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 $\geq$ 130 mm Hg and/or a diastolic BP $\geq$ 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 $\geq$ 150 mg/dL and/or HDL-C $\leq$ 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.

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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.

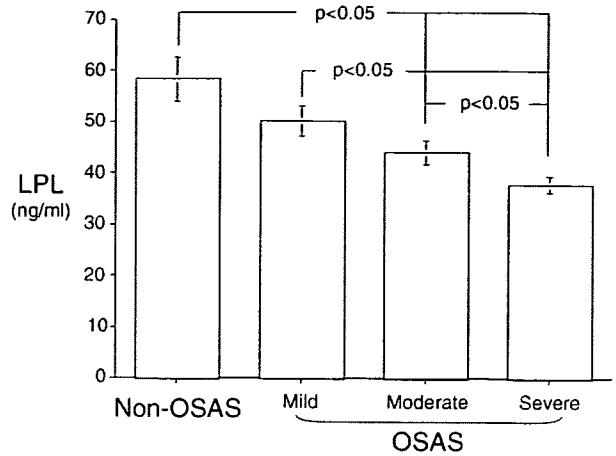

Fig 1. Serum concentrations of lipoprotein lipase (LPL) in patients with mild, moderate and severe obstructive sleep apnea syndrome (OSAS). LPL concentrations in severe OSAS group are significantly lower compared with those in mild and moderate OSAS group. Values are mean±standard errors.

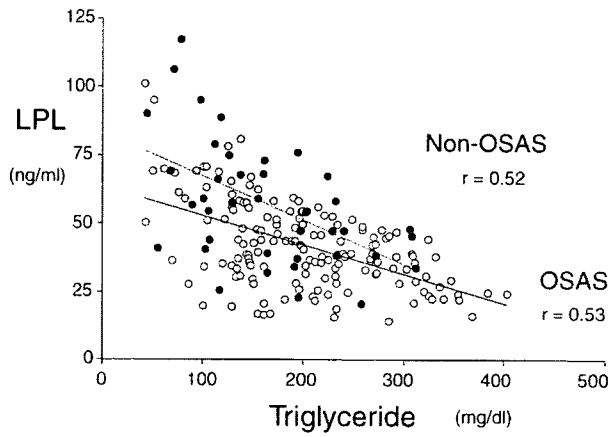

Fig 2. Relationship between serum concentrations of triglycerides (TG) and lipoprotein lipase (LPL) in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS. The solid and dashed regression lines describe the relationship between serum LPL concentrations and TG in OSAS and non-OSAS patients, 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).

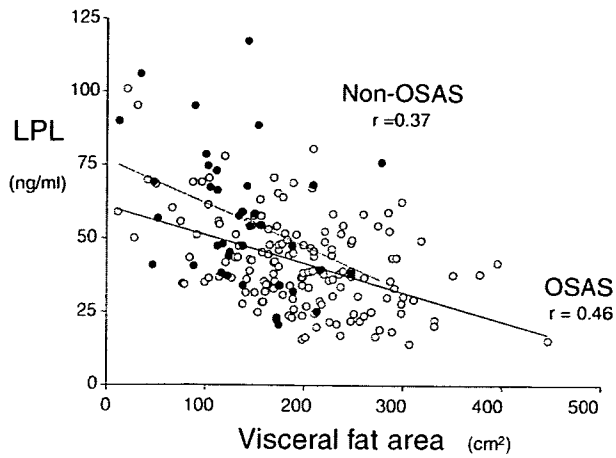

Fig 3. Relationship between visceral fat area (VFA) and serum concentrations of lipoprotein lipase (LPL) in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS. The solid and dashed regression lines describe the relationship between serum LPL concentrations and VFA in OSAS and non-OSAS 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).

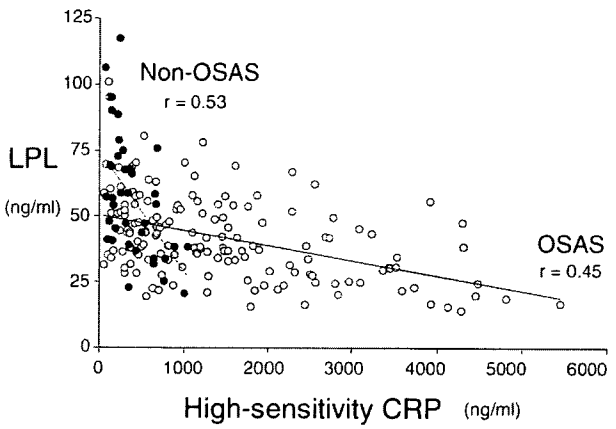

Fig 4. Relationship between serum concentrations of lipoprotein lipase (LPL) and C-reactive protein (CRP) in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS. The solid and dashed regression lines describe the relationship between serum LPL concentrations and CRP in OSAS and non-OSAS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

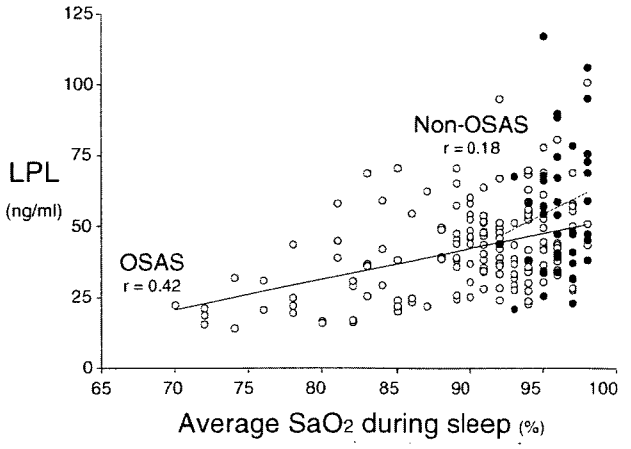

Fig 5. Relationship between average SaO_2 during sleep and serum concentrations of lipoprotein lipase (LPL) in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS. The solid and dashed regression lines describe the relationship between serum LPL concentrations and average SaO_2 during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

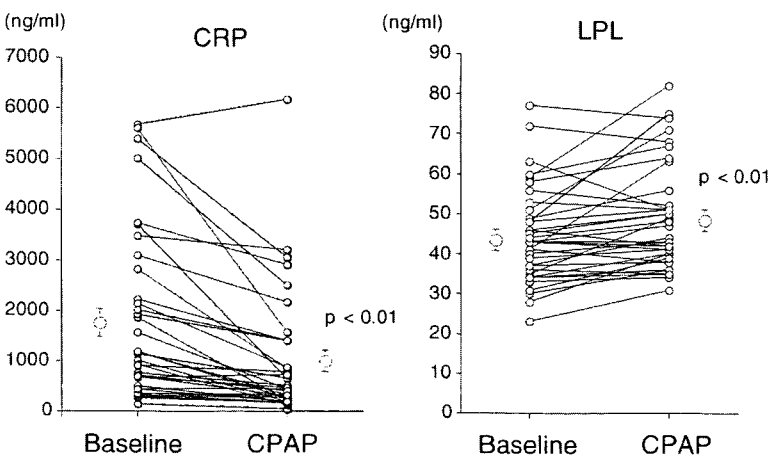

Fig 6. Effects of nasal continuous positive airway pressure (CPAP) on blood concentrations of high-sensitivity C-reactive protein (CRP) and lipoprotein lipase (LPL) in patients with obstructive sleep apnea syndrome (OSAS) (n=36). CRP decreased and LPL increased 3 months after treatment with nasal CPAP. 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? 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?[1] 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.

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CHEST Original Research

SLEEP MEDICINE

Daytime Hypercapnia in Obstructive Sleep Apnea Syndrome*

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Background: **The pathogenesis of daytime hypercapnia ($PaCO_2 \geq 45$ 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 $\geq$ 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 1.1 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.

For editorial comment see page 1729

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 $P(A\text{-}a)O_2$ values were higher in the OSAS group. $PaCO_2$ values were not statistically different between two groups (Table 1).

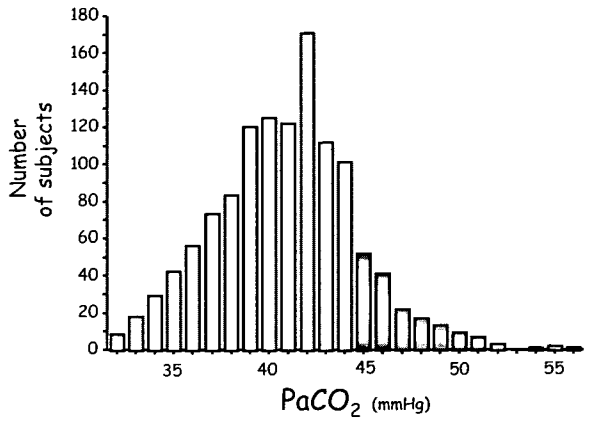

FIGURE 1. Distribution of patients according to $PaCO_2$. Open and closed bar show patients without and with hypercapnia, respectively.

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. $P(A\text{-}a)O_2$ 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
$P(A\text{-}a)O_2$, 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
$P(A\text{-}a)O_2$, 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.

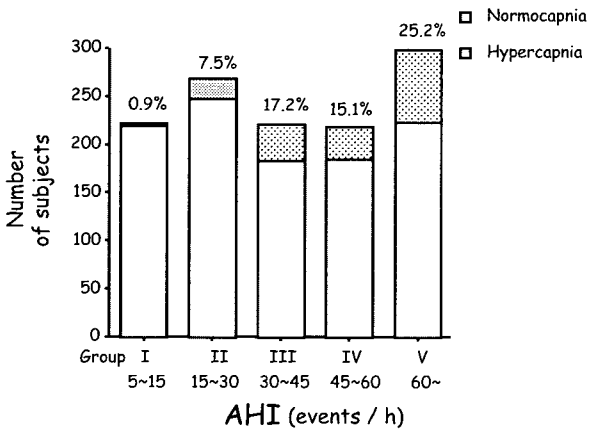

FIGURE 2. Prevalence of daytime hypercapnia in patients with OSAS distributed according to AHI.

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

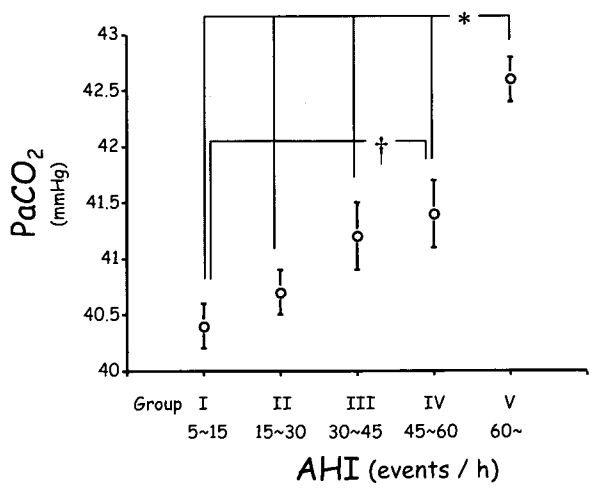

FIGURE 3. $PaCO_2$ values in patients with OSAS distributed according to AHI. *$p < 0.05$ vs every other group. †$p < 0.05$ vs group 1.

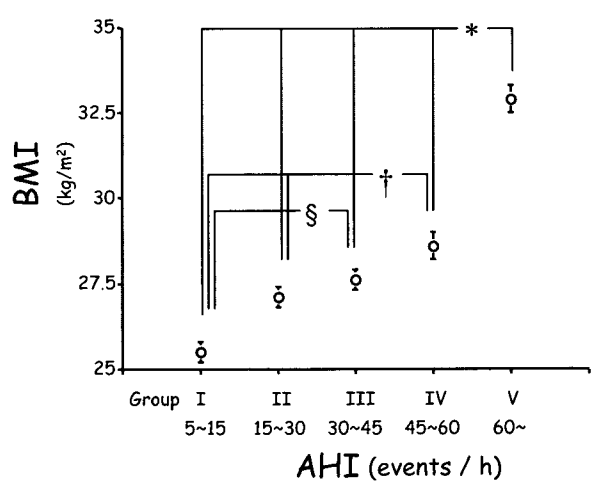

FIGURE 4. BMI in patients with OSAS distributed according to AHI. *$p < 0.05$ vs every other group. †$p < 0.05$ vs groups 1 and 2. §$p < 0.05$ vs group 1.

Table 5—*Good Responders, Poor Responders, and Nonadherents to CPAP Therapy**

Variables	Good Responders (n = 19)	Poor Responders (n = 18)	Nonadherents (n = 18)
Men/women, No.	19/0	15/3	15/3
Age, yr	44.4 ± 2.4	48.1 ± 3.2	63.8 ± 2.3§
%VC	97.6 ± 4.8	90.9 ± 3.0	94.0 ± 6.1
FEV_1/FVC, %	84.3 ± 1.3	86.4 ± 1.4	79.4 ± 1.5§
PaO_2, mm Hg	71.0 ± 2.4	65.3 ± 2.7	76.8 ± 1.5§
$PaCO_2$, mm Hg	48.8 ± 0.6	49.2 ± 0.8	47.2 ± 0.5§
AHI, events/h	61.6 ± 6.5	63.2 ± 6.9	51.2 ± 1.7§
Lowest SaO_2, %	63.6 ± 3.0	53.9 ± 2.9	68.6 ± 2.1§
Average SaO_2, %	83.8 ± 1.8	79.1 ± 2.3	90.1 ± 0.7§
BMI before therapy, kg/m^2	32.5 ± 1.1	42.4 ± 2.7†	26.1 ± 1.0§
BMI after therapy, kg/m^2	31.9 ± 1.1†	42.0 ± 2.8†‡	26.0 ± 1.1§

*Data are presented as mean ± SE unless otherwise indicated.
†$p < 0.05$ compared with BMI before CPAP therapy.
‡$p < 0.05$ compared with good responders.
§$p < 0.05$ compared with poor responders.

changes, in hypercapnic patients with OSAS (n = 5), suggesting that depressed chemoresponsiveness plays a role independent of obesity in the development of CO_2 retention in some of these patients; and it may be a response to sleep-disordered breathing. In the present study, one possible pathomechanism of hypercapnia in good responders may be upper airway resistance because in this group BMI was slightly lower than in poor responders and upper airway resistance was easily ameliorated after CPAP therapy. However, daytime $PaCO_2$ levels in OSAS patients may be an end product of a complex conglomerate, influenced by factors such as severity of sleep apnea; obesity; daytime PaO_2; chemosensitivity; respiratory mechanics; respiratory muscle strength; metabolic rate; daytime symptoms of sleepiness; endocrine modulation; cardiac function; and face, nose, and cranial bony structure (cephalometry). Several undefined pathomechanisms of daytime hypercapnia may exist in patients with OSAS, whose $PaCO_2$ did not decrease after CPAP therapy.

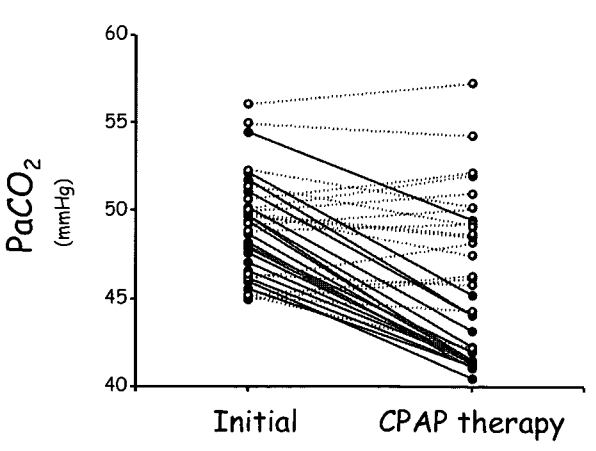

FIGURE 5. The responses of $PaCO_2$ to CPAP therapy. Closed circle with solid line represents good responder, while open circle with dashed line represents poor responder.

Our study did not focus on the causal relationship between OSAS and OHS. It has been reported that OHS can occur without significant OSAS[18] (*ie*, OHS patients could exhibit nocturnal hypoventilation unrelated to upper airway obstruction).[8] Forty-three percent (73 of 168 patients) of our hypercapnic patients with OSAS satisfied the criteria of OHS, when obesity was defined as BMI ≥ 30 kg/m^2. In other words, more than half of hypercapnic patients with OSAS were not obese based on Western criteria. In addition, nocturnal desaturation in our hypercapinc patients with OSAS was mostly due to upper airway obstruction, partly because the degrees of daytime hypercapnia and obesity were mild compared with those of previous reports from Western countries.[1–5] There may exist some ethnic differences regarding the characteristics of OHS between Japan and Western countries. In the present study, logistic regression analysis showed that BMI could be a predictor of daytime hypercapnia ($p = 0.051$), suggesting that obesity may have partly contributed to the presence of daytime hypercapnia in our patients. Therefore, the predictive value of AHI may not be independent of BMI; rather, BMI could be a modifier.

Our data showed that chronic airflow limitation was not a prerequisite for the presence of daytime hypercapnia.[6] We did not intend to exclude any patient suspected of COPD in our study, and no patients showed an $FEV_1\% < 60\%$. Only 3.5% of the patients with hypercapnia (6 of 168 patients) had mild obstructive airflow limitation ($FEV_1\% \geq 60\%$ to $< 70\%$). Overlap syndrome (the association of OSAS with COPD)[19] may be rare in the Japanese population. However, a relationship of obstructive impairment with hypercapnia in patients with OSAS cannot be ruled out because our study population was a convenient sample of patients attending a sleep clinic.

The poor responders to CPAP therapy showed a decrease of AHI after receiving auto-CPAP therapy, and their clinical conditions (the degree of daytime sleepiness decreased) improved, although the levels of daytime $PaCO_2$ did not decrease ≥ 5 mm Hg. Current therapeutic options available for hypoventilation syndrome include bilevel pressure support ventilation with or without supplemental oxygen.[20] A future challenge is to investigate whether poor responders to CPAP therapy would respond to bilevel pressure support ventilation.

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Part 2　睡眠時無呼吸症候群の病態・合併症

9. 女性の睡眠時無呼吸

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☞ *Point*

- 疫学的調査による睡眠時無呼吸症候群の有病率の性差は、男性：女性は2～4：1である。一方、睡眠時無呼吸症候群の患者数は、男性：女性は5～10：1であり、疫学調査との解離がある。
- 睡眠時無呼吸症候群は一般に男性優位の病態であるが、その性差の機序としては、肥満を含む解剖学的な性差と、性ホルモン・呼吸調節機能を含む機能的な性差の双方が関与している可能性がある。
- 睡眠時無呼吸症候群における増悪因子としての肥満には、全身的な肥満と局所的な肥満がある。局所的な肥満としては、頸部脂肪と腹部脂肪を発症機序の点から考慮する必要がある。
- 男性のほうが、一般に頸周り・腹周りは太いが、身長で補正すると性差は消失する。BMIに有意差のない男女の睡眠時無呼吸症候群症例を比較したとき、男性の方が無呼吸低呼吸指数（AHI）は高値であった。
- 身長で補正した頸部周囲径・腹部周囲径が男女で有意差がない症例を比較したときでも、男性の睡眠時無呼吸症候群症例のほうがAHIは高値であった。同程度の局所肥満が存在するとき、男性のほうが睡眠時無呼吸症候群の程度は強いことが示唆された。逆に考えると、女性であることは、睡眠時無呼吸症候群に対して防御的に作用しているのかもしれない。
- 閉経前後の女性睡眠時無呼吸症候群症例の検討で、閉経前の群の方がBMIは高値であったが、AHIで評価した睡眠時無呼吸症候群の程度は同様であった。女性ホルモンの存在は、睡眠時無呼吸症候群に防御的に作用している可能性が示唆された。

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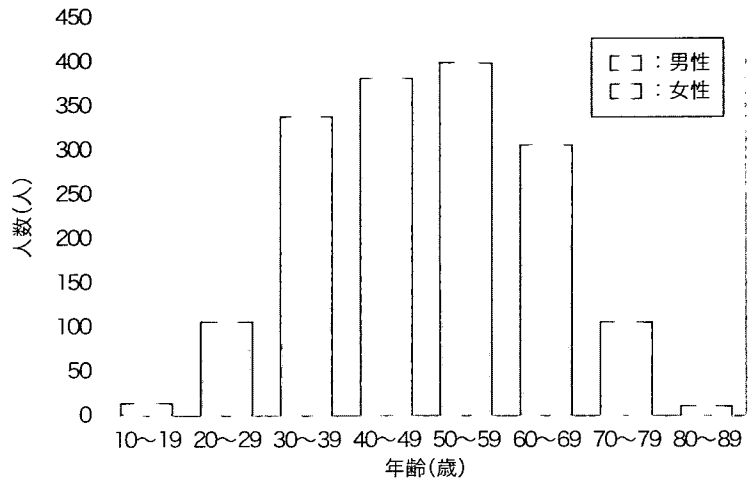

図1　睡眠呼吸障害にてPSGを受けた患者数の性差

睡眠時無呼吸症候群の性差

睡眠時無呼吸症候群*1は疫学的にも臨床的にも男性優位の疾患であるとされている。睡眠クリニック・外来受診患者における、睡眠呼吸障害*2の男女比は、およそ10：1であると諸外国では報告されている[1-3]。日本では、これほどの男女性はないようであるが、これに近い数字であると推定される。われわれの経験した、睡眠呼吸障害にて受診して睡眠ポリグラフ検査(polysomnography；PSG)を受けた患者(n＝1,657)の男女比は、およそ6：1であった(図1)。医療機関を受診した睡眠呼吸障害の患者さんの多くは、昼間の眠気を伴っており、この眠気が社会生活上で支障があるという場合が多い。一般的に、女性の場合は眠気があっても、医療機関への受診率が低いことが理由の一部となり、このような大きな男女差が生じているといわれているが、何故このような性差があるのかは現状では不明といわざるをえない。個人的な印象では、睡眠の量的・質的不足に対して、概して女性の方が眠気に対して抵抗性がある(眠気を生じにくい)気がする。

一方、一般住民における疫学調査では、睡眠呼吸障害/睡眠時無呼吸症候群の男女比は、2：1から4：1であるとされている[4-6]。この男女差の要因としては、解剖学的な差と機能的な差が考えられる(表1)。

女性ホルモンの睡眠時無呼吸への影響

女性ホルモンが、睡眠時無呼吸の発症に防御的に関与しているとすれば、更年期後に無呼吸は増加するはずである[7]。われわれの経験した睡眠呼吸障害患者数は、更年期後(n＝148)のほうが、更年期前(n＝86)の約1.7倍であった。もちろん、この数字で、更年期後に睡眠呼吸障害が増加するとはいえない。これまでの研究では、睡眠呼吸障害の有病率は更年期後に増加するという結果が多いが[5,8,9]、増加しないという結果もある[10]。更年期前後での変化として考慮すべきは、ホルモン変化という機能的な変化だけでなく、加齢・老化による解剖学的な変化も生じているかもしれない。

睡眠呼吸障害に対して、女性ホルモンレベルを増加させるホルモン補充療法(hormonal replacement therapy；HRT)の影響に関する研究でも、効果ありという報告[11,12]と、効果なしという報告[13,14]がある。

＊1…睡眠時無呼吸症候群(sleep apnea syndrome)
睡眠呼吸障害があり、それに伴う自覚症状(傾眠、など)・他覚所見(心血管系の合併症)を伴う場合に定義される。

＊2…睡眠呼吸障害(sleep disordered breathing)
睡眠中に呼吸努力関連覚醒反応(respiratory effort-related arousal；RERA)を含む呼吸異常が、1時間あたり5回以上出現する場合に睡眠呼吸障害とする。睡眠時無呼吸症候群に伴う自覚症状(眠気、など)のない場合も含んでいる。

1)解剖学的な性差(structural differences in upper airway dimensions)
1. 横断面での差：顔面形態(骨構造)に性差があるかもしれない、咽頭腔周囲の軟部組織圧(気道に対する圧力、脂肪沈着の程度(body fat distribution)に性差があるかもしれない。
2. 縦断面での差：男性のほうが、頭から足の方向に頸が長ければ、無呼吸は起こりやすいかもしれない。
2)機能的な性差
1. 性ホルモンの差(hormonal differences)：女性ホルモンの存在は、気道閉塞に対して防御的に作用している可能性がある。男性ホルモンの作用は必ずしも明らかでない。
2. 神経学的反応(呼吸調節機能)の性差(abnormalities in upper airway mechanics、differences in control of breathing)：気道狭窄(気流制限：flow limitation)に対して、それを感知したときの換気増加反応に性差があるかもしれない。閉塞性無呼吸から回復した後の換気増大は呼吸調節系の不安定を引き起こすと考えられるが、この反応に性差があるかもしれない。無呼吸に伴う低酸素血症・高炭酸ガス血症に対する反応性に性差があるかもしれない。

表1　睡眠時無呼吸症候群における性差に関係する要因

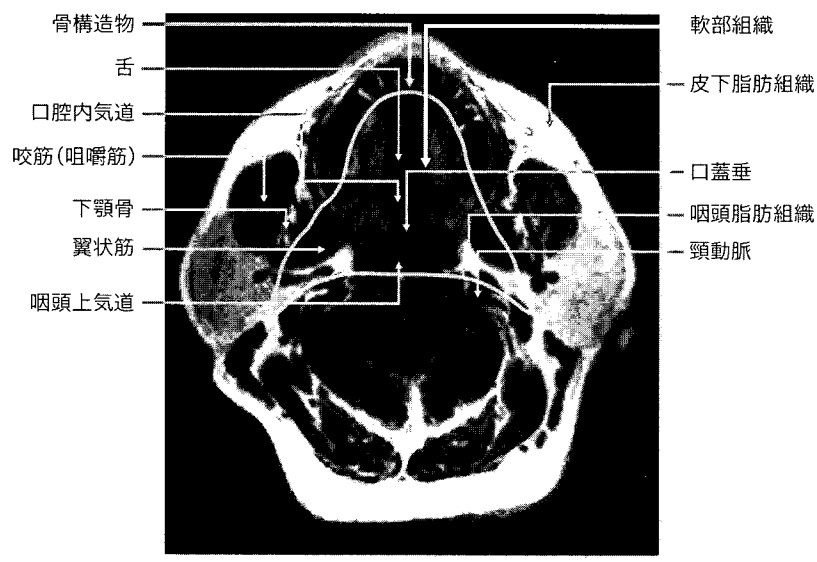

図2　上気道横断面のMR画像

上気道は、骨構造物のなか、さらに軟部組織に囲まれている。

睡眠時無呼吸症候群における肥満の性差

睡眠時無呼吸症候群の発症機序として、肥満を含む解剖学的な異常は、上気道維持(開存)機構に影響を及ぼす。上気道は、骨構造物(脊椎、下顎骨)のなかで、さらに軟部組織(舌、扁桃組織、筋肉、脂肪組織)に囲まれて存在している(図2)。理論的に考えると、気道内圧は肥満/脂肪沈着による軟部組織圧の上昇により増加して、気道閉塞は生じやすくなる(図3)。

体重・body mass index(BMI)で評価した肥満は、睡眠時無呼吸症候群の重症度に影響を及ぼすことは周知の事実である。同様に、局所的肥満の程度も、睡眠時無呼吸症候群の重症度に影響を及ぼしうる。頸が短く太い場合は、睡眠時無呼吸症候群に陥りやすいことが容易に推定されうる。頸

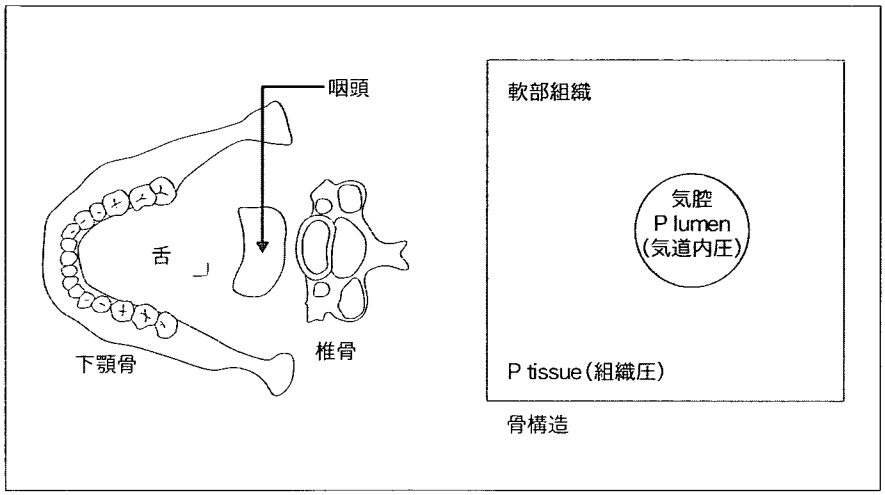

図3　上気道内圧と組織圧の関係
(Isono S, et al. J Appl Physiol 2004; 97: 339.より引用改変)
骨構造が一定であれば、組織圧が高くなると気道内圧は増加する。

	男性(n=261)	女性(n=158)	
年齢(年)	50.0± 0.8	55.4± 1.0	p<0.01
身長(m)	1.69± 0.01	1.54± 0.01	p<0.01
体重(kg)	78.4± 0.8	63.2± 1.0	p<0.01
BMI (kg/m^2)	27.3± 0.2	26.6± 0.4	p=ns
頸周り(cm)	40.6± 0.2	37.5± 0.5	p<0.01
頸周り/身長(cm/m)	24.0± 0.1	24.3± 0.3	p=ns
腹囲(cm)	96.8± 0.7	83.6± 1.2	p<0.01
腹囲/身長(cm/m)	57.0± 0.5	56.3± 0.7	p=ns
AHI (events/h)	40.3± 1.5	32.1± 2.0	p<0.01
Low SpO_2(%)	77.0± 0.6	77.8± 0.8	p=ns

表2　BMIを男女間でmatchさせた睡眠時無呼吸症候群症例の比較

部上気道周囲の脂肪沈着・頸部周囲径・腹部脂肪・腹部周囲径などには性差があり、睡眠時無呼吸症候群の病態に影響を及ぼしている可能性がある[15]。腹部脂肪(内臓肥満)の増加は、横隔膜を挙上させ、さらに可動性も低下させることにより、睡眠時無呼吸症候群の重症度に影響をしている可能性がある。一般的に、男性の肥満症はウエスト径が増加する傾向にあるが、女性の肥満症は臀部径(ヒップ径)が増加する傾向があることが欧米人では知られている[16]。しかし、日本人において、局所肥満の何が(頸部vs.腹部脂肪)、睡眠時無呼吸症候群の性差に影響を及ぼしているのかは必ずしも明らかではない。

以下、BMIを37未満としてBMIを男女間で有意差のないように設定した、睡眠時無呼吸症候群[無呼吸低呼吸指数(apnea hypopnea index ; AHI)≧ 5]の男性261例と、女性158例を対象としたわれわれのデータを示す(表2)。残念ながら、平均年齢は男女で有意差を認め、女性のほうが高値であった。BMIに有意差はない対象群であるが、身長・体重は女性が低値であった。頸周り、腹囲は男性の方が太かったが、身長で補正すると差は消失していた。BMIの一致する対象群を選