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.

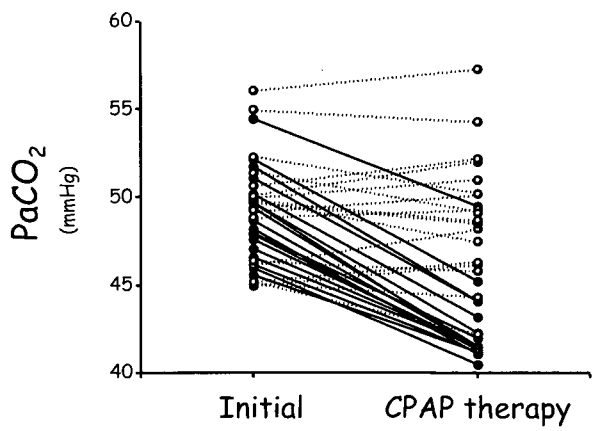

FIGURE 5. The responses of $PaCO_2$ to CPAP therapy. Closed circle with solid line represents good responder, while open circle with dashed line represents poor responder.

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.

Downloaded from chestjournal.org on December 13, 2007
Copyright © 2007 by American College of Chest Physicians

References

1 Krieger J, Sforza E, Apprill M, et al. Pulmonary hypertension, hypoxemia, and hypercapnia in obstructive sleep apnea patients. Chest 1989; 96:729–737

2 Bradley TD, Rutherford R, Lue F, et al. Role of diffuse airway obstruction in the hypercapnia of obstructive sleep apnea. Am Rev Respir Dis 1986; 134:920–924

3 Resta O, Barbaro MPF, Brindicci C, et al. Hypercapnia in overlap syndrome: possible determinant factors. Sleep Breath 2002; 6:11–17

4 Chaouat A, Weitzenblum E, Krieger J, et al. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. Am J Respir Crit Care Med 1995; 151:82–86

5 Laaban J-P, Chailleux E. Daytime hypercapnia in adult patients with obstructive sleep apnea syndrome in France, before initiating nocturnal nasal continuous positive airway pressure therapy. Chest 2005; 127:710–715

6 Leech JA, Onal E, Baer P, et al. Determinant of hypercapnia in occlusive sleep apnea syndrome. Chest 1987; 92:807–813

7 Weitzenblum E, Chaouat A, Kessler R, et al. Daytime hypoventilation in obstructive sleep apnoea syndrome. Sleep Med Rev 1999; 3:79–93

8 Rapoport DM, Garay SM, Epstein H, et al. Hypercapnia in the obstructive sleep apnea syndrome: a reevaluation of the Pickwickian syndrome. Chest 1986; 89:627–635

9 Kim J, In K, Kim J, et al. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am J Respir Crit Care Med 2004; 170:1108–1113

10 Ip MS, Lam B, Lauder IJ, et al. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. Chest 2001; 119:62–69

11 Udwadia ZF, Doshi AV, Lonkar SG, et al. Prevalence of sleep-disordered breathing and sleep apnea in middle-aged urban Indian men. Am J Respir Crit Care Med 2004; 169:168–173

12 Akashiba T, Kawahara S, Kosaka N, et al. Determinants of chronic hypercapnia in Japanese men with obstructive sleep apnea syndrome. Chest 2002; 121:415–421

13 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; NIH Publication No. 204

14 Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep 2005; 28:499–521

15 Report of WHO consultation: obesity; preventing and managing the global epidemic. Geneva WHO Technical Report Series 2000; 894:1–253

16 Young T, Peppard PE, Gottleib DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002; 165:1217–1239

17 Han F, Chen E, Wei H, et al. Treatment effects on carbon dioxide retention in patients with obstructive sleep apnea-hypopnea syndrome. Chest 2001; 119:1814–1819

18 Sugerman HJ, Fairman PR, Sood RK, et al. Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. Am J Clin Nutr 1992; 55:597S–601S

19 Flenley DC. Sleep in chronic obstructive lung disease. Clin Chest Med 1985; 6:51–61

20 Porte P. Consensus conference report: clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation. Chest 1999; 116:521–534

Downloaded from chestjournal.org on December 13, 2007
Copyright © 2007 by American College of Chest Physicians

Jpn. J. Clin. Physiol., Vol. 36, No. 2, 2006.

Original Article

Vascular Endothelial Growth Factor in Obstructive Sleep Apnea Syndrome

Koichiro TATSUMI, Nobuhiro TANABE, Yuichi TAKIGUCHI and Takayuki KURIYAMA

ABSTRACT

Background: Repeated hypoxemia upregulates vascular endothelial growth factor (VEGF) production. It has been reported that blood levels of VEGF are elevated in patients with obstructive sleep apnea syndrome (OSAS), and that VEGF elevation correlates with the degree of nocturnal hypoxia and apnea-hypopnea index (AHI). Serum VEGF includes that released by activated platelets during the in vitro clotting process. In vitro experiments have shown that VEGF is released by platelets even if not stimulated by hypoxia. It is possible that serum VEGF derives entirely from platelets activated during the in vitro clotting process. Therefore, the relationship between serum and plasma VEGF is unclear in patients with OSAS.

Objective: In the present study, we compared serum and plasma VEGF levels in patients with OSAS to examine whether both serum and plasma VEGF levels could be used as the marker of repeated intermittent nocturnal hypoxemic insults. In addition, the levels of hypoxemia, partly reflected by mean SpO_2 values during sleep, as well as the number of hypoxemic episodes, partly reflected by AHI, may influence the blood levels of VEGF. Therefore, we examined which of two variables, mean SpO_2 or AHI, play a major role in determining the blood levels of VEGF.

Methods: The study population consisted of 181 consecutive men clinically suspected to have OSAS, who were examined by polysomnography (PSG). We measured blood levels of VEGF in 143 patients with OSAS and 38 patients with non-OSAS. Serum and plasma VEGF 121 levels in patients with OSAS were measured in duplicate by a colorimetric enzyme-linked immunosorbent assay. The analytical sensitivity of this assay was assessed by measuring serially diluted recombinant human VEGF 121 ranging from 0 to 1,000 pg/ml.

Results: The mean serum and plasma VEGF levels were 101 ± 5 and 72 ± 4 pg/ml, respectively. The serum levels of VEGF were significantly higher than plasma levels of VEGF ($P < 0.01$). Linear regression analysis showed that serum VEGF concentrations significantly correlated with plasma VEGF concentrations ($r = 0.82$, $P < 0.01$). The concentration of serum VEGF decreased linearly as a function of mean SpO_2 ($r = -0.49$, $P < 0.01$), although a large between-patients' variability in serum VEGF concentrations existed to sleep mean SpO_2 levels. They increased linearly as a function of AHI ($r = 0.32$, $P < 0.01$) or BMI ($r = 0.31$, $P < 0.01$), and decreased as a function of PaO_2 ($r = -0.21$, $P = < 0.01$). Multiple regression analysis identified the sleep average

Department of Respirology, Graduate School of Medicine, Chiba University
(Received December 20, 2005)

SpO_2 (P=0.0001), but not PaO_2 (P=0.74), AHI (P=0.36) or BMI (P=0.32), as the only significant predictor of serum VEGF levels.

Conclusions: Serum and plasma VEGF levels correlated with each other and that serum VEGF levels were 1.4 times higher than those in plasma in OSAS patients. The levels of hypoxemia may play an important role in the production of VEGF. It is plausible that a certain degree of repeated hypoxemia is required to produce VEGF.

INTRODUCTION

Hypoxia is known to be the major stimulant that upregulates vascular endothelial growth factor (VEGF) synthesis by controlling hypoxia-inducible factor-1 (HIF-1) gene transcription and mRNA stabilization, while intermittent hypoxia is also found to upregulate HIF-1 expression.[1] Recent studies have shown that blood levels of VEGF are elevated in patients with obstructive sleep apnea syndrome (OSAS), and that VEGF elevation correlates with the degree of nocturnal hypoxia and apnea-hypopnea index (AHI),[2-5] although no study has directly demonstrated the upregulation of HIF-1 in OSAS.

Serum VEGF may include that released by activated platelets during the in vitro clotting process. In vitro experiments have shown that VEGF is released by platelets even if not stimulated by hypoxia.[6] It is therefore possible that serum VEGF derives entirely from platelets activated during the in vitro clotting process. Therefore, the relationship between serum and plasma VEGF is unclear in patients with OSAS.

In the present study, we compared serum and plasma VEGF levels in patients with OSAS to examine whether both serum and plasma VEGF levels could be used as the marker of repeated intermittent nocturnal hypoxemic insults. In addition, the levels of hypoxemia, partly reflected by mean SpO_2 values during sleep, as well as the number of hypoxemic episodes, partly reflected by AHI, may influence the blood levels of VEGF. Therefore, we examined which of two variables, mean SpO_2 or AHI, play a major role in determining the blood levels of VEGF.

METHODS

Subjects

The study population consisted of 181 consecutive men clinically suspected to have OSAS, who were examined by polysomnography (PSG) from July 2003 to June 2004. The patients were recruited from the sleep clinic where they had been referred for investigation for snoring or possible OSAS. Presenting symptoms were either snoring or daytime sleepiness or both.

None of the patients had heart failure or other respiratory problems, such as COPD, at the time of PSG. The diagnosis of OSAS was established on the basis of clinical and polysomnographic criteria. AHI was calculated as the mean number of events per hour of sleep-disordered breathing. In addition to clinical symptoms, an AHI of more than 5 events per hour was also used as an OSAS diagnosis criterion.

Polysomnography

Polysomnography (PSG) (Compumedics, Melbourne, Australia) was performed between 9:00 P.M. and 6:00 A.M. PSG records were staged manually according to standard criteria.[7] Respiratory events were scored according to AASM criteria[8]: apnea was defined as complete cessation of airflow lasting 10 seconds or more; hypopnea was defined as either a $\geq$ 50% reduction in airflow for 10 seconds or more or a less than 50%, but discernible, reduction in airflow accompanied either by a decrease in oxyhemoglobin saturation of $>$3% or an arousal. Severity of OSAS was determined by the AHI and mean and lowest oxygen saturation (SpO_2) during sleep (mean SpO_2 and lowest SpO_2).

Measurements of blood VEGF

Venous blood in patients with OSAS was obtained in the fasting state at 7 A.M. after overnight PSG. Serum and plasma VEGF 121 levels in patients with OSAS were measured in duplicate by a colorimetric enzyme-linked immunosorbent assay with slight modifications of a chemiluminescence enzyme immunoassay previ-

ously described by Hanatani et al.[9] The analytical sensitivity of this assay was assessed by measuring serially diluted recombinant human VEGF 121 ranging from 0 to 1,000 pg/ml. The intra- and inter-assay coefficients of variation were both less than 10% throughout the range.

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.

Statistics

The results are expressed as mean values ± standard errors (SEM). Univariate linear regression analysis was applied to examine the relationship between serum and plasma VEGF levels, as well as that between serum VEGF levels and the severity of OSAS. The patients were distributed into 5 groups according to their AHI (–5, 5–20, 20–40, 40–60, 60–) and their mean SpO_2 (–80, 80–85, 85–90, 90–95, 95–). Analysis of variance was used to compare the levels of VEGF among the groups. This was followed by a post hoc Bonferroni's multiple-comparison test. Multiple regression analysis was applied to predict serum VEGF levels using mean SpO_2, lowest SpO_2, PaO_2 during wakefulness, BMI and age as potential predictors. The level of statistical significance was set at $P < 0.05$.

RESULTS

Patient characteristics

They were first divided into two groups according to their AHI (AHI ≥ 5: n = 143, and AHI < 5: n = 38). Then, we divided the patients into 5 groups according to their mean SpO_2 (Table 1). The mean age of the 5 groups was similar, while BMI was higher in the 4 groups with a mean $SpO_2 < 95\%$ compared with the group with a mean $SpO_2 \geq 95\%$. The awake PaO_2 level was lower in the 4 groups with a mean $SpO_2 < 95\%$ compared with the group with a mean $SpO_2 \geq 95\%$, while the awake $PaCO_2$ level was higher in the group with $SpO_2 < 80\%$ compared with the group with a mean $SpO_2 \geq 95\%$. AHI was higher and the lowest SpO_2 level was lower in the 4 groups with a mean SpO_2

Table 1 Anthropometric, blood gas and sleep study data of OSAS patients distributed according to the levels of mean SpO_2 during sleep.

Mean SpO_2 (%)	< 80 (n = 12)	80 ≤ < 85 (n = 13)	85 ≤ < 90 (n = 25)	90 ≤ < 95 (n = 75)	95 ≤ (n = 56)
Age (yr)	42.8 ± 2.9	45.9 ± 2.9	53.7 ± 2.1	50.3 ± 1.7	51.4 ± 1.8
BMI (kg/m^2)	36.9 ± 2.0*	32.1 ± 1.2*	29.4 ± 0.7*	28.5 ± 2.1*	25.0 ± 0.5
PaO_2 (mmHg)	74.7 ± 2.8*	74.6 ± 2.1*	79.5 ± 2.0*	85.1 ± 1.1*	90.1 ± 1.6
$PaCO_2$ (mmHg)	44.5 ± 1.6*	43.0 ± 1.0	41.9 ± 0.7	41.3 ± 0.4	42.1 ± 0.5
AHI (events/hr)	81.1 ± 8.3	62.8 ± 4.8	47.6 ± 3.4	28.5 ± 2.1	6.4 ± 1.0
Lowest SpO_2 (%)	55.6 ± 1.9	61.2 ± 2.1	65.3 ± 1.2	75.3 ± 0.8	85.2 ± 0.9
Serum VEGF (pg/ml)	199 ± 28*	136 ± 26*	105 ± 10*	98 ± 7*	78 ± 7

Data are presented as mean values ± SE. BMI = body mass index; Lowest SpO_2 = the lowest value of SpO_2 during sleep (%). * $P < 0.05$ versus those with mean $SpO_2 \geq 95\%$.

Table 2 Anthropometric, blood gas and sleep study data of OSAS patients distributed according to their AHI.

AHI	< 5 (n = 38)	5 ≤ < 20 (n = 42)	20 ≤ < 40 (n = 34)	40 ≤ < 60 (n = 41)	60 ≤ (n = 26)
Age (yr)	48.4 ± 2.2	56.1 ± 2.3	53.3 ± 2.0	48.9 ± 2.1	43.5 ± 2.0
BMI (kg/m^2)	25.6 ± 0.6	27.9 ± 0.8	28.3 ± 0.6*	28.5 ± 0.6*	33.7 ± 1.3*
PaO_2 (mmHg)	89.4 ± 1.9	86.3 ± 1.7	86.2 ± 1.4	81.9 ± 1.5*	76.0 ± 2.3*
$PaCO_2$ (mmHg)	41.6 ± 0.6	41.5 ± 0.6	41.1 ± 0.5	42.0 ± 0.6	43.3 ± 0.8
Mean SpO_2 (%)	96.3 ± 0.2	94.2 ± 0.3*	90.9 ± 0.5*	88.0 ± 0.*	82.5 ± 1.3*
Lowest SpO_2 (%)	87.2 ± 0.9	78.8 ± 1.4*	71.7 ± 1.6*	68.7 ± 1.5*	64.6 ± 1.7*
Serum VEGF (pg/ml)	84 ± 12	80 ± 7	103 ± 9	124 ± 12*	153 ± 13*

Data are presented as mean values ± SE. BMI = body mass index; Mean SpO_2 = mean value of SpO_2 during sleep (%); Lowest SpO_2 = the lowest value of SpO_2 during sleep (%). * $P < 0.05$ versus those with AHI < 5.

$< 95\%$ compared with the group with a mean $SpO_2 \geq 95\%$. Thus, patients with more severe hypoxia during sleep had a higher BMI, lower PaO_2 and higher AHI. Serum VEGF level was higher in the 4 groups with a mean $SpO_2 < 95\%$ compared with the group with a mean $SpO_2 \geq 95\%$.

Next, we divided the patients into 4 groups of OSAS and one of non-OSAS according to their AHI (Table 2). The mean SpO_2 was $\geq 95\%$ in all 38 non-OSAS patients (AHI < 5). There were no significant differences in age among the 5 groups, while BMI was higher in the 3 groups with an AHI ≥ 20 compared with the group with an AHI < 5 (non-OSAHS). The PaO_2 value was lower in 2 groups with an AHI ≥ 40 compared with the non-OSAS patients, while all 5 groups had a similar $PaCO_2$ level. The mean and lowest SpO_2 in patients with OSAS (AHI ≥ 5) were lower than those in non-OSAS patients. The serum VEGF level was higher in the 4 groups with an AHI ≥ 40 compared with the group of non-OSAS patients.

Serum versus plasma VEGF in OSAS

The mean serum and plasma VEGF levels were 101 ± 5 and 72 ± 4 pg/ml, respectively. The serum levels of VEGF were significantly higher than plasma levels of VEGF ($P < 0.01$). Linear regression analysis showed that serum VEGF concentrations significantly correlated with plasma VEGF concentrations ($r = 0.82$, $P < 0.01$) (Fig. 1).

Serum VEGF levels in OSAS

The concentration of serum VEGF decreased linearly as a function of mean SpO_2 ($r = -0.49$, $P < 0.01$), although a large between-patients' variability in serum VEGF concentrations existed to sleep mean SpO_2 levels[10] (Fig. 2). They increased linearly as a function of AHI ($r = 0.32$, $P < 0.01$) or BMI ($r = 0.31$, $P < 0.01$), and decreased as a function of PaO_2 ($r = -0.21$, $P = < 0.01$). They did not correlate with $PaCO_2$ ($r = 0.02$, $P =$ NS) or age ($r = 0.08$, $P =$ NS). However, multiple regression analysis identified the sleep average SpO_2 ($P = 0.0001$), but not PaO_2 ($P = 0.74$), AHI ($P = 0.36$) or BMI ($P = 0.32$), as the only significant predictor of serum VEGF levels.

DISCUSSION

In the present study we confirmed previous findings that the blood levels of VEGF correlated negatively with the degree of nocturnal oxygen desaturation in OSAS patients.[2-5] This negative correlation between blood levels of VEGF and mean SpO_2 suggested that the most likely trigger of VEGF production or release in patients with OSAS is hypoxia, although numerous

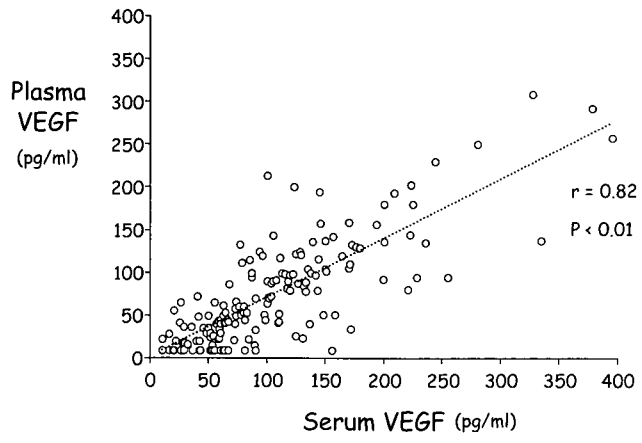

Fig. 1 Serum versus plasma levels of vascular endothelial growth factor (VEGF) in patients with obstructive sleep apnea-hypopnea syndrome. Each circle represents one patient, and the dashed regression line represents the relationship between these two variables. A significant positive correlation was observed between these two variables.

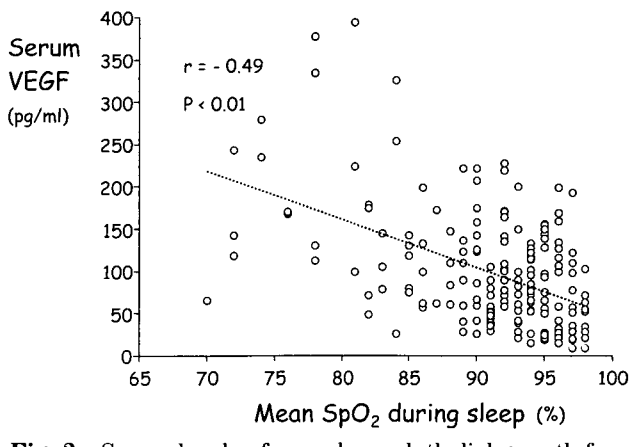

Fig. 2 Serum levels of vascular endothelial growth factor (VEGF) in patients with obstructive sleep apnea-hypopnea syndrome distributed by their mean SpO_2 during sleep. Each circle represents one patient, and the dashed regression line represents the relationship between these two variables. A significant negative correlation was observed between these two variables.

factors may influence blood VEGF levels.[11]

The levels of hypoxia/hypoxemia at which VEGF production is stimulated in vivo could not be determined in this study, although previous clinical studies have suggested that the degree of hypoxemia plays an important role in determining the blood levels of VEGF,[2-5] and expression of the VEGF gene is mainly stimulated by hypoxia through mediation of HIF-1.[12]

The blood levels of VEGF correlated negatively with the degree of nocturnal oxygen desaturation and positively with AHI. However, the role or clinical significance of blood levels of VEGF in OSAS has not been determined as yet. Whether enhanced VEGF production in severely hypoxemic patients with OSAS constitutes an adaptive mechanism to counterbalance the emergence of cardiovascular disease, or plays an important role in the pathogenesis of vascular-related diseases, including atherosclerosis of the coronary arteries and vascular dysfunction, remains unclear.

Serum and plasma VEGF levels correlated with each other and serum VEGF levels were 1.4 times higher than those in plasma in OSAS patients. This finding suggested that increased serum VEGF levels may partly reflect platelet activation and subsequent release of VEGF in OSAS patients, although the exact source of blood VEGF has not been clearly defined. In addition, this also suggested that serum VEGF may not derive entirely from platelets activated during the in vitro clotting process. Both serum and plasma VEGF levels could be used as markers of repeated intermittent nocturnal hypoxemic insults, resulting in increased hypoxia-sensitive upregulation of the protein production.

Both mean SpO_2 values during sleep and AHI related to the blood levels of VEGF in this study. However, multiple regression analysis identified the sleep average SpO_2, but not AHI, as the only significant predictor of VEGF levels. This suggested that the levels of hypoxemia may play an important role in the production of VEGF, although repeated hypoxemia is a strong stimulus of HIF-1.[12] Thus, it is plausible that a certain degree of repeated hypoxemia is required to produce VEGF.

In conclusion, repeated hypoxemia could be a strong stimulus of VEGF production in patients with OSAS. Both serum and plasma levels of VEGF are upregulated by apnea-related intermittent hypoxemia in patients with OSAS.

We greatly thank Mr. Katsuhiko Matsuo, Tsukuba Research Laboratory, Toagosei Co., Ltd., Tsukuba, Japan, for measuring both serum and plasma VEGF.

This study was supported by a Grant-in-Aid for Scientific Research (C) (16590735) from the Japanese Ministry of Education, Science, Sports and Culture, and grants from the Japanese Ministry of Health, Labour and Welfare awarded to the Respiratory Failure Research Group.

REFERENCES

1) Yuan G, Adhikary G, Prabhakar NR: Activation of HIF-2a by intermittent hypoxia requires CaMKII [abstract]. *FASEB J* 2001, **15**: A154
2) Imagawa S, Yamaguchi Y, Higuchi M, Neichi T, Hasegawa Y, Mukai HY, Suzuki N, Yamamoto M, Nagasawa T: Levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea-hypopnea syndrome. *Blood* 2001, **98**: 1255–1257
3) 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
4) Gozal D, Lipton AJ, Jones KL: Circulating vascular endothelial growth factor levels in patients with obstructive sleep apnea. *Sleep* 2002, **25**: 59–65
5) Lavie L, Kraiczi H, Hefetz A, Ghandour J, Perelman A, Hedner J, Lavie P: Plasma vascular endothelial growth factor (VEGF) in sleep apnea syndrome: effects of nCPAP treatment. *Am J Respir Crit Care Med* 2002, **165**: 1624–1628
6) Koehne P, Willam C, Strauss E, Schindler R, Eckhardt KU, Buhrer C: Lack of hypoxic stimulation of VEGF secretion from neutrophils and platelets. *Am J Physiol* 2000, **279**: H817–824
7) Rechtschaffen A, Kales AA, editors: A Manual of Standardized Terminology, Techniques and Scoring System for Sleep stages of Human Subjects. NIH Publication No. 204, Washington, D.C., US Government Printing Office, 1968
8) American Academy of Sleep Medicine: 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
9) Hanatani M, Tanaka Y, Kondo S, Ohmori I, Suzuki H:

Sensitive chemiluminescence enzyme immunoassay for vascular endothelial growth factor/vascular permeability factor in human serum. *Biosci Biotech Biochem* 1995, **59**: 1958–1959

10) Schultz A, Lavie L, Hochberg I, Beyar R, Stone T, Skorecki, Lavie P, Roguin A, Levy AP: Interindividual heterogeneity in the hypoxic regulation of VEGF: significance for the development of the coronary artery collateral circulation. *Circulation* 1999, **100**: 547–552

11) Takahashi S, Nakamura Y, Nishijima T, Sakurai S, Inoue H: Essential roles of angiotensin II in vascular endothelial growth factor expression in sleep apnea syndrome. *Resp Med* 2005, **99**: 1125–1131

12) Semenza GL, Wang GL: A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. *Mol Cell Biol* 1992, **12**: 5447–5454

Q J Med 2006; **99**:545–553
doi:10.1093/qjmed/hcl074

Effect of nCPAP therapy on heart rate in patients with obstructive sleep apnoea-hypopnoea

K. SUMI[1], K. CHIN[2], K. TAKAHASHI[1], T. NAKAMURA[1], H. MATSUMOTO[1], A. NIIMI[1] and M. MISHIMA[1]

From the [1]Department of Respiratory Medicine, Kyoto University Graduate School of Medicine, and [2]Department of Physical Therapeutics, Kyoto University Hospital of Medicine, Kyoto, Japan

Received 2 February 2006 and in revised form 5 May 2006

Summary

Background: Elevated heart rate (HR) is a risk factor for cardiovascular disease. The effects of obstructive sleep apnoea-hypopnoea syndrome (OSAHS) on HR are controversial.

Aim: To investigate the effect of nasal continuous positive airway pressure (nCPAP) therapy on HR in OSAHS patients.

Methods: Sixty-two OSAHS patients underwent 24-h electrocardiographic recording, both before and 3 or 4 days after instigation of nCPAP.

Results: After nCPAP was started, HR significantly decreased (mean ± SD 71.8 ± 10.6 vs. 67.5 ± 9.4 bpm, $p<0.0001$), both in the daytime (0600–2200 h, 76.3 ± 12.2 vs. 72.2 ± 10.2 bpm, $p<0.0001$) and at night-time (2200–0600 h, 64.5 ± 9.1 vs. 60.0 ± 8.9 bpm, $p<0.0001$). HR was significantly reduced in both periods in the 44 patients with hypertension and/or diabetes mellitus, but only during the night-time in the 18 with neither condition. Before nCPAP treatment, HR was positively correlated with percentage time of arterial O_2 saturation <90% during sleep ($p=0.008$) and with the apnoea-hypopnoea index during sleep ($p=0.003$). In 15 patients undergoing HR for 2 days before starting nCPAP, the mean HRs for the two periods were similar ($p=0.95$).

Discussion: nCPAP therapy appears to decrease HR in OSAHS patients, and may thereby reduce their risk of cardiovascular disease.

Introduction

Approximately 9% of women and 24% of men have >5 episodes of obstructive sleep apnoea and hypopnoea per hour, and approximately 4% of women and 9% of men have >15 episodes per hour.[1] Obstructive sleep apnoea (OSA) is an independent risk factor for systemic hypertension, and may be a risk factor for myocardial infarction and stroke.[2] Nasal continuous positive airway pressure (nCPAP) therapy in patients with OSA reduced their blood pressure, the frequency of arrhythmia, and the risk of cardiovascular events.[2–6]

Elevated heart rate is an important risk factor for cardiovascular disease.[7] In several large-scale cohort studies, such as the CASTEL and Framingham studies, individuals with an elevated heart rate had a poorer cardiovascular prognosis.[8–11] There have been several reports on the results of spectral analysis of RR interval variability in OSA patients,[12,13] but few on the heart rate of OSA patients. The results on the effect of nCPAP therapy on the heart rate of OSA patients are controversial, because there are characteristic patterns of bradycardia and tachycardia during sleep in OSA patients.[5,12,14–16] It is thus uncertain whether nCPAP therapy changes the heart rate of OSA patients throughout the day. Recently, Ziegler *et al.*[17] reported that CPAP treatment lowered the daytime heart rate in OSA patients ($p<0.05$),

Address correspondence to Dr K. Chin, Department of Physical Therapeutics, Kyoto University Hospital of Medicine, 54 Shogoin Kawahara-cho, Sakyo-Ku, 606-8507 Kyoto, Japan. email: chink@kuhp.kyoto-u.ac.jp

© The Author 2006. Published by Oxford University Press on behalf of the Association of Physicians.
All rights reserved. For Permissions, please email: journals.permissions@oxfordjournals.org

but not the night-time heart rate. However, the number of patients in their study was small (20 patients vs. 18 controls), and they did not analyse the effect of CPAP treatment on the heart rate of OSA patients with clinical conditions such as hypertension and diabetes mellitus.[17] In addition, they measured the heart rate every 15 or 30 min. To investigate the effect of OSA with hypoxaemia, we measured the heart rate in obstructive sleep apnoea-hypopnoea syndrome (OSAHS) patients throughout the day before and after nCPAP treatment.

Adiponectin is a recently discovered 247-amino-acid peptide,[18] whose plasma adiponectin concentration is reportedly lower in patients with cardiovascular disease than in normal subjects,[19] and significantly negatively correlated with heart rate.[20] To elucidate the risk of OSA patients for cardiovascular disease, it is important to investigate the change in heart rate over 24 h. In addition, it seems clinically easier to understand the effect of nCPAP therapy on heart rate rather than on frequency ratio. We hypothesized that obstructive sleep apnoea with hypoxaemia has a significant effect on the heart rate of patients throughout the day, and that nCPAP therapy improves the heart rate. To test the hypothesis, we measured the heart rate in OSAHS patients throughout the day before and the day after nCPAP treatment. We also measured the plasma adiponectin concentration in these patients, to investigate the relationship between plasma adiponectin and heart rate.

Methods

Subjects

We studied 62 patients with OSAHS who were candidates for nCPAP therapy[6] (60 male, 2 female). Their mean ± SD age was 53.5 ± 12.1 years, mean ± SD apnoea-hypopnoea index (AHI) was 48.3 ± 15.7 events/h, and mean ± SD body mass index (BMI) was 27.7 ± 4.1 kg/m^2. Subjects were selected from a group of 69 consecutive OSA patients who had completed a sleep study and Holter monitoring. Seven patients were excluded from the study because of insufficient polysomnograph or Holter monitor data (e.g. an electrode had been off). The two women were both post-menopausal. The diagnosis of the obstructive sleep apnoea-hypopnoea syndrome (OSAHS) was established based on clinical symptoms and an AHI of >5 events/h on polysomnography.[21,22] In Japan, an AHI of >20 events/h is used as a selection criterion for nCPAP treatment.

Table 1 Characteristics of patients with obstructive sleep apnoea-hypopnoea syndrome

	Patients
Total	62
Hypertension patients	38
Taking calcium inhibitor	34
Taking ACE inhibitor	6
Taking angiotensin II receptor antagonist	11
Taking alpha-blocker	10
Taking beta-blocker	10
Taking diuretic	6
Taking nitrous drug	2
Diabetes mellitus patients	13
Hyperlipidaemia patients	31
Age (years)	53.5 ± 12.1
Apnoea-hypopnoea index (events/h)	48.3 ± 15.7
Body mass index (kg/m^2)	27.7 ± 4.1

Data are numbers or means ± SD. ACE, angiotensin-converting enzyme.

Mean ± SD ejection fraction (determined by the Teichholz method on two-dimensional echocardiography) was 69.0 ± 7.6% (range 55.0–82.8%). None of the 62 patients showed signs of congestive heart failure.

Of the 62 patients, 38 had hypertension, and 13 had diabetes mellitus. The medications that the patients were taking for hypertension are summarized in Table 1. The drug regimens of the patients were not changed during the interval from 1 month before the first polysomnography recording to after completion of the second polysomnography recording.

To investigate the possibility of significant changes in heart rate between the two Holter ECG measurements, 15 patients were randomly selected from the 62. These 15 patients underwent Holter monitor recording for 2 days before nCPAP therapy was started. Their age, AHI, body mass index, and anti-hypertensive drug medications did not significantly differ from the respective values for the whole group of 62 before nCPAP therapy was started (Table 1). In addition, the age, AHI, and body mass index of the 15 patients did not differ significantly from the respective values for the remaining 47 patients.

The study was approved by the medical ethics committee of our hospital, and all patients provided informed consent.

Polysomnography

Polysomnography was done before nCPAP therapy, and then again on the first night of nCPAP therapy.

The interval between the two polysomnographic recordings was one week. Both nCPAP therapy and second polysomnography were started at 2200 h, and finished at 0600 h. Blood pressure was measured, and a blood sample obtained, at 0700 h. The blood sample was obtained immediately after blood pressure measurement. Polysomnography was done using standard methods.[23] The total sleep time, AHI, lowest arterial O_2 saturation, and percentage time of arterial O_2 saturation <90% during sleep were calculated in each patient.

Measurement of heart rate and other parameters, and nCPAP treatment

Electrocardiographic recording using a Holter monitor over an approximately 24-h (24.1 ± 1.3 h) period was done in all 62 patients before nCPAP therapy was started and 3 or 4 days after nCPAP therapy was started. In each patient, the interval between the two Holter monitor recordings was one week. In all patients, polysomnography was performed on a Monday and Holter monitor recording was performed on the following Wednesday or Thursday, both before and after nCPAP therapy was started. After the first polysomnography, the patient remained in the hospital until completion of the first Holter monitor recording, after which they returned home. On the following Monday, the patient came to our hospital for the first night of nCPAP therapy and the second polysomnographic recording. The patient remained in the hospital until after the second Holter monitor recording, which was on a Wednesday or Thursday with nCPAP therapy. The 15 control OSA patients from among the 62 patients underwent Holter monitor recording for two consecutive days instead of for one day.

Preliminary education or habituation for nCPAP therapy was performed for approximately 30 min in the daytime before the first night of nCPAP treatment. Manual CPAP titrations were performed throughout the night for OSAHS patients on the first night of nCPAP therapy. The mean pressure of nasal CPAP therapy was 9.6 ± 2.7 cm H_2O. All of the patients tolerated nCPAP treatment well during the study. We measured blood pressure in the supine position, before and after each polysomnography, in the morning and in the evening.

Diabetes mellitus and heart rate are known to be closely related. Eight patients had already been diagnosed with diabetes mellitus at another hospital. A 75 g oral glucose tolerance test (OGTT) was administered to the remaining 54 patients before nCPAP treatment. A patient was defined as having diabetes if their plasma glucose concentration 2 h after glucose load was ⩾200 mg/dl, or if their fasting plasma glucose concentration was ⩾126 mg/dl.[24]

Determination of plasma adiponectin

We measured plasma adiponectin level before nCPAP therapy was started in the 19 patients most recently enrolled in the study, using a commercially available enzyme-linked immunosorbent assay kit (Otsuka Pharmaceuticals, Tokyo, Japan). The intra- and inter-assay coefficients of variation were 4.06% and 4.69%, respectively.

Data analysis

We analysed the electrocardiographic data and calculated the mean heart rate during each one-hour interval (expressed as bpm). Then, we compared the heart rate before nCPAP therapy was started and the heart rate after nCPAP therapy was started. Data were expressed as means ± SD. Data were analysed by a non-parametric method. The heart rates during each 1-h interval were compared between the first and second Holter monitor recordings using Wilcoxon signed rank test. Comparisons of heart rate and other parameters between the whole group of 62 patients and the control subgroup of 15 used the Mann-Whitney U test and the χ^2 test. Statistical analyses used StatView software for Windows (Version 5.0; Abacus Concepts). A p value <0.05 was considered significant.

Results

Effects of nCPAP on sleep apnoea

Polysomnography was performed before nCPAP therapy was started and again on the first night of nCPAP therapy. In the 62 patients with OSAHS, nCPAP therapy reversed the sleep apnoea, with improvements (before vs. after) in AHI (48.3 ± 15.7 vs. 3.6 ± 4.6 events/h, $p<0.0001$), mean arterial O_2 saturation (94.8% ± 2.1% vs. 96.5% ± 1.4%, $p<0.0001$), lowest arterial O_2 saturation (67.7% ± 13.2% vs. 85.7% ± 10.0%, $p<0.0001$), and percentage time of arterial O_2 saturation <90% (24.2% ± 17.7% vs. 0.7% ± 1.7%, $p<0.0001$).

Heart rate before and after nCPAP

Holter monitor recording was done before nCPAP therapy was started and again 3 or 4 days after nCPAP therapy was started. nCPAP therapy significantly reduced mean heart rate over the 24-h interval (from 1300 h to 1300 h the following day)

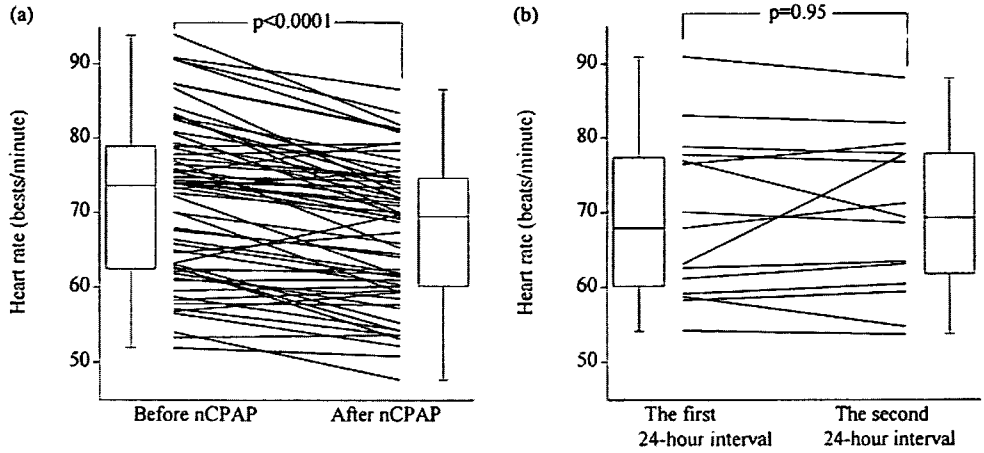

Figure 1. **a** Comparison of the heart rate over a 24-h interval before nCPAP therapy was started and 3 or 4 days after nCPAP therapy was started, in 62 OSAHS patients. **b** Comparison of the heart rate during the first 24-h interval and the second 24-h interval before nCPAP therapy was started, in 15 OSAHS patients.

Table 2 Reduction in heart rate after nCPAP therapy was started, according to clinical conditions, and at different times of day

	n	Time period	Before	After	*p*
All	62	Daytime	76.3 ± 12.2	71.8 ± 10.2	<0.0001
		Night-time	64.5 ± 9.1	60.0 ± 8.9	<0.0001
		Through the day	71.8 ± 10.6	67.5 ± 9.4	<0.0001
Hypertension, no diabetes	31	Daytime	73.9 ± 11.8	70.4 ± 10.9	0.003
		Night-time	63.3 ± 9.3	58.5 ± 8.9	<0.0001
		Through the day	69.8 ± 10.7	65.9 ± 9.9	0.001
Diabetes, no hypertension	6	Daytime	77.9 ± 15.0	70.7 ± 10.5	0.027
		Night-time	68.5 ± 8.4	61.4 ± 10.5	0.027
		Through the day	74.2 ± 12.1	67.0 ± 10.4	0.027
Both diabetes and hypertension	7	Daytime	77.1 ± 11.2	70.5 ± 9.2	0.028
		Night-time	65.4 ± 7.5	61.1 ± 11.0	0.13
		Through the day	72.7 ± 9.4	67.0 ± 9.7	0.028
Neither diabetes nor hypertension	18	Daytime	79.6 ± 12.5	76.4 ± 8.5	0.058
		Night-time	65.1 ± 9.6	61.6 ± 7.9	0.004
		Through the day	74.0 ± 10.7	70.8 ± 7.7	0.014

Data are means ± SD. Daytime, 0600–2200 h. Night-time, 2200–0600 h. Through the day, 0600 h to 0600 h the next day.

(71.8 ± 10.6 vs. 67.5 ± 9.4 bpm, $n = 62$, $p < 0.0001$) (Figure 1a).

We also compared heart rates before and after nCPAP therapy for the daytime (0600 h to 2200 h) and in the night-time (2200 h to 0600 h). Both were significantly reduced (daytime 76.3 ± 12.2 vs. 72.2 ± 10.2 bpm, $n = 62$, $p < 0.0001$; night-time 64.5 ± 9.1 vs. 60.0 ± 8.9 bpm, $n = 62$, $p < 0.0001$) (Table 2). However, there was no significant difference in heart rate before and after nCPAP treatment (66.4 ± 9.3 vs. 65.8 ± 10.7 bpm, $p = 0.65$) among the 10 OSAHS patients who were receiving a beta-blocker.

nCPAP therapy reduced heart rate over the 24-h interval in 50 of the 62 patients (Figure 1a). Figure 2a shows the heart rate for each 1-h interval after nCPAP therapy was started, compared with during the respective interval before nCPAP therapy. In the 62 patients, nCPAP therapy did not significantly affect time of waking, nor the time of going to bed.

Heart rate and the severity of OSAHS

In the 62 patients, before nCPAP therapy, heart rate over the 24-h period (beats/min) was positively

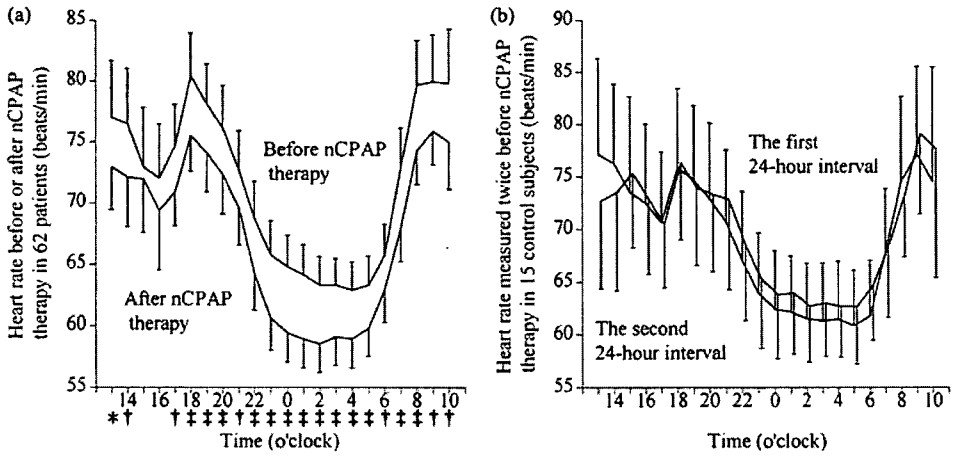

Figure 2. **a** Heart rates before and after nCPAP therapy was started at 1-h intervals in 62 OSAHS patients. **b** Heart rates during the first 24-h interval and the second 24-h interval before nCPAP therapy was started, at 1-h intervals, in 15 OSAHS patients. $^{*}p<0.05$, $^{\dagger}p<0.01$, $^{\ddagger}p<0.001$.

correlated with AHI during sleep ($r=0.38$, $p=0.003$). It was also positively correlated with the percentage time of arterial O_2 saturation <90% during sleep ($r=0.34$, $p=0.008$). The degree of the reduction in heart rate after nCPAP therapy was positively correlated with the degree of the decrease in AHI during sleep ($r=0.32$, $p=0.015$). It was also positively correlated with the degree of the decrease in percentage time of arterial O_2 saturation <90% during sleep ($r=0.56$, $p<0.0001$).

Among the 15 patients whose heart rate was measured for 2 days before nCPAP treatment, heart rates did not differ significantly between the first (1300 h to 1300 h the next day) and the second 24-h interval (69.3 ± 10.8 vs. 69.7 ± 10.4 bpm, $p=0.95$) (Figures 1b and 2b). This result was unaltered (70.5 ± 10.8 vs. 70.8 ± 10.2 bpm, $p=0.81$) if the two patients (of the 15) who were receiving a beta-blocker were excluded from the analysis.

Heart rate response to nCPAP according to clinical condition

Table 2 shows heart rates before and after nCPAP therapy was started, according to clinical condition (with or without diabetes mellitus or hypertension), during the daytime, night-time, and throughout the day.

Blood pressure and arrhythmia

Blood pressure was measured before and after each polysomnography, in the morning (0700 h) and evening (2100 h). The two evening measurements did not differ significantly ($118\pm9/80\pm8$ vs. $117\pm12/77\pm9$ mmHg). However, the morning measurement after nCPAP therapy was started was significantly lower than that before nCPAP therapy was started (Table 3).

Ventricular premature contraction (VPC), and supraventricular premature contraction (SVPC) after nCPAP therapy did not significantly differ from the respective parameters before nCPAP therapy was started (Table 3).

Heart rate and plasma adiponectin level

Adiponectin levels were determined for the last 19 patients enrolled. Plasma adiponectin was negatively correlated with heart rate (over 24 h) before nCPAP therapy was started ($r=-0.51$, $p=0.032$) (Figure 3), but not correlated with AHI nor with the percentage time of arterial O_2 saturation <90% during sleep. There was no significant difference in plasma adiponectin level before nCPAP therapy and that after 3 or 4 days of nCPAP therapy (5.78 ± 4.78 vs. 5.33 ± 4.18 mg/l, $p=0.09$). There was also no significant difference between the degree of the change in heart rate and the degree of the change in plasma adiponectin level, before and 3 days after nCPAP therapy was started ($r=0.24$, $p=0.32$). Of the 19 patients in whom the adiponectin level was measured, only one was receiving a beta-blocker. Among the remaining 18 patients, there remained a significant correlation between heart rate and plasma adiponectin level ($p=0.016$, $r=-0.58$).

Discussion

In our patients with OSAHS, AHI and percentage time of arterial O_2 saturation <90% during sleep

Table 3 Changes in blood pressure and arrhythmia in OSAHS patients before and after starting nCPAP therapy

	Before	After	p
Systolic blood pressure in the morning (mmHg)	130.0 ± 15.6	117.8 ± 16.4	0.0018
Diastolic blood pressure in the morning (mmHg)	87.6 ± 10.2	77.0 ± 10.2	0.0003
Supraventricular premature contraction, beats/h (through the day)	1.3 ± 2.3	1.6 ± 4.0	0.55
Supraventricular premature contraction, beats/h (daytime)	3.3 ± 10.4	1.8 ± 4.4	0.06
Supraventricular premature contraction, beats/h (night-time)	2.0 ± 4.4	1.7 ± 4.0	0.21
Ventricular premature contraction, beats/h (through the day)	6.3 ± 36.5	3.3 ± 13.1	0.64
Ventricular premature contraction, beats/h (daytime)	1.3 ± 4.3	1.2 ± 3.5	0.24
Ventricular premature contraction, beats/h (night-time)	4.5 ± 24.6	2.5 ± 9.4	0.83

Blood pressure was measured in the supine position, before and after each polysomnography, in the morning and in the evening. Data are means ± SD.

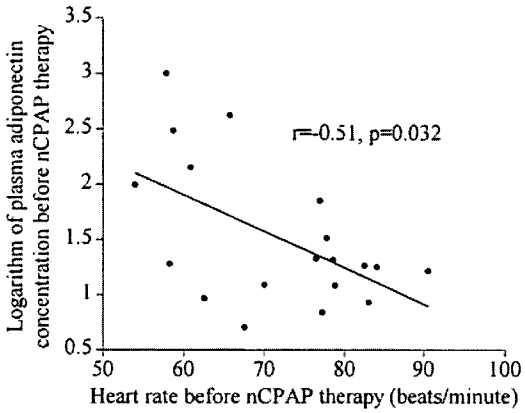

Figure 3. Relationship between heart rate and plasma adiponectin level before nCPAP therapy was started.

were significantly correlated with heart rate throughout the day, and the improvements in AHI and desaturation during sleep resulting from nCPAP therapy significantly reduced the heart rate. There was also a significant relationship between heart rate and plasma adiponectin level before nCPAP therapy.

Spectral analysis of heart rate variability is frequently used as a non-invasive means of assessing cardiac autonomic function,[25,26] with the power of the high-frequency band (0.15–0.4 Hz) widely accepted as a measure of parasympathetic activity.[25] The ratio of low-frequency (0.04 to 0.15 Hz) power to high-frequency power (LHR) has been suggested by some researchers to represent sympathetic modulation of heart rate.[26] Several studies have reported the results of spectral analysis of RR interval variability in OSAHS patients, which showed an increase in low frequency power, a decrease in high frequency power and an increase in the ratio of low to high frequency power, compared with the respective values in normal controls.[12,13,27] However, there have only been a few reports on the heart rate of OSAHS patients.

Many previous studies have reported no difference in the heart rate between patients with OSAHS and normal controls, and no difference in the heart rate among sleep apnoea patients before and with nCPAP treatment.[12,14] These results may have been obtained due to the characteristic pattern of bradycardia and tachycardia during sleep in sleep apnoea patients. In addition, the time interval over which the heart rate was recorded in previous studies was relatively short. It was reported that in OSAHS patients with overt congestive heart failure, nCPAP therapy significantly reduced the heart rate at one point in the morning.[16] In this study, AHI with hypoxaemia had a significant effect on the heart rate of the OSAHS patients without heart failure throughout a day. In a previous study, nCPAP therapy reduced the blood pressure not only during sleep, but also while the OSAHS patient was awake.[3,28] As to the mechanism by which nCPAP therapy reduces blood pressure, it has been proposed that hypoxaemia in addition to OSA during sleep may contribute to elevation of the blood pressure during waking hours.[29,30] Somers *et al.*[31,32] suggested that OSAHS patients have high sympathetic nerve activity, which may also contribute to elevation of heart rate in OSAHS patients.

Measuring the heart rate every 15 or 30 min, Ziegler *et al.*[17] reported that nCPAP treatment lowered daytime heart rate ($p<0.05$) and that this effect differed significantly from that of placebo CPAP; nCPAP treatment also lowered the night-time heart rate but not significantly differently from placebo.[17] In their report, the placebo nCPAP treatment was associated with a 23% drop in respiratory disturbance index (RDI), which may have affected the decrease in night-time heart rate. Based on the results of the present study, hypoxaemia with AHI during sleep may contribute

to elevation of the heart rate of OSAHS patients, not only during sleep but also during waking hours.

In this study, nCPAP therapy significantly reduced the mean heart rate throughout the day, regardless of the presence of diabetes mellitus or hypertension (Table 2), suggesting a possible improvement cardiovascular prognosis. In the OSAHS patients who had neither diabetes mellitus nor hypertension, there was no significant difference in daytime heart rates before and after nCPAP therapy (Table 2). Thus although our results may have been affected by the small number of subjects, nCPAP therapy may reduce the daytime heart rate to a greater extent in OSAHS patients with cardiovascular risk factors than in those without. Recently, Gami *et al.* studied cases of sudden death from cardiac causes and the time of death, and reported that people with obstructive sleep apnoea showed a peak in sudden death from cardiac causes during sleeping hours.[33] Since elevated heart rate is an important risk factor for cardiovascular diseases, our report supports their findings that OSAHS patients are more likely to die due to cardiovascular disease while they are asleep.

It was recently reported that young men with high-normal blood pressure have a faster heart rate and lower serum adiponectin level than young men with normal blood pressure.[20] In addition, hypoadiponectinaemia may be associated with cardiovascular disease in humans.[19] In the present study, OSAHS patients with a higher heart rate also had a lower plasma adiponectin level, suggesting that adiponectin level might also regulate heart rate, in addition to AHI and hypoxaemia. A high heart rate combined with low adiponectin level might be a poor prognostic factor in OSAHS patients.[34] Because of the small number of patients in this study, further studies are warranted on plasma adiponectin levels and heart rate of OSAHS patients over a long period of time after nCPAP therapy is started.

The total number of heart beats was measured during a 24-h interval, 3 to 4 days after nCPAP therapy was started. We had ascertained that the nCPAP mask was fitted properly on the patient more than twice during the night of the second Holter monitor recording. All patients had returned to their homes after the first polysomnography and Holter monitor recording, and after 2 or 3 days they came to our hospital for the second polysomnography and Holter monitor recording; in each patient, the number of days between the first polysomnography and the start of the first Holter monitor recording, and the number of days between the second polysomnography and the second Holter monitor recording were the same. Therefore, it seems likely that length of stay in the hospital prior to the start of Holter monitor recording did not affect the heart rate trends in this study. Although various pharmacological agents can affect the heart rate, the OSAHS patients in this study were receiving the same medical regimen, which consisted of antihypertensive agents in 34 patients and oral drugs for diabetes in five, beginning 1 month before the start of this study and throughout the study. Taking these drugs thus seems unlikely to affect the nCPAP therapy-induced changes in heart rate in this study.

We could not perform a randomized control trial by offering sham CPAP treatment. All patients in Japan are under the government insurance system, making it difficult for us to administer sham CPAP treatment to severe OSA patients in this trial. To minimize this limitation and to investigate the possibility of significant changes in heart rates between Holter ECG measurements before nCPAP treatment, we measured Holter ECG over two days for 15 of the 62 patients before nCPAP was started. These 15 were matched in age, BMI, AHI and antihypertensive medications to the overall group of 62 patients, and also matched to the remaining 47. The difference in heart rates between two measurements in the 15 patients was small.

Although this study has limitations, it suggests that OSAHS patients have an elevated heart rate and low plasma adiponectin before treatment, and that nCPAP therapy significantly reduces daytime heart rate in these patients. This implies that nCPAP therapy reduces the risk of patients with OSAHS for cardiovascular disease by lowering the heart rate, especially in those with hypertension or diabetes mellitus.

Acknowledgements

This work was supported by a Grant-in-Aid for the Respiratory Failure Research Group of the Japanese Ministry of Health, Labour and Welfare, and Japan Vascular Disease Research Foundation. We are grateful to Tomoko Toki for assistance with the manuscript preparation.

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; **328**:1230–5.
2. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA* 2003; **290**:1906–14.

3. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet* 2002; **359**:204–10.
4. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005; **365**:1046–53.
5. Bonsignore MR, Parati G, Insalaco G, Castiglioni P, Marrone O, Romano S, Salvaggio A, Mancia G, Bonsignore G, Di Rienzo M. Baroreflex control of heart rate during sleep in severe obstructive sleep apnoea: effects of acute CPAP. *Eur Respir J* 2006; **27**:128–35.
6. Engleman HM, McDonald JP, Graham D, Lello GE, Kingshott RN, Coleman EL, Mackay TW, Douglas NJ. Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. *Am J Respir Crit Care Med* 2002; **166**:855–9.
7. Palatini P, Julius S. Heart rate and the cardiovascular risk. *J Hypertens* 1997; **15**:3–17.
8. Dyer AR, Persky V, Stamler J, Paul O, Shekelle RB, Berkson DM, Lepper M, Schoenberger JA, Lindberg HA. Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. *Am J Epidemiol* 1980; **112**:736–49.
9. Kannel WB, Kannel C, Paffenbarger RS Jr., Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J* 1987; **113**:1489–94.
10. Greenland P, Daviglus ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, Stamler J. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. *Am J Epidemiol* 1999; **149**:853–62.
11. Palatini P, Casiglia E, Julius S, Pessina AC. High heart rate: a risk factor for cardiovascular death in elderly men. *Arch Intern Med* 1999; **159**:585–92.
12. Roche F, Gaspoz JM, Court-Fortune I, Minini P, Pichot V, Duverney D, Costes F, Lacour JR, Barthelemy JC. Screening of obstructive sleep apnea syndrome by heart rate variability analysis. *Circulation* 1999; **100**:1411–15.
13. Khoo MC, Belozeroff V, Berry RB, Sassoon CS. Cardiac autonomic control in obstructive sleep apnea: effects of long-term CPAP therapy. *Am J Respir Crit Care Med* 2001; **164**:807–12.
14. Bonsignore MR, Romano S, Marrone O, Chiodi M, Bonsignore G. Different heart rate patterns in obstructive apneas during NREM sleep. *Sleep* 1997; **20**:1167–74.
15. Bonsignore MR, Parati G, Insalaco G, Marrone O, Castiglioni P, Romano S, Di Rienzo M, Mancia G, Bonsignore G. Continuous positive airway pressure treatment improves baroreflex control of heart rate during sleep in severe obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2002; **166**:279–86.
16. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley TD. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med* 2003; **348**:1233–41.
17. Ziegler MG, Mills PJ, Loredo JS, Ancoli-Israel S, Dimsdale JE. Effect of continuous positive airway pressure and placebo treatment on sympathetic nervous activity in patients with obstructive sleep apnea. *Chest* 2001; **120**:887–93.
18. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* 1995; **270**:26746–9.
19. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 2004; **291**:1730–7.
20. Kazumi T, Kawaguchi A, Sakai K, Hirano T, Yoshino G. Young men with high-normal blood pressure have lower serum adiponectin, smaller LDL size, and higher elevated heart rate than those with optimal blood pressure. *Diabetes Care* 2002; **25**:971–6.
21. Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakao K, Ohi M. 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**:706–12.
22. Chin K, Nakamura T, Takahashi K, Sumi K, Ogawa Y, Masuzaki H, Muro S, Hattori N, Matsumoto H, Niimi A, Chiba T, Nakao K, Mishima M, Ohi M. Effects of obstructive sleep apnea syndrome on serum aminotransferase levels in obese patients. *Am J Med* 2003; **114**:370–6.
23. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; **22**:667–89.
24. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**:539–53.
25. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; **93**:1043–65.
26. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991; **84**:482–92.
27. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998; **98**:1071–7.
28. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation* 2003; **107**:68–73.
29. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. *J Clin Invest* 1997; **99**:106–9.
30. Fletcher EC, Lesske J, Qian W, Miller CC, 3rd, Unger T. Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. *Hypertension* 1992; **19**:555–61.

31. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995; **96**:1897–904.

32. Narkiewicz K, Somers VK. The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. *J Hypertens* 1997; **15**:1613–19.

33. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med* 2005; **352**:1206–14.

34. Pawlak DB, Kushner JA, Ludwig DS. Effects of dietary glycaemic index on adiposity, glucose homoeostasis, and plasma lipids in animals. *Lancet* 2004; **364**:778–85.

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

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

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

Abstract

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

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

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

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

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

(DOI: 10.2169/internalmedicine.45.1747)

Introduction

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

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

Received for publication February 3, 2006; Accepted for publication July 26, 2006

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

DOI: 10.2169/internalmedicine.45.1747

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

Patients and Methods

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

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

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

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

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

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

Table 1. Baseline Characteristics in Subjects

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

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

Statistical analysis

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

Results

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

DOI: 10.2169/internalmedicine.45.1747

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

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

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

Table 3. Pulmonary Functions and Blood Gas Analysis

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

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

Table 4. Comparisons between OHS and Markedly Obese OSAS

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

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

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

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