Cardiovascular risk factors and ultrasound evaluation of intima-media thickness at common carotids, carotid bulbs, and femoral and abdominal aorta arteries in patients with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab 92:1015–1018
8. Kapur VK (2010) Obstructive sleep apnea: diagnosis, epidemiology, and economics. Respir Care 55:1155–1167
9. Lovas K, Loge JH, Husebye ES (2002) Subjective health status in Norwegian patients with Addison's disease. Clin Endocrinol 56:581–588
10. Lovas K, Husebye ES, Holsten F, Bjorvatn B (2003) Sleep disturbance in patients with Addison's disease. Eur J Endocrinol 148:449–456
11. Lavigne GJ, Montplaisir JY (1994) Restless legs syndrome and sleep bruxism. Sleep 17:739–743
12. Maurice MO, Kasey KL, Christian G (2001) Risk factors for sleep bruxism in the general population. Chest 119:53–61
13. Macaluso GM, Guerra P, Giovanni GD, Boselli M, Parrino L, Terzano MG (1998) Sleep bruxism is a disorder related to periodic arousals during sleep. J Dent Res 77:565–573
14. Kato T, Rompre P, Montplaisir JY, Sessle BJ, Lavigne GJ (2001) Sleep bruxism: an oromotor activity secondary to micro-arousal. J Dent Res 80:1940–1944
15. Somers VK, Dyken ME, Clary MP, Abboud FM (1995) Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 96:1897–1904

Sleep Breath (2012) 16:473–481
DOI 10.1007/s11325-011-0528-7

ORIGINAL ARTICLE

Analysis of anatomical and functional determinants of obstructive sleep apnea

Kensaku Aihara · Toru Oga · Yuka Harada · Yuichi Chihara · Tomohiro Handa · Kiminobu Tanizawa · Kizuku Watanabe · Takefumi Hitomi · Tomomasa Tsuboi · Michiaki Mishima · Kazuo Chin

Received: 19 November 2010 / Revised: 7 April 2011 / Accepted: 4 May 2011 / Published online: 15 May 2011

Abstract
Purpose Craniofacial abnormalities have an important role in the occurrence of obstructive sleep apnea (OSA) and may be particularly significant in Asian patients, although obesity and functional abnormalities such as reduced lung volume and increased airway resistance also may be important. We conducted simultaneous analyses of their interrelationships to evaluate the relative contributions of obesity, craniofacial structure, pulmonary function, and airway resistance to the severity of Japanese OSA because there are little data in this area.
Methods A cross-sectional observational study was performed on 134 consecutive Japanese male patients. A sleep study, lateral cephalometry, pulmonary function tests, and impulse oscillometry (IOS) were performed on all patients.
Results Age, body mass index (BMI), position of the hyoid bone, and proximal airway resistance on IOS (R20) were significantly related to the apnea/hypopnea index (AHI) ($p<0.05$) in multiple regression analysis. Subgroup analysis showed that, for moderate-to-severe OSA (AHI≥15 events/h), neck circumference and R20 were predominantly related to AHI, whereas for non-to-mild OSA (AHI<15 events/h), age and expiratory reserve volume were the predominant determinants. In obese subjects (BMI≥25 kg/m^2), alveolar–arterial oxygen tension difference, position of the hyoid bone, and R20 were significantly associated with AHI, whereas age alone was a significant factor in nonobese subjects (BMI<25 kg/m^2).
Conclusions Aside from age and obesity, anatomical and functional abnormalities are significantly related to the severity of Japanese OSA. Predominant determinants of AHI differed depending on the severity of OSA or the magnitude of obesity.

Keywords Obstructive sleep apnea · Obesity · Cephalometry · Pulmonary function · Impulse oscillometry

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction. The critical pathophysiological feature of OSA is sleep-related narrowing or closure of the upper airway at the level of the pharynx [1, 2]. Anatomical abnormality is an important risk factor for OSA, and most patients with OSA have craniofacial abnormalities such as a small mandible, enlarged tongue, enlarged soft palate, inferior displacement of the hyoid bone, and imbalance between soft tissue volume and bony enclosure size [3–5]. Dempsey et al. [6] analyzed the interactive effects of obesity and craniofacial structure on sleep-disordered breathing and reported that body mass index (BMI) and cephalometric dimensions equally contributed to the elevated apnea/hypopnea index (AHI). However, a recent study showed that craniofacial

Electronic supplementary material The online version of this article (doi:10.1007/s11325-011-0528-7) contains supplementary material, which is available to authorized users.

K. Aihara · Y. Harada · Y. Chihara · T. Handa · K. Tanizawa · K. Watanabe · M. Mishima
Department of Respiratory Medicine,
Graduate School of Medicine, Kyoto University,
Kyoto, Japan

T. Oga (✉) · T. Hitomi · T. Tsuboi · K. Chin
Department of Respiratory Care and Sleep Control Medicine,
Graduate School of Medicine, Kyoto University,
54 Kawahara, Shogoin, Sakyo-ku,
Kyoto 606-8507, Japan
e-mail: ogato@kuhp.kyoto-u.ac.jp

structure and obesity contributed differently to OSA between Caucasian and Asian patients [7]. In addition, Dempsey et al. pointed out some additional factors that might explain elevations in the AHI and speculated that functional abnormalities such as impaired neural control of upper airway muscles and ventilatory instability, which may cause increased airway resistance, might be candidates [6].

It has been shown that pharyngeal patency in OSA patients is lung volume dependent [8, 9], and previous reports indicated a significant correlation between a reduced lung volume and nocturnal obstructive apnea and desaturation [10, 11]. Increased upper airway resistance also was shown to play a role in the pathogenesis of OSA [12, 13] through the association with increased susceptibility of airway narrowing and collapse [2, 14]. Thus, in addition to anatomical abnormalities, functional abnormalities such as reduced lung volume and increased airway resistance have been shown to play important roles in the pathogenesis of OSA.

Obesity, the most important risk factor for OSA, is known to affect craniofacial structures [15], lung volume [16], and airway resistance [17, 18]. However, given the substantial number of nonobese OSA patients in Japan [19], we hypothesized that there would be significant relationships between OSA and anatomical and functional factors as well as obesity, reflecting a multi-factorial pathophysiological feature of OSA. Therefore, in the present study, we simultaneously analyzed the interrelationships among craniofacial structure, pulmonary function, airway resistance, obesity, and OSA to investigate the relative contributions of these factors to the severity of OSA.

Materials and methods

Study subjects

We performed a cross-sectional observational study of 134 consecutive Japanese male patients who visited the Sleep Unit of Kyoto University Hospital between January 2009 and February 2010 for evaluation of OSA. None had been previously diagnosed with or treated for OSA. Patients with pulmonary diseases such as asthma or chronic obstructive pulmonary disease and who were diagnosed as having central sleep apnea were excluded. This study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee, and informed consent was obtained from all patients. A sleep study, lateral cephalometry, pulmonary function tests, and impulse oscillometry (IOS) were performed on all patients. To establish smoking history, the Brinkman index was calculated by the following formula:

$$\text{Brinkman index} = \text{number of cigarettes smoked per day} \times \text{number of smoking years.}$$

Arterial blood gas analysis, including arterial partial pressure of oxygen (PaO_2) and arterial partial pressure of carbon dioxide ($PaCO_2$), was performed with patients' breathing room air at rest in the supine position at 19:00. Alveolar–arterial oxygen tension difference ($A\text{-}aDO_2$) was calculated according to the standard formula, using the respiratory exchange ratio of 0.8.

Polysomnography

Diagnosis of OSA was confirmed by polysomnography (SomnoStar pro, Cardinal Health, Dublin, OH, USA), which was started at 22:00 and ended at 6:00 the following morning. Surface electrodes were attached using standard techniques to obtain an electrooculogram, electromyogram of the chin, and 12-lead electroencephalograph. Sleep stages were defined according to the criteria of Rechtschaffen and Kales [20]. Ventilation was monitored by inductive plethysmography (Respitrace QDC, Viasys Healthcare, Palm Springs, CA, USA). Airflow was monitored by a nasal air pressure transducer (PTAFlite, Pro-Tech Services Inc., Mukilteo, WA, USA) and supplemented by an oronasal thermal sensor (Sleepmate Technologies, Midlothian, VA, USA). Arterial oxygen saturation (SpO_2) was monitored continuously with a pulse oximeter (Adult Flex System, Nonin Medical, Plymouth, MN, USA).

Apnea was defined as the complete cessation of airflow and hypopnea as a clear decrease in airflow of 30% or more lasting for 10 s or more, accompanied by a decrease in SpO_2 of at least 4% [21]. All AHI values were expressed as the number of episodes of apnea and hypopnea per hour over the total sleep time. The lowest SpO_2 during sleep and the percentage of time of SpO_2 90% during sleep also were calculated in each patient. OSA severity was defined by the AHI as follows: non-OSA ($AHI<5$), mild OSA ($5\leq AHI<15$), moderate OSA ($15\leq AHI<30$), and severe OSA ($AHI\geq 30$).

Cephalometry

A lateral cephalogram was obtained for each subject. The cephalograms were taken on image plates (ST-VI, Fuji Medical Systems, Tokyo, Japan) with the subject in the sitting position at a film focus distance of 2 m, with a left to right view. Exposures were made at 75 kV and 320 mA at the end-expiratory phase during quiet breathing through the

nose, and a cephalostat was used to keep the subject's head in a position such that the Frankfort horizontal line was parallel to the floor during exposure. Images of the cephalograms were digitized and input into a computer, previewed and processed for sharp visibility of both the soft tissues and bony structures, and printed out through a computed radiography system (FCR Profect CS, Fuji Medical Systems). A total of 22 variables related to both craniofacial skeletal and soft tissue morphology were measured as angular (degrees), linear (millimeters), or area (square centimeters) by a single observer in a single-blind manner. Images were analyzed using Image J software (US NIH, Bethesda, MD, USA). Every measurement was made by the same observer, who had no knowledge of the clinical status of the patient.

The cephalometric landmarks and reference lines are defined in Table 1 and illustrated anatomically in Fig. 1. The following angles and dimensions were measured: SNA, antero-posterior position of the maxilla in relation to the anterior cranial base (angle between S–N and N–A); SNB, antero-posterior position of the mandible in relation to the anterior cranial base (angle between S–N and N–B); ANB, relative position of the mandible to the maxilla (angle between N–A and N–B); facial axis, vertical position of the mandible in relation to the skull (angle between Pt–Gn and N–Ba); G–VL, antero-posterior position of the chin in relation to the vertebra (linear distance along the perpendicular plane from G to VL); N–Ba, the length of the cranial base (distance between N and Ba); S–N, the length of the anterior cranial base (distance between S and N); ANS–PNS, the length of the hard palate (distance between ANS and PNS); PNS–Ba, bony nasopharynx (distance between PNS and Ba); PNS–P, the length of the soft palate (distance between PNS and P); PNS–V, the length of the pharyngeal airway (distance between PNS and V); MPT, greatest thickness of the soft palate; TGL, the length of the tongue (distance between V and TT); TGH, height of the tongue (linear distance along the perpendicular bisector of the V–TT line to the tongue dorsum); Me–Go, the length of the mandible (distance between Me and Go); MP–H, vertical position of the hyoid bone (linear distance along the perpendicular plane from H to MP); H–VL, antero-posterior position of the hyoid bone (linear distance along the perpendicular plane from H to VL); AW1, upper oropharyngeal airway caliber (narrowest part of the airway between PNS and P); AW2, lower oropharyngeal airway caliber (narrowest part of the airway between P and Go); airway area, dimensions of the oropharynx (area outlined by the inferior border of the nasopharynx, the posterior surface of the soft palate and tongue, the line parallel to the palatal plate through the point V, and the posterior pharyngeal wall); tongue area, dimensions of the tongue (area outlined by the dorsal aspect of the tongue surface and lines that join TT, G, H, and V); and the lower face cage,

Table 1 Definitions of cephalometric landmarks and reference lines

S	Sella, midpoint of the fossa hypophysealis
N	Nasion, anterior point at the frontonasal suture
ANS	Anterior nasal spine, most anterior point of the nasal spine
PNS	Posterior nasal spine, most posterior point of the nasal spine
A	Deepest anterior point in the concavity of the anterior maxilla
B	Deepest anterior point in the concavity of the anterior mandible
Cd	Medial condylar point of the mandible
Cd′	A point that Pg projects onto the perpendicular line to the Cd–A line at the Cd point
Go	Gonion, a mid-plane point at the gonial angle located by bisecting the posterior and inferior borders of the mandible
Me	Menton, most inferior point of the chin bone
Ba	Basion, most posteroinferior point on the clivus
G	Most posterior point on the symphysis of the mandible
Pg	Prognathion, most anterior point on the symphysis of the mandible
P	Lowest point of the soft palate
TT	Most anterior point of the tip of the tongue
H	Most anterosuperior point of the hyoid bone
V	Most antero-inferior point of the epiglottic fold
Pt	Intersection of the posterior pharyngeal wall and most inferior margin of the foramen rotundum
Gn	Gnathion, the most antero-inferior point of body chin
NL	Nasal line, a line through ANS and PNS
MP	Mandibular plane, a plane constructed from Me through Go
VL	A line across C3 and C4

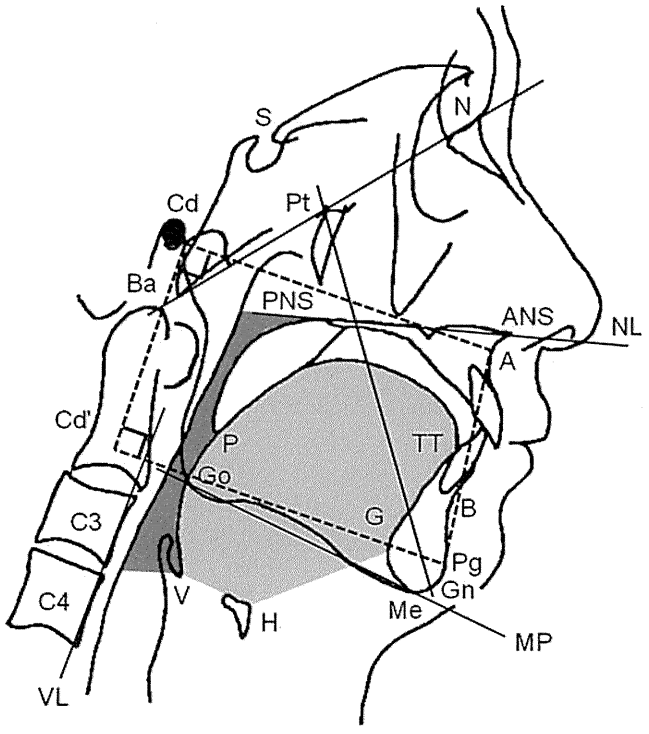

Fig. 1 Cephalometric landmarks and reference lines. For definitions, see Table 1. *Shaded area* indicates cross-sectional area of the tongue. *Dark-stained area* indicates cross-sectional area of the airway. *Lower face cage* was defined as a trapezoid formed by Cd–A–Pg–Cd′ (*dotted lines*)

the maxillomandibular enclosure size of the upper airway (cross-sectional area of the trapezoid enclosed by Cd–A–Pg–Cd′). Upper airway anatomical balance was assessed by the ratio between the tongue area and lower face cage as described in a previous study [5].

Pulmonary function tests

Pulmonary function tests were performed in the sitting position using CHESTAC (Chest M.I. Inc., Tokyo, Japan). Subjects underwent spirometric testing according to the recommended method [22]. Residual volume (RV) and total lung capacity (TLC) were measured by the closed circuit helium method, and diffusing capacity for carbon monoxide (DL_{CO}) was measured using a single-breath technique.

IOS

The assessment of respiratory impedance was performed by IOS (Masterscreen IOS-J, Jaeger, Wurzburg, Germany). IOS is different from the classical forced oscillation technique (FOT) because an impulse rather than a pseudo-random noise signal is applied by the loudspeaker. Data processing is also different between IOS and FOT. But IOS yields respiratory system resistance and reactance values similar to those provided by FOT [23]. Subjects were measured first in the sitting position and then in the supine position, fulfilling standard recommendations [24], as previously reported in detail elsewhere [25, 26]. In short, rectangular mechanical impulses containing the whole frequency spectrum were applied to the respiratory system through a mouthpiece while the patient was breathing quietly. The resulting pressure and flow signals were analyzed for amplitude, and the impedance (Z) represents the total mechanical load of the subject's respiratory system from which the resistance (R) and the reactance (X) of the respiratory system can be derived. The frequency range of the signal was from 5 to 35 Hz. The impedance at 5 Hz (Z5) represents the impedance of the total respiratory system. In the present study, we used respiratory resistance at 5 and 20 Hz (R5 and R20) as indices of total and proximal airway resistance, respectively. In IOS, low frequency oscillations are transmitted to the lung periphery, while those at frequencies ≥20 Hz are thought to be damped out before reaching the peripheral airways [27]. The reactance at 5 Hz (X5) may be determined by homogeneous distribution of ventilation, effective ventilation capacity, and compliance of the lung and chest wall. These indices have been shown to be useful for the evaluation of upper airway patency in OSA [12, 13].

Statistics

All statistical analyses were performed using StatView version 5.0 for Windows (Abacus Concepts, Berkeley, CA, USA). Continuous variables are expressed as means ± standard deviation (SD). Intra-observer agreement for the cephalometric measurements was evaluated by the intra-class correlation coefficient (ICC) [28]. The natural logarithm of the AHI was used as the dependent variable since the absolute values were not distributed normally. Chi-square tests were used to compare dichotomous variables and unpaired Student's t tests were used to compare continuous data between two groups. Relationships between two variables were analyzed by Pearson's correlation coefficient tests. Stepwise multiple regression analyses were performed to identify variables that could best explain AHI. A p value less than 0.05 was considered to indicate statistical significance.

Results

Relative contributions of obesity, craniofacial structure, pulmonary function, and IOS measurements to AHI in all subjects

Patient characteristics and polysomnographic data are shown in Table 2. The study group of 134 patients comprised 19

Table 2 Clinical characteristics and polysomnographic data on 134 patients

Age (years)	56.5±14.5
BMI (kg/m^2)	26.5±4.2
Neck circumference (cm)	40.2±3.2
Smoking history (current/ex/never)	37/70/27
Brinkman index	528±603
AHI (events/h)	26.0±22.5
Logarithmic AHI	2.8±1.3
Minimum SpO_2 (%)	79.0±10.5
SpO_2 <90% time/TST (%)	14.8±21.4
$PaCO_2$ (kPa)	5.6±0.5
PaO_2 (kPa)	11.4±1.5
A-aDO_2 (kPa)	1.6±1.5

Data presented as mean ± SD

BMI body mass index, *AHI* apnea/hypopnea index, *TST* total sleep time, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *A-aDO_2* alveolar–arterial oxygen tension difference

Table 3 Stepwise multiple regression analysis to predict AHI (n=134)

	r^2
Age (years)	0.08
BMI (kg/m^2)	0.09
Neck circumference (cm)	–
PaO_2 (kPa)	–
A-aDO_2 (kPa)	–
Tongue area (cm^2)	–
PNS–P (mm)	–
TGL (mm)	–
MP-H (mm)	0.05
ERV (L)	–
%ERV (% pred)	–
R5 (kPa/L/s)	–
Z5[a] (kPa/L/s)	–
R5[a] (kPa/L/s)	–
R20[a] (kPa/L/s)	0.06
Cumulative r^2	0.28

AHI apnea/hypopnea index, *BMI* body mass index, *PaO_2* arterial partial pressure of oxygen, *A-aDO_2* alveolar–arterial oxygen tension difference, *ERV* expiratory reserve volume

[a] In the supine position

non-OSA, 32 mild OSA, 37 moderate OSA, and 46 severe OSA patients. Regarding cephalometric measurements, intra-observer agreement was excellent (ICC ranged from 0.92 to 0.99) for all variables except for ANB and TGL, which had good intra-observer agreement (ICC=0.82 in ANB and 0.83 in TGL). We investigated the associations between anthropometric variables, arterial blood gas data, cephalometric parameters, pulmonary function, IOS measurements, and AHI. The AHI had a significant positive correlation with age (r=0.26, p=0.003), BMI (r=0.32, p=0.0002), neck circumference (r=0.33, p=0.0001), and A-aDO_2 (r=0.37, p< 0.0001) and a negative correlation with PaO_2 (r=−0.31, p= 0.0003) (Table E1). Examination of cephalometric parameters showed that the AHI had a significant positive correlation with the tongue area (r=0.18, p=0.04), PNS–P (r=0.30, p=0.0004), TGL (r=0.23, p=0.008), and MP–H (r=0.28, p=0.001) (Table E2). Regarding pulmonary function, there was a significant negative correlation between the AHI and only with the expiratory reserve volume (ERV) (r=−0.28, p=0.001) and %ERV (r=−0.24, p=0.007) (Table E3). The results of IOS measurements revealed that the AHI had a significant positive correlation with R5 (r=0.22, p=0.01) in the sitting position and Z5 (r= 0.19, p=0.03), R5 (r=0.24, p=0.006), and R20 (r=0.25, p= 0.004) in the supine position (Table E3).

Stepwise multiple regression analysis was performed to examine the relationships with AHI using the preselected variables that were significantly related to AHI in the above analyses (Table 3). Age, BMI, MP–H by cephalometry, and R20 in the supine position on IOS significantly explained 28% of the variance in AHI [r^2 (coefficient of determination)=0.08, 0.09, 0.05, and 0.06, respectively].

Relative contributions of obesity, craniofacial structure, pulmonary function, and IOS measurements to the AHI based on the severity of OSA

We then compared the predominant determinants of AHI between 83 moderate-to-severe (AHI≥15) and 51 non-to-mild (AHI<15) OSA subjects. The clinical characteristics and polysomnographic data for these patients are shown in Table 4. The BMI and neck circumference were significantly higher, and the PaO_2 was significantly lower in moderate-to-severe OSA than in non-to-mild OSA (p= 0.007, 0.002, and 0.004, respectively). As we did for the overall group of 134 patients, we performed stepwise multiple regression analyses to account for AHI in the moderate-to-severe and the non-to-mild groups, using the preselected variables that were significantly related to AHI. They included BMI, neck circumference, PaO_2, A-aDO_2, R5 and R20 in the sitting position, and Z5, R5, and R20 in the supine position in moderate-to-severe OSA and included age, $PaCO_2$, VC, ERV, FEV_1, RV/TLC, and $\%DL_{CO}$ in non-to-mild OSA. In moderate-to-severe OSA, neck circumference and R20 in the supine position on IOS (r^2=0.11 and 0.10, respectively) significantly explained 21% of the variance in AHI. By contrast, in non-to-mild OSA, age and ERV (r^2=0.19 and 0.10, respectively) significantly explained 29% of the variance in AHI.

Table 4 Comparison of clinical characteristics and polysomnographic data between groups based on the severity of OSA

	AHI≥15 (n=83)	AHI<15 (n=51)	p value
Age (years)	57.6±12.3	54.7±17.4	0.26
BMI (kg/m^2)	27.2±4.6	25.2±3.2	0.007
Neck circumference (cm)	40.9±3.5	39.1±2.3	0.002
Smoking history (current/ex/never)	18/46/19	9/24/18	0.18
Brinkman index	578±595	446±613	0.22
AHI (events/h)	38.1±20.6	6.5±4.4	<0.0001
Logarithmic AHI	3.5±0.5	1.5±1.2	<0.0001
Minimum SpO_2 (%)	74.5±10.4	86.3±5.0	<0.0001
SpO_2 <90% time/TST (%)	22.9±23.7	1.6±2.4	<0.0001
$PaCO_2$ (kPa)	5.6±0.5	5.7±0.4	0.32
PaO_2 (kPa)	11.1±1.4	11.9±1.5	0.004
A-aDO_2 (kPa)	1.9±1.4	1.0±1.5	0.0008

Data presented as mean ± SD. Unpaired t tests were performed except for the chi-square test for smoking history

BMI body mass index, *AHI* apnea/hypopnea index, *TST* total sleep time, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *A-aDO_2* alveolar–arterial oxygen tension difference

Relative contributions of obesity, craniofacial structure, pulmonary function, and IOS measurements to AHI based on the magnitude of obesity

We then compared the predominant determinants of AHI between 79 obese (BMI≥25) and 55 nonobese (BMI<25) subjects. The clinical characteristics and the polysomnographic data on these patients are shown in Table 5. There was a trend for more current smokers or ex-smokers to be present among the obese subjects. Neck circumference and the mean AHI were significantly higher, and the PaO_2 was significantly lower in obese subjects than in nonobese subjects (p<0.0001, p=0.002, and p<0.0001, respectively). We also performed stepwise multiple regression analyses to account for AHI in obese and nonobese subjects using the preselected variables that were significantly related to AHI. They included BMI, neck circumference, PaO_2, A-aDO_2, PNS–P, TGL, MP-H, ERV, and R5 and R20 in the sitting and supine positions in obese subjects and age and A-aDO_2 in nonobese subjects. In obese subjects, A-aDO_2, MP-H by cephalometry, and R20 in the sitting position on IOS (r^2=0.08, 0.10, and 0.07, respectively) significantly accounted for 25% of the variance in AHI. In contrast, in nonobese subjects, age alone was significantly related to AHI (r^2=0.25).

Discussion

We simultaneously analyzed the interrelationships between OSA and obesity, anatomical abnormalities measured by cephalometry, and functional abnormalities measured by pulmonary function testing and IOS. By multiple regression analysis, we found that age, BMI, MP-H by cephalometry, and R20 on IOS significantly contributed to AHI. In addition, separate analyses revealed that significant determinants of OSA differed between moderate-to-severe OSA and non-to-mild OSA and between obese subjects and nonobese subjects.

In addition to age and obesity (BMI), an anatomical abnormality (inferior displacement of the hyoid bone) and a functional abnormality (increased proximal airway resis-

Table 5 Comparison of clinical characteristics and polysomnographic data between groups based on the magnitude of obesity

	BMI≥25 (n=79)	BMI<25 (n=55)	p value
Age (years)	55.9±13.2	57.3±16.3	0.58
BMI (kg/m^2)	28.9±3.7	22.9±1.4	<0.0001
Neck circumference (cm)	41.7±3.0	38.1±2.2	<0.0001
Smoking history (current/ex/never)	19/44/16	8/26/21	0.02
Brinkman index	611±618	408±566	0.054
AHI (events/h)	31.0±25.6	18.9±14.6	0.002
Logarithmic AHI	3.0±1.2	2.5±1.3	0.03
Minimum SpO_2 (%)	77.1±11.5	81.8±8.2	0.009
SaO_2 <90% time/TST (%)	20.7±25.5	6.3±8.2	<0.0001
$PaCO_2$ (kPa)	5.6±0.5	5.6±0.4	0.47
PaO_2 (kPa)	10.9±1.5	12.0±1.4	<0.0001
A-aDO_2 (kPa)	2.1±1.4	0.9±1.4	<0.0001

Data presented as mean ± SD. Unpaired t tests were performed except for the chi-square test for smoking history

BMI body mass index, *AHI* apnea/hypopnea index, *TST* total sleep time, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *A-aDO_2* alveolar–arterial oxygen tension difference

tance) were significantly related to OSA. Obesity and age have been considered to be the characteristic risk factors for OSA [29]. On the other hand, certain forms of craniofacial abnormalities measured by cephalometry [3–5], reduced lung volume [8–11], and increased upper airway resistance [12, 13] also have been suggested as predisposing factors for upper airway obstruction during sleep. Although these factors may be significantly affected by age and obesity [15–17, 30, 31], the relative contributions of anatomical and functional abnormalities, age, and obesity to OSA have remained to be elucidated. Our findings indicate that OSA is the result of independent interrelationships among anatomical abnormalities, functional abnormalities, age, and obesity, which reflects a multi-factorial pathophysiological feature of OSA.

We found that, compared with pulmonary function, airway resistance on IOS was related more closely to AHI. Structurally, the pharyngeal airway is surrounded by soft tissue, which is enclosed by bony structures and is caudally pulled by the thorax. As has been suggested, an imbalance between the amount of soft tissue and the size of the surrounding bony structures [32] and decreased thoracic traction [33] due to a reduced lung volume may result in increased tissue pressure surrounding the pharyngeal airway and decreased longitudinal tension of the pharyngeal airway wall, leading to increased upper airway resistance. Moreover, airway resistance was shown to increase when the body position changed from a sitting to a supine position [34]. In nonobese subjects, the falls in lung volume in a supine position are likely to lead to increased airway resistance, while in obese subjects in a supine position, such falls are smaller than in nonobese subjects and can only partly explain an increase in airway resistance [34]. Hence, there must be additional causes and sites of increased airway resistance in obese subjects. Our results showed the importance and usefulness of demonstrations of increased airway resistance on IOS in explaining the severity of OSA.

In one subgroup analysis, predominant determinants of AHI differed depending on the severity of OSA. In moderate-to-severe OSA, neck circumference and airway resistance were predominantly related to AHI, whereas in non-to-mild OSA, age and ERV were predominantly related to AHI. There was no overlap in those factors that were significantly associated with AHI, indicating a different pathogenesis of the disease between moderate-to-severe versus non-to-mild OSA. Asians were reported to have more severe OSA than Caucasians even when the BMI was similar between the two groups [7]. Our results indicate the importance of increased fat deposition adjacent to the upper airway rather than total body fat volume in Japanese individuals with moderate-to-severe OSA, which may partially explain this difference. Although it has been suggested that the consequences of craniofacial abnormalities are more severe in Japanese than in Caucasian OSA patients [3], craniofacial abnormalities were not significantly related to AHI in both moderate-to-severe and non-to-mild OSA groups in the present study after adjustment for other risk factors, although further study is needed. Moreover, that age independently correlated with non-to-mild OSA but not moderate-to-severe OSA may partly support the evidence that with increasing age, OSA prevalence increases but that its severity does not [19, 29].

Another subgroup analysis showed that in obese subjects, A-aDO_2, the distance between the hyoid bone and mandible, and airway resistance were predominantly related to AHI. Recent studies suggested that subclinical lung injury may be present in OSA possibly through local oxidative stress in the alveolus [35, 36]. Although the magnitude of the injury might not be great, given the effect of ventilation–perfusion inequality due to obesity [16], A-aDO_2 can be significantly related to AHI in obese OSA subjects. The position of the hyoid bone is correlated with accumulations of adipose tissue in pharyngeal regions, and its inferior displacement may give rise to the posterior relocation of the tongue and reduce upper airway patency [3, 37, 38]. Abdominal fat is likely to have direct effects on the downward movement of the diaphragm and is associated with increased airway resistance through the reduction in lung volume [16, 39]. Our results may also imply the importance of abundant parapharyngeal and intraabdominal distribution of adipose tissue in obese subjects. Additionally, in nonobese subjects, age alone had a significant relationship with the AHI. The unexplained variance by age may be related to structural or functional abnormalities that were not measured, indicating the complicated pathogenesis of OSA in lean individuals.

Unfortunately, the four crucial features in our study account for only 28% of the variance in AHI. There are several possible explanations. Firstly, various determinants of OSA, not limited to obesity, might be characteristic in Japanese subjects. Secondly, all of our anatomical and functional measurements were obtained during wakefulness, which may have limited relevance to the sleeping state. Furthermore, some cephalometric measurements, including that of the position of the hyoid bone, may be affected by muscle contraction required for central occlusion of the jaw. Thirdly, we did not evaluate the degree of ventilatory control stability. It is termed "loop gain", whose increase is suggested to play an important role in the pathogenesis of OSA [40, 41]. Additional assessments might have explained a certain proportion of the residual variance in AHI.

As a limitation, the present study had a small sample size (especially non-OSA subjects) with only male subjects from one university hospital, which might have limited the

generalization of the results. Moreover, we only studied Japanese subjects and did not directly assess inter-ethnic differences in OSA risk factors. Considering that OSA is highly prevalent worldwide, inter-ethnic differences in OSA risk factors is an important issue. Although we discussed inter-ethnic differences by comparing the results with previous studies, such as those of a recent study by Lee et al. [7], further studies directly comparing OSA risk factors in different ethnic groups would more clearly elucidate those risk factors. Another limitation is that we assessed craniofacial structures only by cephalometry. Our limited measures of craniofacial morphology may underestimate the actual contributions of craniofacial morphology, especially of upper airway anatomical imbalance. Additional three-dimensional, volumetric evaluations using computed tomography [42] or magnetic resonance imaging [43] might show more sensitively the impact of anatomical imbalance on the pathogenesis of OSA.

OSA is a multi-factorial disease in which age and obesity play important roles. However, aside from age and obesity, our results indicated that both anatomical and functional abnormalities play significant roles in the pathogenesis of OSA. The severity of OSA or obesity appears to determine the relative contribution of these abnormalities to sleep-related collapse of the upper airway.

Role of funding sources Kazuo Chin has received grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (nos. 20590921 and 22590760), Respiratory Failure Research Group and Health Science Research Grants (Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus) from the Ministry of Health, Labor and Welfare of Japan, and the Japan Vascular Disease Research Foundation.

References

1. Hudgel DW (1992) Mechanisms of obstructive sleep apnea. Chest 101:541–549
2. Ryan CM, Bradley TD (2005) Pathogenesis of obstructive sleep apnea. J Appl Physiol 99:2440–2450
3. Sakakibara H, Tong M, Matsushita K, Hirata M, Konishi Y, Suetsugu S (1999) Cephalometric abnormalities in non-obese and obese patients with obstructive sleep apnoea. Eur Respir J 13:403–410
4. Yu X, Fujimoto K, Urushibata K, Matsuzawa Y, Kubo K (2003) Cephalometric analysis in obese and nonobese patients with obstructive sleep apnea syndrome. Chest 124:212–218
5. Tsuiki S, Isono S, Ishikawa T, Yamashiro Y, Tatsumi K, Nishino T (2008) Anatomical balance of the upper airway and obstructive sleep apnea. Anesthesiology 108:1009–1015
6. Dempsey JA, Skatrud JB, Jacques AJ, Ewanowski SJ, Woodson BT, Hanson PR, Goodman B (2002) Anatomic determinants of sleep-disordered breathing across the spectrum of clinical and nonclinical male subjects. Chest 122:840–851
7. Lee RW, Vasudavan S, Hui DS, Prvan T, Petocz P, Darendeliler MA, Cistulli PA (2010) Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. Sleep 33:1075–1080
8. Heinzer RC, Stanchina ML, Malhotra A, Fogel RB, Patel SR, Jordan AS, Schory K, White DP (2005) Lung volume and continuous positive airway pressure requirements in obstructive sleep apnea. Am J Respir Crit Care Med 172:114–117
9. Tagaito Y, Isono S, Remmers JE, Tanaka A, Nishino T (2007) Lung volume and collapsibility of the passive pharynx in patients with sleep-disordered breathing. J Appl Physiol 103:1379–1385
10. Bradley TD, Martinez D, Rutherford R, Lue F, Grossman RF, Moldofsky H, Zamel N, Phillipson EA (1985) Physiological determinants of nocturnal arterial oxygenation in patients with obstructive sleep apnea. J Appl Physiol 59:1364–1368
11. Appelberg J, Nordahl G, Janson C (2000) Lung volume and its correlation to nocturnal apnoea and desaturation. Respir Med 94:233–239
12. Lin CC, Wu KM, Chou CS, Liaw SF (2004) Oral airway resistance during wakefulness in eucapnic and hypercapnic sleep apnea syndrome. Respir Physiol Neurobiol 139:215–224
13. Cao J, Que C, Wang G, He B (2009) Effect of posture on airway resistance in obstructive sleep apnea–hypopnea syndrome by means of impulse oscillation. Respiration 77:38–43
14. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP (2010) Pathophysiology of sleep apnea. Physiol Rev 90:47–112
15. Mayer P, Pepin JL, Bettega G, Veale D, Ferretti G, Deschaux C, Levy P (1996) Relationship between body mass index, age and upper airway measurements in snorers and sleep apnoea patients. Eur Respir J 9:1801–1809
16. Salome CM, King GG, Berend N (2010) Physiology of obesity and effects on lung function. J Appl Physiol 108:206–211
17. Zerah F, Harf A, Perlemuter L, Lorino H, Lorino AM, Atlan G (1993) Effects of obesity on respiratory resistance. Chest 103:1470–1476
18. Watson RA, Pride NB (2005) Postural changes in lung volumes and respiratory resistance in subjects with obesity. J Appl Physiol 98:512–517
19. Ohdaira F, Nakamura K, Nakayama H, Satoh M, Ohdaira T, Nakamata M, Kohno M, Iwashima A, Onda A, Kobayashi Y, Fujimori K, Kiguchi T, Izumi S, Kobayashi T, Shinoda H, Takahashi S, Gejyo F, Yamamoto M (2007) Demographic characteristics of 3,659 Japanese patients with obstructive sleep apnea–hypopnea syndrome diagnosed by full polysomnography: associations with apnea–hypopnea index. Sleep Breath 11:93–101
20. Rechtschaffen A, Kales A (1968) A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. National Institutes of Health, Washington
21. Iber C, Ancoli-Israel S, Chesson A, Quan S (2007) The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. American Academy of Sleep Medicine, Westchester
22. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J (2005) Standardisation of spirometry. Eur Respir J 26:319–338
23. Hellinckx J, Cauberghs M, De Boeck K, Demedts M (2001) Evaluation of impulse oscillation system: comparison with forced oscillation technique and body plethysmography. Eur Respir J 18:564–570
24. Oostveen E, MacLeod D, Lorino H, Farre R, Hantos Z, Desager K, Marchal F (2003) The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J 22:1026–1041
25. Takeda T, Oga T, Niimi A, Matsumoto H, Ito I, Yamaguchi M, Matsuoka H, Jinnai M, Otsuka K, Oguma T, Nakaji H, Chin K, Mishima M (2010) Relationship between small airway function

and health status, dyspnea and disease control in asthma. Respiration 80:120–126
26. Haruna A, Oga T, Muro S, Ohara T, Sato S, Marumo S, Kinose D, Terada K, Nishioka M, Ogawa E, Hoshino Y, Hirai T, Chin K, Mishima M (2010) Relationship between peripheral airway function and patient-reported outcomes in COPD: a cross-sectional study. BMC Pulm Med 10:10
27. Goldman MD, Saadeh C, Ross D (2005) Clinical applications of forced oscillation to assess peripheral airway function. Respir Physiol Neurobiol 148:179–194
28. Bédard M, Martin NJ, Krueger P, Brazil K (2000) Assessing reproducibility of data obtained with instruments based on continuous measurements. Exp Aging Res 26:353–365
29. Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P, Samet JM (2002) Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med 162:893–900
30. Pecora NG, Baccetti T, McNamara JA Jr (2008) The aging craniofacial complex: a longitudinal cephalometric study from late adolescence to late adulthood. Am J Orthod Dentofacial Orthop 134:496–505
31. Janssens JP (2005) Aging of the respiratory system: impact on pulmonary function tests and adaptation to exertion. Clin Chest Med 26:469–484
32. Watanabe T, Isono S, Tanaka A, Tanzawa H, Nishino T (2002) Contribution of body habitus and craniofacial characteristics to segmental closing pressures of the passive pharynx in patients with sleep-disordered breathing. Am J Respir Crit Care Med 165:260–265
33. Van de Graaff WB (1988) Thoracic influence on upper airway patency. J Appl Physiol 65:2124–2131
34. Michels A, Decoster K, Derde L, Vleurinck C, Van de Woestijne KP (1991) Influence of posture on lung volumes and impedance of respiratory system in healthy smokers and nonsmokers. J Appl Physiol 71:294–299
35. Lederer DJ, Jelic S, Basner RC, Ishizaka A, Bhattacharya J (2009) Circulating KL-6, a biomarker of lung injury, in obstructive sleep apnoea. Eur Respir J 33:793–796
36. Aihara K, Oga T, Harada Y, Chihara Y, Handa T, Tanizawa K, Watanabe K, Tsuboi T, Hitomi T, Mishima M, Chin K (2011) Comparison of biomarkers of subclinical lung injury in obstructive sleep apnea. Respir Med 105(6):939–945
37. Guilleminault C, Riley R, Powell N (1984) Obstructive sleep apnea and cephalometric roentgenograms. Am Rev Respir Dis 130:145–146
38. Maltais F, Carrier G, Cormier Y, Series F (1991) Cephalometric measurements in snorers, non-snorers, and patients with sleep apnoea. Thorax 46:419–423
39. Begle RL, Badr S, Skatrud JB, Dempsey JA (1990) Effect of lung inflation on pulmonary resistance during NREM sleep. Am Rev Respir Dis 141:854–860
40. White DP (2005) Pathogenesis of obstructive and central sleep apnea. Am J Respir Crit Care Med 172:1363–1370
41. Verbraecken JA, De Backer WA (2009) Upper airway mechanics. Respiration 78:121–133
42. Shigeta Y, Ogawa T, Ando E, Clark GT, Enciso R (2011) Influence of tongue/mandible volume ratio on oropharyngeal airway in Japanese male patients with obstructive sleep apnea. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 111:239–243
43. Saigusa H, Suzuki M, Higurashi N, Kodera K (2009) Three-dimensional morphological analyses of positional dependence in patients with obstructive sleep apnea syndrome. Anesthesiology 110:885–890

Sleep Medicine 13 (2012) 321–323

Contents lists available at SciVerse ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Letters to the Editor

Beneficial effects of continuous positive airway pressure therapy in a pediatric intestinal transplant recipient with obstructive sleep apnea

To the editor,

The association of pediatric obstructive sleep apnea (OSA) with mortality and respiratory diseases was demonstrated in a recent study [1]. We encountered a pediatric intestinal posttransplant recipient with OSA in whom continuous positive airway pressure (CPAP) therapy may have a preventive effect on respiratory tract infection.

A 3-year-old Japanese boy received an intestinal transplant from a living donor (his mother) because of short-bowel syndrome. During the 5 years following transplantation, he required hospitalization 19 times, including four episodes of acute rejection and three of respiratory tract infection. At the age of four, he developed severe pneumonia and congestive heart failure and needed noninvasive positive pressure ventilation. He was subsequently hospitalized twice for pneumonia. At the age of eight, severe pediatric OSA was diagnosed based on daytime sleepiness, snoring, and 3% oxygen desaturation index (3% ODI) of 10.1 [2]. Nasal auto-set CPAP therapy with the pressure between 4 and 12 cm H_2O was started, and the 3% ODI decreased from 10.1 to 1.8. After the beginning of CPAP therapy, the number of hospitalizations markedly decreased to six times during the next seven years. The causes of six hospitalizations were abdominal problems (including suspected rejection) for five of the times and influenza without pneumonia for another time. He experienced no further episodes of severe respiratory tract infection.

This course suggests a significant association between OSA and respiratory tract infection. Pulmonary aspiration of gastric contents is common in children with apnea episodes or recurrent pneumonia [3]. CPAP therapy can reduce gastroesophageal reflux [4], which may prevent pneumonitis from gastric acid aspiration. CPAP therapy was also reported to decrease the risk of postoperative pulmonary complications, atelectasis, and pneumonia in patients undergoing abdominal surgery [5]. In patients with OSA, CPAP therapy can also decrease microatelectasis that otherwise would facilitate lower respiratory tract infection. The detection of OSA and application of CPAP therapy can provide an additional benefit in managing immunosuppressed children, especially when experiencing recurrent airway infections.

Conflicts of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2011.10.019.

References

[1] Tarasiuk A, Greenberg-Dotan S, Simon-Tuval T, et al. Elevated morbidity and health care use in children with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2007;175:55–61.

[2] Saito H, Araki K, Ozawa H, et al. Pulse-oximetery is useful in determining the indications for adeno-tonsillectomy in pediatric sleep-disordered breathing. Int J Pediatr Otorhinolaryngol 2007;71:1–6.

[3] Ravelli AM, Panarotto MB, Verdoni L, Consolati V, Bolognini S. Pulmonary aspiration shown by scintigraphy in gastroesophageal reflux-related respiratory disease. Chest 2006;130:1520–6.

[4] Kerr P, Shoenut JP, Millar T, Buckle P, Kryger MH. Nasal CPAP reduces gastroesophageal reflux in obstructive sleep apnea syndrome. Chest 1992;101:1539–44.

[5] Ferreyra GP, Baussano I, Squadrone V, et al. Continuous positive airway pressure for treatment of respiratory complications after abdominal surgery: a systematic review and meta-analysis. Ann Surg 2008;247:617–26.

Kiminobu Tanizawa
Department of Respiratory Medicine, Kyoto University, Graduate School of Medicine, 54 Shogoin-kawaracho, Sakyo-ku, Kyoto 606-8507, Japan
E-mail address: tanizawa@kuhp.kyoto-u.ac.jp

Shinya Okamoto
Department of Transplantation Surgery, Kyoto University, Graduate School of Medicine, 54 Shogoin-kawaracho, Sakyo-ku, Kyoto 606-8507, Japan
E-mail address: shinyaps@kuhp.kyoto-u.ac.jp

Shinji Uemoto
Department of Transplantation Surgery, Kyoto University, Graduate School of Medicine, 54 Shogoin-kawaracho, Sakyo-ku, Kyoto 606-8507, Japan
E-mail address: uemoto@kuhp.kyoto-u.ac.jp

Kazuo Chin *
Department of Respiratory Care and Sleep Control Medicine, Kyoto University, Graduate School of Medicine, 54 Shogoin-kawaracho, Sakyo-ku, Kyoto 606-8507, Japan
* *Tel.: +81 75 751 3852; fax: +81 75 751 3854.*
E-mail address: chink@kuhp.kyoto-u.ac.jp

Available online 9 December 2011

1389-9457/$ - see front matter
doi:10.1016/j.sleep.2011.10.019

Recurrent hypersomnia due to occult hepatic encephalopathy

To the Editor

Hepatic encephalopathy can give rise to stupor. However, the pathology is typically structural damage and is usually chronic rather than intermittent. We report a case of hepatic vascular dysfunction giving rise to recurrent hypersomnia.

doi: 10.1111/j.1365-2869.2011.00912.x

Effects of the presence of hypertension on the relationship between obstructive sleep apnoea and sleepiness

YUKA HARADA[1], TORU OGA[2], KAZUO CHIN[2], MISA TAKEGAMI[3], KEN-ICHI TAKAHASHI[2], KENSUKE SUMI[4], TAKAYA NAKAMURA[5], YUKIYO NAKAYAMA-ASHIDA[6], ITSUNARI MINAMI[6], SACHIKO HORITA[7], YASUNORI OKA[8], TOMOKO WAKAMURA[9], SHUNICHI FUKUHARA[3], MICHIAKI MISHIMA[1] and HIROSHI KADOTANI[10]

Departments of [1]Respiratory Medicine and [2]Respiratory Care and Sleep Control Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [3]Department of Epidemiology and Healthcare Research, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan, [4]Department of Respiratory Medicine, National Hospital Organization Minami Kyoto Hospital, Kyoto, Japan, [5]Department of Respiratory Medicine, Kyoto City Hospital, Kyoto, Japan, [6]Horizontal Medical Research Organization, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [7]Department of Human Nursing, Faculty of Human Health, Sonoda Women's University. Hyogo, Japan, [8]Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan, [9]Department of Environmental Health Nursing, Graduate School of Medicine, Human Health Sciences, Kyoto University, Kyoto, Japan and [10]Center for Genomic Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Accepted in revised form 13 January 2011; received 21 October 2010

SUMMARY Obstructive sleep apnoea (OSA) plays a significant role in increasing blood pressure. Significant decreases were reported in blood pressure of hypertensive OSA patients with sleepiness who underwent continuous positive airway pressure (CPAP) treatment, but not in non-sleepy hypertensive OSA patients. More recently, however, significant decreases in blood pressure in non-sleepy hypertensive OSA patients following CPAP were shown. Effects of sleepiness on hypertension in OSA patients have been investigated, but not the effects of hypertension on sleepiness in OSA patients. We investigated the relationships between hypertension and sleepiness in patients with OSA. We analysed data on 275 middle-aged male subjects from a cross-sectional epidemiological health survey. We measured blood pressure and sleep duration objectively using an actigraph for 7 days and the respiratory disturbance index (RDI) with a type 3 portable device for 2 nights, and assessed sleepiness using the Epworth Sleepiness Scale (ESS). The RDI correlated significantly with ESS scores in the 88 hypertensive subjects ($r = 0.33$, $P = 0.0024$), but not in the 187 non-hypertensive subjects ($r = -0.01$, $P = 0.91$). Short sleep duration correlated significantly with ESS scores in both groups. Both the RDI and short sleep duration were related independently to sleepiness in only hypertensive subjects. Furthermore, the RDI was related negatively significantly to sleep duration in hypertensive subjects. Although short sleep duration was related significantly to sleepiness in both groups, hypertension may be important for the sleepiness in OSA patients. Detailed mechanisms of the difference in the relationship between sleepiness and the severity of OSA with or without hypertension should be studied further.

KEYWORDS hypertension, sleep apnoea, sleep duration, sleepiness

Correspondence: Kazuo Chin, Department of Respiratory Care and Sleep Control Medicine, Graduate School of Medicine, Kyoto University, 54 Kawara-machi, Shogoin, Sakyo-ku, Kyoto-city, Kyoto, 606-8507, Japan. Tel.: +81-75-751-3852; fax: +81-75-751-3854; e-mail: chink@kuhp.kyoto-u.ac.jp

INTRODUCTION

A large body of work has shown that obstructive sleep apnoea (OSA) plays a significant role in increasing blood pressure (Garvey *et al.*, 2009). Systemic hypertension in OSA, often underdiagnosed, is a large clinical problem, as it may increase the cardiovascular risk of OSA. Currently, continuous positive airway pressure (CPAP) treatment is the first-line treatment of OSA. However, there has been some conflict over whether CPAP can reduce systemic blood pressure in patients with OSA (Robinson *et al.*, 2004). There may be subgroups of patients with OSA who benefit from CPAP treatment in terms of blood pressure control (Robinson *et al.*, 2004). From this viewpoint, several studies suggested that OSA patients with prior daytime sleepiness were likely to experience a lowering of blood pressure after CPAP treatment (Barbé *et al.*, 2001; Robinson *et al.*, 2004, 2006, 2008), while Barbé *et al.* (2010) recently reported a decrease in blood pressure in non-sleepy hypertensive patients with OSA after CPAP treatment. Thus, the effects of sleepiness on hypertension in OSA patients have been investigated, but the effects of hypertension on sleepiness in these patients have not been studied.

We hypothesized that hypertension and sleepiness in OSA patients have a significant relationship. To investigate this relationship, using information from a cross-sectional epidemiological health survey in a group of middle-aged male employees in Japan (Chin *et al.*, 2010; Nakayama-Ashida *et al.*, 2008), we analysed the relationship between sleepiness and OSA in subjects with or without hypertension, taking into account objectively measured sleep duration by actigraph. Accurate measurements of sleep duration are important in investigating the effects of hypertension on sleepiness in OSA patients, as sleep duration has been shown to be an important factor for sleepiness in OSA patients (Vakulin *et al.*, 2009). Although most epidemiological studies used subjective self-reported sleep duration, such self-reports may be inaccurate and cause misclassification of sleep duration (Lauderdale *et al.*, 2008; Van Den Berg *et al.*, 2008). Thus, actigraphic measurements used in this study will ensure greater accuracy in sleep duration data than in previous reports.

METHODS

Subjects

Study subjects were male employees of an urban wholesale company in Japan, as reported previously elsewhere in detail (Chin *et al.*, 2010; Nakayama-Ashida *et al.*, 2008). Of the 322 male employees who were first entered into the study (Nakayama-Ashida *et al.*, 2008), 275 were investigated further to examine the relationship between OSA and metabolic syndrome (Chin *et al.*, 2010). In the present study, we analysed data on those 275 subjects regarding the relationship between sleepiness, sleep duration and OSA with or without hypertension. The study protocol was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee. Written informed consent was obtained from all subjects.

Measurements of weight, waist circumference and blood pressure

Trained research staff performed measurements of weight, waist circumference and blood pressure. Blood pressure was measured seven times using OMRON HEM-759P (Kyoto, Japan) after subjects were seated and rested for 1–2 min, with the average of the last three measurements used for the analyses. Individuals who had systolic blood pressure readings of more than 140 mmHg, diastolic readings of more than 90 mmHg, a history of a diagnosis of hypertension before the study measurements or were currently using anti-hypertensive medications were defined as having hypertension (Joint National Committee, 1993).

Home monitoring of sleep

We determined sleep duration by actigraphy (Littner *et al.*, 2003), in conjunction with a sleep diary. Each subject was asked to wear an actigraph (Actiwatch AW-Light; Mini Mitter, Brend, OR, USA) (Littner *et al.*, 2003) for 7 days to estimate sleep–wake time, and a type 3 portable monitor (PM) (Morpheus; Teijin, Tokyo, Japan, which is the same as Somté; Compumedics, Vic., Australia) (Chesson *et al.*, 2003), an alternative for polysomnography in the diagnosis of OSA (Kushida *et al.*, 2005), for 2 nights at home.

Actigraph and PM data analysis

The respiratory disturbance index (RDI: number of apnoea and hypopnoea episodes per hour of the analysed time) was calculated from both the actigraphy and PM. Records of the PM were inspected visually and scored by at least two medical doctors specialized in respiratory medicine. Apnoea is defined as the cessation of breathing for at least 10 s and hypopnoea as a more than 50% reduction in the amplitude of nasal pressure or respiratory effort associated with more than 3% reduction in oxyhaemoglobin saturation for at least 10 s. Apnoea and hypopnoea were scored while blinded to other information, except for sleep–wake time by actigraphy. Data without oxygen saturation values and illegible recordings were excluded from analysis. Data for <2 h were also excluded, because the Medicare guidelines require at least 2 h of documented sleep time. When data from both recorded nights were available, records from the second night were analysed further.

Assessment of sleepiness

The modified Japanese version of the Epworth Sleepiness Scale (ESS) was used to assess subjective sleepiness (Takegami *et al.*, 2009). A separate sleep diary was also completed during the survey period (Nakayama-Ashida *et al.*, 2008).

Statistical analysis

Results are expressed as mean ± standard deviation (SD). Unpaired *t*-tests were used to compare the backgrounds

between the hypertensive and non-hypertensive subjects and between treated and untreated hypertensive subjects. Relationships between the two sets of data were analysed by Pearson's correlation coefficient tests. Multiple regression analyses were performed to identify those variables that could best predict sleepiness by the ESS scores using the RDI and sleep duration as explanatory variables. *P*-values < 0.05 were considered to be statistically significant. All analyses were performed using Statview 5.0 (SAS Institute, Inc. Cary, NC, USA).

RESULTS

Characteristics of the subjects

Characteristics of the subjects are presented in Table 1. A total of 88 subjects (32.0%) had hypertension; among these, 25 (28.4%) were being treated with anti-hypertensive medicine. From our examination of the subjects, we could not identify any subject who took medicine during the daytime that could affect sleepiness. RDI, sleep duration and ESS scores of the hypertensive subjects treated with anti-hypertensive medicine and the untreated hypertensive subjects did not differ significantly ($P = 0.20$, 0.061 and 0.87, respectively). A total of 161 subjects (58.5%) had OSA ($5 \leq$ RDI). The hypertensive subjects were older ($P < 0.001$) and had a higher RDI than those without hypertension ($12.2 \pm 12.0\ h^{-1}$ versus $9.3 \pm 10.0\ h^{-1}$, $P = 0.034$), while the body mass index (BMI), waist circumference, sleep duration and ESS scores did not differ between the two groups.

Among the 88 hypertensive subjects, 59 (67.0%) had OSA ($5 \leq$ RDI) and 23 (26.1%) had moderate-to-severe OSA ($15 \leq$ RDI). Among the 187 non-hypertensive subjects, 102 (54.5%) had OSA and 35 (18.7%) had moderate-to-severe OSA.

Relationships between sleepiness and OSA, and between sleepiness and sleep duration

Fig. 1 shows the relationships between sleepiness estimated by ESS scores and OSA in the hypertensive and non-hypertensive groups. The RDI was correlated significantly but weakly with ESS scores in the hypertensive subjects [correlation coefficient (r) = 0.33, $P = 0.0024$] but not in the non-hypertensive subjects ($r = -0.01$, $P = 0.91$) (Table 2a). With regard to relationships between sleepiness and sleep duration in the hypertensive and non-hypertensive groups, as well as in all subjects taken together, although sleep duration was correlated significantly with ESS scores in the hypertensive subjects ($r = -0.30$, $P = 0.0050$) this relationship was also seen in the non-hypertensive subjects ($r = -0.18$, $P = 0.014$) (Table 2a) and in the entire subject population ($r = -0.22$, $P < 0.001$). Lastly, multiple regression analyses to predict sleepiness estimated by ESS scores were performed using the RDI and sleep duration as explanatory variables in the hypertensive and non-hypertensive groups. These analyses revealed that both the RDI and sleep duration explained ESS scores independently only in the hypertensive group [contribution rate (R^2) = 8.6% and 6.9%, respectively] but, in contrast, sleep duration alone explained the ESS scores independently in the non-hypertensive group ($R^2 = 3.2\%$) (Table 2b,c).

Relationship between RDI and sleep duration

We examined further the relationship between RDI and sleep duration. As a whole, RDI and sleep duration had a negative relationship ($r = -0.19$, $P = 0.0017$). As shown in Fig. 2, in the hypertensive group the RDI was related negatively significantly to sleep duration ($r = -0.29$, $P = 0.0056$), but there was no significant relationship in the non-hypertensive group ($r = -0.13$, $P = 0.084$) (Table 2a).

DISCUSSION

In the present cross-sectional epidemiological survey in an urban company in Japan, we compared the relationships between sleepiness and OSA in subjects with or without hypertension. We found that short sleep duration was related to sleepiness both in the hypertensive and non-hypertensive subjects, but that the RDI was also related significantly to sleepiness independently of sleep duration only in the hypertensive subjects. In addition, we observed an inverse

Table 1 Characteristics of the subjects

	All subjects	*Subjects with hypertension*	*Subjects without hypertension*	P-*value*
Number of subjects (%)	275	88 (32.0)	187 (68.0)	
Age (years)	44 ± 8	48 ± 7	42 ± 8	< 0.001
BMI ($kg\ m^{-2}$)	23.9 ± 3.1	24.2 ± 3.6	23.8 ± 2.9	0.42
Waist circumference (cm)	83.6 ± 8.5	85.0 ± 9.3	83.0 ± 8.0	0.075
RDI (h^{-1})	10.2 ± 10.7	12.2 ± 12.0	9.3 ± 10.0	0.034
Sleep duration (h)	6.0 ± 0.8	6.0 ± 0.8	6.0 ± 0.8	0.51
ESS score	8.2 ± 4.3	7.9 ± 4.3	8.3 ± 4.3	0.43
Systolic blood pressure (mmHg)	129 ± 14	143 ± 12	122 ± 8	< 0.001
Diastolic blood pressure (mmHg)	81 ± 11	91 ± 9	76 ± 8	< 0.001

Values are presented as mean ± standard deviation or n (%) unless stated otherwise. BMI, body mass index; ESS, Epworth Sleepiness Scale; RDI, respiratory disturbance index.

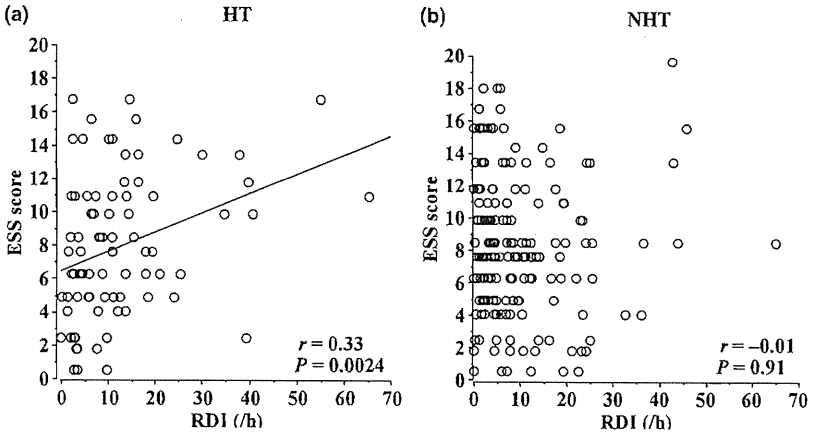

Figure 1. Relationship between Epworth Sleepiness Scale scores and respiratory disturbance index in the subjects with hypertension (HT) (a) and in the subjects without hypertension (NHT) (b). ESS, Epworth Sleepiness Scale; RDI, respiratory disturbance index.

Table 2 (a) Univariate analyses of correlation coefficient among sleepiness assessed by ESS scores, the severity of OSA assessed by RDI and sleep duration. Multiple regression analyses to predict sleepiness assessed by ESS scores in subjects (b) with hypertension (n = 88) and (c) without hypertension (n = 187)

	Subjects with HT	*Subjects without HT*
(a)		
ESS score and RDI	0.33*	−0.01
ESS score and sleep duration	−0.30*	−0.18*
RDI and sleep duration	−0.29*	−0.13

	β	γ	R^2 (%)
(b)			
RDI (h^{-1})	0.26	0.33	8.6
Sleep duration (h)	−0.23	−0.30	6.9
Cumulative R^2			15.5
(c)			
RDI (h^{-1})	NA	NA	NA
Sleep duration (h)	−0.18	−0.18	3.2
Cumulative R^2			3.2

ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea; RDI, respiratory disturbance index; HT, hypertension; NA, not applicable. In (a), data are expressed as correlation coefficient and *$P < 0.05$; in (b and c), β, standard regression coefficient, r, correlation coefficient and R^2, contribution rate.

relationship between the RDI and sleep duration in the hypertensive subjects.

In the present study, insufficient sleep was an important determinant of sleepiness regardless of the existence of hypertension. Pack *et al.* (2006) also reported that among commercial driver's licence holders, chronic short sleep duration rather than sleep apnoea was a risk factor for sleepiness. In addition, a recent report showed that OSA patients were more vulnerable than healthy subjects to the effects of sleep restriction (Vakulin *et al.*, 2009). Indeed, the patients with OSA made more mistakes in the driving simulation test following sleep restriction than the subjects without OSA (Vakulin *et al.*, 2009). Thus, adequate sleep duration would be necessary for patients with OSA as well as for subjects without OSA. In this study, sleep duration was measured in home settings. Although, in many studies, sleep duration was assessed by overnight polysomnography in laboratory settings, in that situation subjects tended to sleep more poorly than at home (Kapur *et al.*, 2005). In addition, sleep duration was measured by actigraph for a week in this study. Although most epidemiological studies use self-reported sleep duration, which may not be accurate, differences between actigraph-measured and subjective reported sleep durations were detected, and objectively measured sleep duration is recommended (Lauderdale *et al.*, 2008; Van Den Berg *et al.*, 2008). Thus, in our study, using both actigraphy and a sleep diary under usual circumstances for a week, we could examine sleep duration accurately to explore the importance of adequate sleep.

This study also showed that the significant but weak relationship between RDI and sleepiness was dependent on the existence of hypertension. Despite some conflicting results in interventional trials of treatment of OSA and hypertension, pre-treatment sleepiness is an important factor in determining a reduction in blood pressure after CPAP treatment (Robinson *et al.*, 2004). Thus, it is suggested that there is some relationship between sleepiness in OSA and presence of hypertension. However, in this study there was a significant difference in age between subjects with and without hypertension. Therefore, including objective assessment of sleepiness, such as with the multiple sleep latency test (MSLT), further studies would be needed to investigate the difference in sleepiness in OSA subjects with and without hypertension.

We noticed an inverse relationship between the RDI and sleep duration. There has not been sufficient evidence to suggest that patients with OSA sleep more or less than average, although short sleep duration or sleep fragmentation is reported to be associated with obesity (Knutson *et al.*, 2007; Van Den Berg *et al.*, 2008), a main risk factor for OSA. Interestingly, this relationship was observed with actigraphically determined sleep duration, as in our study, and was undetectable with self-reported sleep duration (Van Den Berg *et al.*, 2008) which indicated the advantage of our study, which included actigraph data.

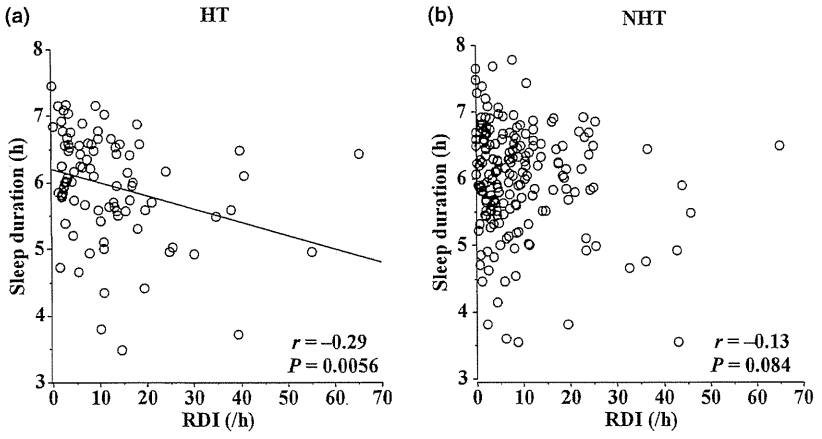

Figure 2. Relationship between respiratory disturbance index and sleep duration in the subjects with hypertension (HT) (a) and in the subjects without hypertension (NHT) (b). RDI, respiratory disturbance index.

The prevalence of males with moderate-to-severe OSA in this study was 21.1%, which is equivalent to the data from the Sleep Heart Health Study showing a prevalence of 25.0% (Baldwin *et al.*, 2004). Among the hypertensive and non-hypertensive subjects, 26.1% and 18.7% had moderate-to-severe OSA, respectively, which is equivalent to findings of another study (Hla *et al.*, 1994). In addition, the prevalence of hypertension among Japanese males in their 40s was 35.5% in 2006 (Ministry of Health, Labor and Welfare, 2006; updated 2008), which is similar to that in this study (32.0%). Therefore, our data are applicable to reflect the current background in Japan.

There are some limitations to this study. First, this was a cross-sectional study and it was difficult to exclude completely the influence of confounders such as age, obesity, and medication, etc., as mentioned above. Secondly, we did not perform polysomnography, partly because we wanted to perform the study under usual lifestyle conditions. However, the interscorer and night-to-night reliability of the RDI were excellent (interclass correlation coefficients of 0.98 and 0.95, respectively) (Nakayama-Ashida *et al.*, 2008). In addition, it has been reported that the non-attached type 3 PM is reliable under the specified conditions in which our study was conducted (Collop *et al.*, 2007). Thirdly, we did not assess sympathetic activity, nor did we administer the MSLT to estimate sleepiness objectively.

In conclusion, although this study had several limitations, we showed that sleepiness was related to the severity of OSA in the hypertensive subjects, but not in the non-hypertensive subjects. Also, we showed that sleepiness was related to short sleep duration in both groups. Furthermore, we observed a relationship between short sleep duration and the severity of OSA in the hypertensive subjects. Thus, in addition to sleep duration, OSA accompanied by hypertension may be important in sleepiness. Further study is needed to determine details of the mechanism of the difference in the relationship between sleepiness and the severity of OSA with or without hypertension.

CONFLICTS OF INTEREST

No authors have indicated any financial conflicts of interest.

ACKNOWLEDGEMENTS

This work was supported in part by a grant from the Japanese Ministry of Education, Culture, Sports, Science and Technology (no.20590921), Respiratory Failure Research Group, a Health Science Research Grants, Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus, from the Japanese Ministry of Health, Labor and Welfare, the Japan Vascular Disease Research Foundation, and research grants from Presto JST, Suzuken Memorial Foundation, Takeda Science Foundation, Mitsui Life Social Welfare Foundation, Chiyoda Kenko Kaihatsu Jigyodan Foundation and Health Science Center Foundation. In addition, we would like to thank all the participants. This was not an industry-supported study.

REFERENCES

Baldwin, C. M., Kapur, V. K., Holberg, C. J., Rosen, C. and Nieto, F. J.; for the Sleep Heart Health Study Group. Associations between gender and measures of daytime somnolence in the Sleep Heart Health Study. *Sleep*, 2004, 27: 305–311.

Barbé, F., Mayoralas, L. R., Duran, J. *et al.* Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. a randomized, controlled trial. *Ann. Intern. Med.*, 2001, 134: 1015–1023.

Barbé, F., Durán-Cantolla, J., Capote, F. *et al.*; for the Spanish Sleep Breathing Group. Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am. J. Respir. Crit. Care Med.*, 2010, 181: 718–726.

Chesson, A. L., Jr, Berry, R. B. and Pack, A. American Academy of Sleep Medicine; American Thoracic Society; American College of Chest Physicians. Practice parameters for the use of portable monitoring devices in the investigation of suspected obstructive sleep apnea in adults. *Sleep*, 2003, 26: 907–913.

Chin, K., Oga, T., Takahashi, K. *et al.* Associations between obstructive sleep apnea, metabolic syndrome and sleep duration, as measured with an actigraph, in an urban male working population in Japan. *Sleep*, 2010, 33: 89–95.

Collop, N. A., Anderson, W. M., Boehlecke, B. *et al.*; for the Portable Monitoring Task Force of the American Academy of Sleep Medicine. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American

Academy of Sleep Medicine. *J. Clin. Sleep Med.*, 2007, 3: 737–747.

Garvey, J. F., Taylor, C. T. and McNicholas, W. T. Cardiovascular disease in obstructive sleep apnoea syndrome: the role of intermittent hypoxia and inflammation. *Eur. Respir. J.*, 2009, 33: 1195–1205.

Hla, K. M., Young, T. B., Bidwell, T., Palta, M., Skatrud, J. B. and Dempsey, J. Sleep apnea and hypertension. A population-based study. *Ann. Intern. Med.*, 1994, 120: 382–388.

Joint National Committee. Fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch. Intern. Med.*, 1993, 153: 154–183.

Kapur, V. K., Baldwin, C. M., Resnick, H. E., Gottlieb, D. J. and Nieto, F. J. Sleepiness in patients with moderate to severe sleep-disordered breathing. *Sleep*, 2005, 28: 472–477.

Knutson, K. L., Spiegel, K., Penev, P. and Van Cauter, E. The metabolic consequences of sleep deprivation. *Sleep Med. Rev.*, 2007, 11: 163–178.

Kushida, C. A., Littner, M. R., Morgenthaler, T. *et al.* Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep*, 2005, 28: 499–521.

Lauderdale, D. S., Knutson, K. L., Yan, L. L., Liu, K. and Rathouz, P. J. Self-reported and measured sleep duration: how similar are they? *Epidemiology*, 2008, 19: 838–845.

Littner, M., Kushida, C. A., Anderson, W. M. *et al.*; for the Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. *Sleep*, 2003, 26: 337–341.

Ministry of Health, Labor and Welfare. Report of National Health and Nutrition Survey. 2006, Available from: http://www.mhlw.go.jp/houdou/2008/04/dl/h0430-2c.pdf. Last updated 30 April 2008 (accessed 29 January 2011).

Nakayama-Ashida, Y., Takegami, M., Chin, K. *et al.* Sleep-disordered breathing in the usual lifestyle setting as detected with home monitoring in a population of working men in Japan. *Sleep*, 2008, 31: 419–425.

Pack, A. I., Maislin, G., Staley, B. *et al.* Impaired performance in commercial drivers: role of sleep apnea and short sleep duration. *Am. J. Respir. Crit. Care Med.*, 2006, 174: 446–454.

Robinson, G. V., Stradling, J. R. and Davies, R. J. Sleep 6: obstructive sleep apnoea/hypopnoea syndrome and hypertension. *Thorax*, 2004, 59: 1089–1094.

Robinson, G. V., Smith, D. M., Langford, B. A., Davies, R. J. and Stradling, J. R. Continuous positive airway pressure does not reduce blood pressure in nonsleepy hypertensive OSA patients. *Eur. Respir. J.*, 2006, 27: 1229–1235.

Robinson, G. V., Langford, B. A., Smith, D. M. and Stradling, J. R. Predictors of blood pressure fall with continuous positive airway pressure (CPAP) treatment of obstructive sleep apnoea (OSA). *Thorax*, 2008, 63: 855–859.

Takegami, M., Suzukamo, Y., Wakita, T. *et al.* Development of a Japanese version of the Epworth Sleepiness Scale (JESS) based on item response theory. *Sleep Med.*, 2009, 10: 556–565.

Vakulin, A., Baulk, S. D., Catcheside, P. G. *et al.* Effects of alcohol and sleep restriction on simulated driving performance in untreated patients with obstructive sleep apnea. *Ann. Intern. Med.*, 2009, 151: 447–455.

Van Den Berg, J. F., Knvistingh Neven, A., Tulen, J. H. *et al.* Actigraphic sleep duration and fragmentation are related to obesity in the elderly: the Rotterdam Study. *Int. J. Obes.*, 2008, 32: 1083–1090.

Respiratory Medicine (2011) 105, 939–945

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Comparison of biomarkers of subclinical lung injury in obstructive sleep apnea

Kensaku Aihara [a], Toru Oga [b,*], Yuka Harada [a], Yuichi Chihara [a], Tomohiro Handa [a], Kiminobu Tanizawa [a], Kizuku Watanabe [a], Tomomasa Tsuboi [b], Takefumi Hitomi [b], Michiaki Mishima [a], Kazuo Chin [b]

[a] *Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan*
[b] *Department of Respiratory Care and Sleep Control Medicine, Graduate School of Medicine, Kyoto University, 54 Kawahara, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan*

Received 17 December 2010; accepted 20 February 2011
Available online 12 March 2011

KEYWORDS
Obstructive sleep apnea;
KL-6;
Surfactant protein-D;
C-reactive protein;
Lung injury

Summary
Background: Obstructive sleep apnea (OSA) has both systemic and local effects partly through the increased oxidative stress caused by intermittent hypoxia and reoxygenation. However, lung-specific biomarkers in OSA have not been fully assessed in comparison with systemic biomarkers such as C-reactive protein (CRP), although results of a recent study having a small sample size indicated KL-6 as one candidate.
Methods: Subjects of the present study were 197 patients suspected to have OSA. In addition to polysomnography, we also measured serum levels of KL-6, surfactant protein-D (SP-D) and CRP and pulmonary function. We examined the relationships of different biomarkers with OSA severity and pulmonary function.
Results: The apnea/hypopnea index (AHI) was significantly positively correlated with serum KL-6 levels even after adjustment for body mass index (BMI) and smoking ($p = 0.03$), but not with SP-D and CRP. Also, a significant trend for an increase in serum KL-6 was noted in accordance with the severity of OSA even after adjustment for BMI and smoking (β coefficient $= 0.18$, $p = 0.02$). Additionally, elevated KL-6 levels were significantly associated with restrictive lung function disturbance and gas exchange derangement after adjustment for obesity and smoking, which contrasted with CRP whose elevations were significantly associated with worsened airflow limitation and increased lung volume.
Conclusions: Serum KL-6 levels may reflect the degree of subclinical lung injury associated with OSA independently of obesity or smoking, unlike CRP. We consider that KL-6 can be a potential candidate as a lung-specific biomarker of OSA and might provide complementary information on systemic biomarkers in assessing OSA.

* Corresponding author. Tel.: +81 75 751 3852; fax: +81 75 751 3854.
E-mail address: ogato@kuhp.kyoto-u.ac.jp (T. Oga).

0954-6111/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2011.02.016

Introduction

Obstructive sleep apnea (OSA) is characterized by repeated episodes of upper airway obstruction accompanied by intermittent hypoxia and reoxygenation, which can cause oxidative stress.[1] It contributes not only to endothelial dysfunction in the peripheral circulation, but possibly also contributes to epithelial and endothelial cell injury in the alveolus causing increased alveolar wall permeability in the lungs.[2,3]

KL-6 is a mucin-like glycoprotein with a molecular weight of 200 kd and is mainly expressed on alveolar type II and bronchiolar epithelial cells in human lungs.[4] Elevated levels of circulating KL-6 have been reported in patients with lung injury.[5,6] Recently, Lederer et al. reported that circulating levels of KL-6 were elevated in some patients with OSA in association with greater endothelial dysfunction, suggesting that subclinical lung injury may be present in OSA.[7] However, the sample size in that study was very small, comprising only 11 OSA patients and 10 controls, and the relationships of elevated levels of KL-6 with other biomarkers or pulmonary function were not examined. Therefore, the role of KL-6 as a biomarker of lung injury in OSA has not been fully elucidated.

In addition to KL-6, circulating levels of surfactant protein-D (SP-D) are elevated in patients with lung injury.[8,9] SP-D is also exclusively produced by alveolar type II cells in the lungs and its values change with the clinical status of patients or with relevant exposures.[10] Therefore, recently, much attention has been paid to SP-D as a potential lung-specific biomarker in diseases such as chronic obstructive pulmonary disease (COPD) where both local and systemic inflammation play respective important roles in disease progression.[10,11] In OSA, increased levels of various systemic inflammatory biomarkers, including C-reactive protein (CRP), tumor necrosis factor-α, interleukin-6, and interleukin-8, have been reported to be associated with future cardiovascular risk.[12] Considering that OSA has respiratory and systemic effects, a lung-specific blood biomarker would be attractive and informative.

We hypothesized that higher serum levels of KL-6 and SP-D would be associated with more severe OSA and more severe impairments in pulmonary function, reflecting the degree of subclinical lung injury unlike CRP, which is the most widely studied systemic biomarker in OSA.[12] Although the magnitude of the injury might not be great, it may not only cause respiratory symptoms such as chronic cough[13] but also may worsen other possible comorbid disorders such as asthma,[14] COPD[15] or idiopathic pulmonary fibrosis (IPF).[16] Therefore, in the present study, we examined the relationships between these three different biomarkers, OSA and pulmonary function and assessed their clinical relevance.

Methods

Study subjects

A total of 197 patients were consecutively recruited from the Sleep Unit of Kyoto University Hospital between April 2009 and April 2010. All had been referred to our sleep unit with symptoms such as habitual snoring or daytime sleepiness. None had been previously diagnosed with or treated for OSA. Patients with pulmonary diseases such as asthma ($n = 14$), COPD ($n = 5$) or interstitial lung diseases ($n = 2$) and who were diagnosed as having central sleep apnea ($n = 6$) were excluded based on clinical history, spirometry, chest radiograph and polysomnography, and a total of 170 patients were examined further. This study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee, and informed consent was obtained from all patients. Arterial blood gas analysis, including arterial partial tension of oxygen (PaO_2) and arterial partial tension of carbon dioxide ($PaCO_2$), was performed while patients were breathing room air at rest in the supine position. The alveolar-arterial oxygen tension difference ($A\text{-}aDO_2$) was calculated according to the standard formula, using the respiratory exchange ratio of 0.8.

Polysomnography

The diagnosis of OSA was confirmed by polysomnography (SomnoStar pro, Cardinal Health, Dublin, OH, USA), which was started at 22:00 and ended at 6:00 the following morning. Surface electrodes were attached using standard techniques to obtain an electrooculogram, electromyogram of the chin, and 12-lead electroencephalograph. Sleep stages were defined according to the criteria of Rechtschaffen and Kales.[17] Ventilation was monitored by inductive plethysmography (Respitrace QDC, Viasys Healthcare, Palm Springs, CA, USA). Airflow was monitored by a nasal pressure transducer (PTAFlite, Pro-Tech Services Inc., Mukilteo, WA, USA) and supplemented by an oronasal thermal sensor (Sleepmate Technologies, Midlothian, VA, USA). Arterial oxygen saturation (SpO_2) was monitored continuously with a pulse oximeter (Adult Flex System, Nonin Medical, Plymouth, MN, USA).

Apnea was defined as the complete cessation of airflow and hypopnea as a clear decrease in airflow of 50% or more lasting for 10 s or more accompanied by a decrease in SpO_2 of at least 3%.[18] All AHI values were expressed as the number of episodes of apnea and hypopnea per hour over the total sleep time. The lowest SpO_2 during sleep was calculated in each patient. OSA severity was defined by the AHI as follows: non OSA ($AHI<5$), mild OSA ($5 \leq AHI<15$), moderate OSA ($15 \leq AHI<30$) and severe OSA ($30 \leq AHI$).

Blood sample collection and measurements of serum biomarkers levels

Following overnight polysomnography, samples of peripheral venous blood were collected in the morning after an overnight fast. Serum KL-6 levels were measured by a sandwich-type electrochemiluminescence immunoassay kit (Picolumi KL-6; Sanko Junyaku, Tokyo, Japan), serum SP-D levels were measured by a sandwich-type enzyme immunoassay kit (SP-D kit Yamasa EIA II; Yamasa Shoyu, Chiba, Japan), and serum CRP levels were measured using a high sensitive assay kit (N-Assay LA CRP-S kit; Nittobo Medical, Tokyo, Japan).

Pulmonary function tests

Pulmonary function tests were performed using CHESTAC (Chest M.I. Inc., Tokyo, Japan). Residual volume (RV) and total lung capacity (TLC) were measured by the closed-circuit helium method, and diffusing capacity for carbon monoxide (DL_{CO}) was measured using a single-breath technique. Percent-predicted values were used for analyses.

Statistics

All statistical analyses were performed using StatView version 5.0 for Windows (Abacus Concepts, Berkeley, CA, USA). Continuous variables are expressed as means ± standard deviation (SD). The unpaired *t*-test was used to compare AHI levels between men and women. The significance of intergroup differences based on the severity of OSA was determined by an analysis of variance (ANOVA). When a significant difference was observed, we used the Fisher's PLSD method to identify where the differences were significant. A chi-square test was used to compare dichotomous variables. Relationships between 2 variables were analyzed by Pearson's correlation coefficient tests. The trend of serum biomarker levels across OSA groups was examined by two models. Model 1 is a linear model with serum biomarker levels as the dependent variable and with three indicator variables for mild, moderate, and severe OSA as the independent variables. We reported the β coefficients for the three OSA variables as mean differences in biomarker levels versus the non OSA group (reference). Model 2 is also a linear model wherein the indicator variables are replaced with a single ordinal variable equal to the median AHI in the mild, moderate and severe OSA groups, respectively and 0 in the non OSA group. Multiple regression analyses were performed to adjust for the confounders. A p value less than 0.05 was considered to indicate statistical significance.

Results

Relationships of clinical indices and serum biomarker levels to AHI

Patient characteristics and polysomnographic data are shown in Table 1. The study group of 170 patients was comprised of 20 non OSA, 25 mild OSA, 52 moderate OSA and 73 severe OSA patients. Significant differences were observed in sex, age, body mass index (BMI) and smoking among the groups. Serum KL-6 levels were also significantly different among the groups ($p = 0.04$), but not SP-D ($p = 0.65$) or CRP ($p = 0.53$). There were significant differences among the groups in PaO_2 and A-aDO_2.

We investigated the relationships between subjects' background, serum biomarker levels and AHI. With regard to clinical characteristics, the AHI was not significantly different between men and women ($p = 0.12$), and had significant positive correlations with BMI [r (correlation coefficient) $= 0.50$, $p < 0.001$] and smoking ($r = 0.23$, $p = 0.003$), but not with age ($r = 0.06$, $p = 0.44$). On the other hand, the AHI had a significant positive correlation with serum levels of KL-6 ($r = 0.20$, $p = 0.01$) and CRP ($r = 0.17$, $p = 0.03$), although a significant correlation was not found between the AHI and serum levels of SP-D ($r = 0.06$, $p = 0.48$). After adjustment for BMI and smoking, which were significantly associated with the AHI as mentioned above, the correlation of the AHI with serum KL-6 levels remained weak but statistically significant (β coefficient $= 0.14$, $p = 0.03$), whereas its correlation with serum CRP levels was far from significant (β coefficient $= 0.00$, $p = 0.97$).

Table 2 shows trends of serum biomarker levels across OSA groups. A significant trend for an increase in serum KL-6 levels was noted in accordance with the severity of OSA even after adjustment for BMI and smoking (β coefficient $= 0.18$, $p = 0.02$ for both Model 1 and 2), whereas no significant trend was found in serum levels of SP-D and CRP.

As to the lowest SpO_2, no significant relationships with serum levels of KL-6, SP-D and CRP were found. Regarding the inter-relationships among the three serum biomarkers examined, there was a significant correlation between serum levels of KL-6 and SP-D ($r = 0.24$, $p = 0.002$), but serum CRP levels did not correlate with either KL-6 or SP-D levels.

Relationships of pulmonary function and arterial blood gas data to serum biomarker levels

Next, to assess the clinical relevance of KL-6 and CRP, which were significantly related to AHI, we compared their relationships with pulmonary function and arterial blood gas data. After adjustment for BMI and smoking, serum KL-6 levels were significantly positively correlated with A-aDO_2 and negatively correlated with vital capacity (VC), forced vital capacity (FVC), TLC and DL_{CO} (Table 3). In contrast, serum CRP levels were significantly positively correlated with TLC and negatively correlated with forced expiratory volume in 1 s (FEV_1) (Table 3).

Discussion

We analyzed the inter-relationships of different serum biomarkers with OSA and pulmonary function. We found that, after adjustment for obesity and smoking, the serum KL-6 levels significantly correlated with the AHI, unlike serum levels of SP-D and CRP. Additionally, elevated serum KL-6 levels were significantly associated with increased A-aDO_2 and decreased VC, FVC, TLC and DL_{CO} even after adjustment for obesity and smoking, whereas elevated serum CRP levels were significantly associated with increased TLC and decreased FEV_1.

Our results indicate the significance of circulating levels of KL-6 as a marker of lung injury associated with OSA. Although Lederer et al. reported elevated circulating levels of KL-6 in some patients with OSA in comparison with controls in a study having a small sample size,[7] we expanded knowledge in this area by confirming the significant relationship between serum KL-6 levels and the severity of OSA with a relatively large number of subjects and, in addition, compared values for serum KL-6 with