Fat Accumulation, Leptin, and Hypercapnia in Obstructive Sleep Apnea-Hypopnea Syndrome*

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Background: **Obesity and visceral fat accumulation (VFA) are risk factors for the development of obstructive sleep apnea-hypopnea syndrome (OSAHS), and a subgroup of OSAHS patients acquire hypoventilation. Circulating leptin, an adipocyte-derived signaling factor, increases in accordance with body mass index (BMI); under experimental conditions, leptin selectively decreases visceral adiposity and it is also a respiratory stimulant.**
Objective: **To investigate whether the location of body fat deposits, *ie*, the distribution of VFA and subcutaneous fat accumulation (SFA), contributes to hypoventilation and whether circulating levels of leptin are involved in the pathogenesis of hypoventilation, which is often observed in OSAHS.**
Methods: **We assessed VFA and SFA by abdominal CT scan, and measured lung function and circulating levels of leptin in 106 eucapnic and 79 hypercapnic male patients with OSAHS.**
Results: **In the whole study group, circulating leptin levels correlated with BMI ($r = 0.56$), VFA ($r = 0.24$), and SFA ($r = 0.47$), but not with Po_2 or sleep mean arterial oxygen saturation (Sao_2). BMI, percentage of predicted vital capacity, FEV_1/FVC ratio, apnea-hypopnea index, sleep mean Sao_2, VFA, and SFA were not significantly different between two groups. Circulating leptin levels were higher in the hypercapnic group than in the eucapnic group. Logistic regression analysis indicated that serum leptin was the only predictor for the presence of hypercapnia ($\beta = 0.21$, $p < 0.01$).**
Conclusions: **These results suggest that the location of body fat deposits may not contribute to the pathogenesis of hypoventilation, and circulating leptin may fail to maintain alveolar ventilation in hypercapnic patients with OSAHS.** ***(CHEST 2005; 127:543–549)***

Key words: hypoventilation syndrome; obesity; respiratory depression; subcutaneous fat; visceral fat

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CSF = cerebrospinal fluid; OSAHS = obstructive sleep apnea-hypopnea syndrome; Sao_2 = oxygen saturation; SFA = subcutaneous fat accumulation; VC = vital capacity; VFA = visceral fat accumulation

Leptin was first described as an adipose-derived hormone, which induces a complex response including control of body weight and energy expenditure after interaction with specific receptors located in the CNS and in peripheral tissues.[1] Leptin receptors are found in the hypothalamus, particularly in the arcuate nucleus, where leptin is thought to exert its primary feedback signaling.[2] Circulating levels of leptin reflect the amount of energy stored in adipose tissue and are reported to correlate with the body mass index (BMI) in humans.[3,4]

Control of body weight is clinically important in patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) because obesity, male gender, and increasing age are recognized to be risk factors for OSAHS. Among these risk factors, obesity plays a major role, because approximately 70% of patients with this disorder are obese and obesity is the only reversible risk factor of importance.[5] Among those with OSAHS, some individuals present an increase

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in resting $PaCO_2$, leading to obesity hypoventilation syndrome.[6] Obesity itself is thought to affect the respiratory control system. The mechanical load imposed by obesity, especially visceral fat accumulation (VFA), on the respiratory system may explain the development of hypoventilation, although the majority of obese people breathe normally.[6] Alternatively, central defects of the respiratory control system may contribute to respiratory depression; however, the precise mechanisms have been undefined.[7]

Leptin may be a modulator of the respiratory control system. The absence of leptin in the C57BL/6J-Lep^{ob} mouse is associated with marked obesity, elevated $PaCO_2$, and a reduced hypercapnic ventilatory response.[8] Conversely, leptin replacement in these mutant mice stimulated ventilation and hypercapnic ventilatory response across all sleep/wake states. The effects of leptin deficiency on respiratory depression, and the effects of leptin administration on respiratory control, were more pronounced during sleep than wakefulness in mice, although the precise mechanism by which leptin influences respiratory control has been undefined.[9,10] However, whether endogenous leptin plays a role in the respiratory control system in healthy humans and/or patients with OSAHS remains unclear. In addition, whether leptin affects visceral adiposity has not been determined in OSAHS, although it has been reported that leptin selectively decreases visceral adiposity in rats.[11]

The purpose of the present study was to examine whether the location of body fat deposits, *ie*, the distribution of VFA and subcutaneous fat accumulation (SFA), contributes to hypoventilation, and whether circulating levels of leptin are involved in the pathogenesis of hypoventilation, which is often observed in OSAHS. We hypothesized that reduced levels of leptin may explain the increase of $PaCO_2$ when BMI is similar in eucapnic and hypercapnic OSAHS patients.

Materials and Methods

The study population consisted of 185 male patients with OSAHS who were examined using polysomnography from April 2001 to December 2003. All patients were free from respiratory infection, heart failure, and other respiratory problems, including COPD, at the time of polysomnography. They were asked to complete a questionnaire on sleep symptoms, medical history, and medications. OSAHS was established on the basis of clinical and polysomnographic criteria. The average number of episodes of apnea and hypopnea per hour of sleep (the apnea-hypopnea index [AHI]) was calculated as the summary measurement of sleep-disordered breathing. In addition to clinical symptoms, an AHI of > 5 was also used as a selection criterion.

A male population with clinical symptoms of sleep apnea ($n = 520$) was first divided into two groups according to AHI (AHI ≥ 5 [$n = 426$] and AHI < 5 [$n = 94$]). Next, patients with AHI ≥ 5 were subclassified into two groups according to $PaCO_2$ level ($PaCO_2 > 45$ mm Hg [$n = 79$] and $PaCO_2 \leq 45$ mm Hg [$n = 327$]). Hypercapnic OSAHS patients ($PaCO_2 > 45$ mm Hg) were more obese and had a higher AHI and a lower arterial oxygen saturation (Sa_{O_2}) during sleep compared with eucapnic OSAHS patients. Then, eucapnic OSAHS patients ($PaCO_2 \leq 45$ mm Hg) were further subclassified into two subgroups according to AHI (AHI > 60 [$n = 45$] and AHI ≤ 60 [$n = 302$]). In addition, to compare hypercapnic and eucapnic patients matched for BMI and age, and to match the number of patients, those with an AHI ≤ 60 were further subclassified into two groups according to BMI (BMI > 30 [$n = 61$] and BMI ≤ 30 [$n = 241$]). Finally, a subgroup with an AHI > 60 ($n = 45$) and a subgroup with an AHI ≤ 60 and a BMI > 30 ($n = 61$) were selected for the eucapnic group (Fig 1).

Pulmonary function tests were performed to determine vital capacity (VC) and FEV_1 using a standard spirometer (Fudac-60; Fukuda Denshi; Tokyo, Japan). Arterial blood gas samples during room air breathing were drawn with the patient in the supine position and measured in a blood gas analyzer (Model 1312; Instrumental Laboratory; Milano, Italy).

Overnight polysomnography (Compumedics; Melbourne, Australia) was performed between 9 PM and 6 AM. Polysomnography consisted of continuous polygraphic recording from surface leads for EEG, electro-oculography, 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. Polysomnographic records were staged manually according to standard criteria.[12] Respiratory events were scored according to American Academy of Sleep Medicine criteria[13]: apnea was defined as complete cessation of airflow lasting ≥ 10 s, and hypopnea was defined as either a $\geq 50\%$ reduction in airflow for ≥ 10 s or a $< 50\%$ but discernible reduction in airflow accompanied either by a decrease in oxyhemoglobin saturation of $> 3\%$ or arousal. Severity of OSAHS was determined based on the AHI and mean and lowest Sa_{O_2}.

At 7 AM on the morning after the sleep study, venous blood was obtained in the fasting state to measure leptin. Serum levels of leptin were determined by radioimmunoassay (Linco Research; St. Louis, MO) with intraassay and interassay coefficients of variation of 2.8 to 3.8% ($n = 10$) and 0.4 to 4.6% ($n = 10$), respectively.[14]

Areas of SFA and VFA were measured by CT in a single cross-sectional scan at the level of the umbilicus.[15] The area of VFA was divided by that of SFA to calculate the VFA/SFA ratio. 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.

Statistical Analysis

The results are expressed as mean ± SEM. Age, BMI, pulmonary function parameters, and sleep parameters were compared between hypercapnic and eucapnic patients using the Mann-Whitney *U* test. Since data were not normally distributed, we used Spearman rank correlation coefficient to examine the association of two parameters. Analysis of covariance was used to compare the influence of BMI, VFA, and SFA on circulating leptin levels between hypercapnic and eucapnic patients. Logistic regression analysis was performed with $PaCO_2$ as the dependent variable and leptin, BMI, VFA, SFA, mean Sa_{O_2} during sleep, percentage of predicted VC, and percentage of predicted FEV_1 as explanatory variables; $p < 0.05$ was considered statistically significant.