chemosensitivity had increased 4 to 6 weeks after CPAP therapy, without body weight

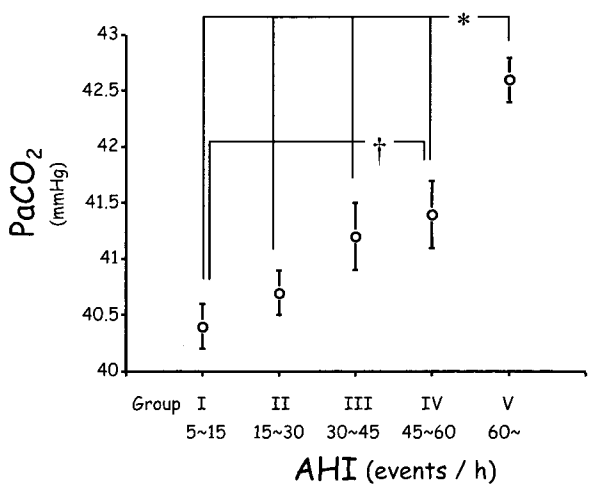

FIGURE 3. $PaCO_2$ values in patients with OSAS distributed according to AHI. *$p < 0.05$ vs every other group. †$p < 0.05$ vs group 1.

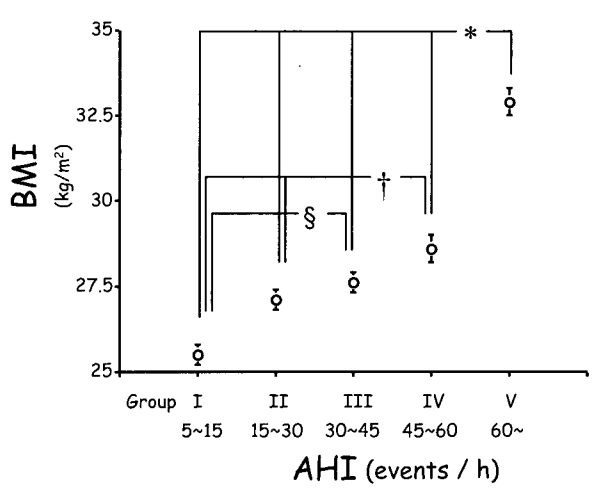

FIGURE 4. BMI in patients with OSAS distributed according to AHI. *$p < 0.05$ vs every other group. †$p < 0.05$ vs groups 1 and 2. §$p < 0.05$ vs group 1.