Upper Airway Anatomical Balance Contributes to Optimal Continuous Positive Airway Pressure for Japanese Patients with Obstructive Sleep Apnea Syndrome

Eiki Ito, M.D., Ph.D.^{1,2,3}; Satoru Tsuiki, D.D.S., Ph.D.^{1,2,3}; Kazuyoshi Namba²; Yuji Takise²; Yuichi Inoue, M.D., Ph.D.^{1,2,3}

¹Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan; ²Yoyogi Sleep Disorder Center, Tokyo, Japan;

³Department of Somnology, Tokyo Medical University, Tokyo, Japan

Background: The aim of this study was to examine whether the upper airway anatomical balance, as reflected by tongue size relative to maxillomandibular size, is related to optimal nasal continuous positive airway pressure (PnCPAP).

Methods: Sixty-six male Japanese obstructive sleep apnea syndrome (OSAS) patients (median apnea-hypopnea index [AHI] = 33.9 episodes/h [10th/90th percentile = 19.5/59.9], median body mass index [BMI] = 25.1 kg/m² [10th/90th percentile = 21.2/30.4]) were recruited. All patients underwent standard polysomnography (PSG), and PnCPAP was determined by nasal continuous positive airway pressure (nCPAP) titration. The anatomical balance was defined as the tongue area (TG) divided by the lower face cage (LFC) measured on cephalometry. A predictive equation of PnCPAP was created using demographic, polysomnographic, and cephalometric variables.

Results: Significant correlations were found between PnCPAP and descriptive variables, including BMI, AHI,

lowest SpO₂, distance from the anterosuperior point of the hyoid bone to the mandibular plane (MP-H), and TG/LFC. Stepwise multiple regression analysis revealed that AHI and TG/LFC were independent predictors of PnCPAP. The predictive equation was: PnCPAP = 1.000 + 0.043 × AHI + 9.699 × TG / LFC, which accounted for 28.0% of the total variance in PnCPAP (R² = 0.280, p < 0.01).

Conclusions: Anatomical balance of upper airway in addition to the severity of OSAS is an important contributing factor for PnCPAP in Japanese OSAS patients.

Keywords: Cephalometry, continuous positive airway pressure, obesity, obstructive sleep apnea syndrome, sleep disordered breathing, upper airway

Citation: Ito E; Tsuiki S; Namba K; Takise Y; Inoue Y. Upper airway anatomical balance contributes to optimal continuous positive airway pressure for Japanese patients with obstructive sleep apnea syndrome. *J Clin Sleep Med* 2014;10(2):137-142.

Nasal continuous positive airway pressure (nCPAP) is the most effective therapy for obstructive sleep apnea syndrome (OSAS).¹ This therapy can suppress respiratory events, leading to alleviation of OSAS-related symptoms and comorbidities.^{2,3} However, the optimal nasal continuous positive airway pressure (PnCPAP) for maintenance of upper airway patency can be determined only by in-lab manual titration with simultaneous polysomnography (PSG). Based on the recommendation of the Positive Airway Pressure Titration Task Force of the American Academy of Sleep Medicine, the pressure level of CPAP should be increased until elimination of obstructive respiratory events, respiratory effort-related arousals, and loud or unambiguous snoring.⁴ Attending technologists with sufficient skills and experience are required to determine PnCPAP.

Previous studies suggested that the PnCPAP could be predicted using several variables, including the apnea-hypopnea index (AHI), oxygen desaturation index, body mass index (BMI), neck circumference, or several craniofacial morphology measures. In addition, several equations incorporating these variables have been used to predict PnCPAP.⁵⁻¹² Although these equations cannot replace the use of proper manual titration to identify PnCPAP, such predictive equations are still useful for determination of the starting pressure of CPAP titration, thereby eliminating the need for frequent changes in pressure

BRIEF SUMMARY

Current Knowledge/Study Rationale: In general, obesity requires a higher optimal nasal continuous positive airway pressure (PnCPAP) in obstructive sleep apnea syndrome (OSAS) patients. However, craniofacial factors may be more important for the PnCPAP in Japanese OSAS subjects.

Study Impact: The anatomical imbalance (the larger tongue size relative to maxillomandibular dimensions), rather than obesity, was significantly associated with PnCPAP. This finding might be specific to Japanese OSAS patients.

and minimizing the time needed to determine the effective pressure.¹³ Among the candidates for predictive variables, BMI may be the most important determinant of PnCPAP, as obesity is clearly associated with an increased risk of developing OSAS.¹⁴ However, a considerable number of non-obese patients, especially in Asian populations, develop severe OSAS requiring relatively high PnCPAP.¹⁵ In these patients, craniofacial morphology may play a more prominent role in the pathophysiology of OSAS.¹⁶ Therefore, upper airway morphology should be further considered in addition to obesity when trying to determine PnCPAP in Asian OSAS patients.

Japanese OSAS patients have a significantly larger tongue size for any given maxillomandibular size, suggesting that

Figure 1—Study flow diagram.

nCPAP, nasal continuous positive pressure; OSAS, obstructive sleep apnea syndrome; AHI, apnea-hypopnea index.

upper airway anatomical imbalance may be involved in the pathogenesis in OSAS.¹⁷⁻¹⁹ This finding led us to hypothesize that the upper airway anatomical imbalance is more strongly correlated with PnCPAP than BMI in Japanese OSAS patients. In order to test this hypothesis, the present study investigated factors associated with PnCPAP in Japanese OSAS patients using demographic, polysomnographic, and cephalometric variables as explanatory variables.

METHODS

Study Subjects

The study protocol was approved by the Ethics Committee for Human Research of the Neuropsychiatric Research Institute, Tokyo, Japan (approval number 54). **Figure 1** shows a flowchart of patient recruitment. Target subjects were patients who were diagnosed with OSAS at the Yoyogi Sleep Disorder Center (Tokyo, Japan) based on overnight PSG. As a routine clinical protocol of the clinic, an upright lateral cephalogram was obtained from all OSAS patients in order to evaluate maxillomandibular dimensions and tongue size as well as tonsillar/adenoidal size. From May 2005 to September 2010, a

total of 544 OSAS patients without a prior history of otolaryngeal surgery, comorbidities other than sleep disorders (especially narcolepsy and periodic limb movement disorder), or psychiatric diseases, who wished to receive treatment with an oral appliance, were referred to the Sleep Apnea Dental Clinic after diagnosis. These included nCPAP users who wanted to use oral appliance as a temporary substitute. Of these patients, 185 had a history of receiving nCPAP treatment after PnCPAP had been determined individually by nCPAP titration study. In the present study, CPAP compliers were defined as those who had been using nCPAP > 6 months with an average compliance > 4 h/night and > 6 nights per week, as measured by CPAP devices.²⁰ In addition, their average AHI was < 5/h with the device in place. Seventy-one of 185 patients were regarded as nCPAP compliers, whereas 114 nCPAP patients had poor compliance or failure to use nCPAP. Of the 71 patients who were compliers, female subjects (N = 5) were excluded to avoid a possible confounding effect. Consequently, 66 male OSAS patients were eligible for the final data analyses.

Sleep Studies

During PSG (Alice 4 or 5, Philips Respironics, Inc., Murrysville, PA, USA), 4-channel electroencephalography (EEG) (C3-A2; C4-A1; O1-A2, O2-A1), bilateral electrooculography, submental electromyography, electromyography of both legs, electrocardiography, airflow through the nose and mouth using pressure and thermal sensors, oxygen saturation (SpO₂), and respiratory inductance plethysmography (with a transducer placed around the chest and abdomen, a microphone sensor to record snoring sounds, and a body position sensor) were recorded simultaneously. Sleep stages were scored manually for every 30-s epoch using the standard criteria of Rechtschaffen and Kales, and EEG arousals were scored using the American Sleep Disorders Academy guidelines.^{21,22} An apnea event was defined as cessation of airflow through the nose and mouth lasting ≥ 10 s on PSG; a hypopnea event was defined as ≥ 50% decrease in airflow lasting ≥ 10 s, associated with ≥ 3% decrease in SpO₂ from the preceding baseline value and/or with an arousal.²³ These criteria were used throughout the study period. The AHI was calculated as the average number of apnea plus hypopnea episodes per hour of sleep.

A second PSG session was undertaken within 2 weeks after polysomnographic OSAS diagnosis to determine PnCPAP. CPAP titration was started at 4 cm H₂O, with 1 cm H₂O pressure increases for each increment until respiratory events (apnea, hypopnea, snoring, and respiratory effort-related arousals) disappeared.^{4,6} The PnCPAP was determined as the pressure level that could suppress respiratory events in any sleep position and in any sleep stage.

Cephalometric Assessments

A lateral cephalometric radiograph was obtained for each subject in the upright position with natural head posture using a pair of earpieces. Before the examination, subjects were instructed to close the jaw in a natural occlusive position and to breathe quietly. The radiograph was taken at the end of expiration, and the exposure parameters were arranged to clearly visualize bony landmarks. Cephalometric parameters, as described in a previous report,¹⁹ were employed in the present

Figure 2—Definitions of cephalometric variables reflecting the position and size of the maxilla and mandible and the size of the tongue.

S, sella; A, subspinale; B, supramentale; Cd, medial condylar point of the mandible; Cd', a point that Pog projects on the perpendicular line to the Cd-A line at the Cd point; Eb, base of the epiglottis; Go, gonion; Gn, gnathion; H, hyoid bone; MP, mandibular plane; MP-H, perpendicular distance from the anterosuperior point of the hyoid bone to the mandibular plane; N, nasion; Pog, pogonion; RGN, retrognathion; TT, tongue tip; PNS, posterior nasal spine; P, soft palate; PNS-P, distance from the posterior nasal spine to the tip of the soft plate. (1) Tongue: area outlined by the dorsal configuration of the tongue surface and the lines that connect TT, RGN, H, and Eb. (2) Soft palate area confined by the outline of the soft palate. The lower face cage was defined as a trapezoid by Cd-A-Pog-Cd' (dotted lines).

study (**Figure 2**). Briefly, the lower face cage (LFC; a dotted trapezoid in **Figure 2**) was determined as maxillomandibular size (bony enclosure size of the upper airway). Tongue size (TG) was the area outlined by dorsal configuration of tongue surface and lines that connect the tongue tip, retrognathia, the hyoid bone, and the base of epiglottis. Anatomical balance was defined as the ratio between TG and LFC (TG/LFC).¹⁹

Statistics

Statistical analyses were performed using the statistical software package, SPSS (Version 11.5, SPSS Japan, Inc., Tokyo, Japan). Results are presented as medians (10th/90th percentile). To identify the variables that contribute to the PnCPAP, serial analyses were performed.¹¹ First, correlations between PnCPAP and clinical descriptive variables, including demographic, polysomnographic, and cephalometric variables, were investigated by calculating Pearson product moment correlation coefficients. Second, a stepwise multiple regression analysis was used to investigate the association between PnCPAP and the variables that showed significant associations according to the Pearson product moment correlation coefficients. The model

Table 1—Descriptive variables of the subjects (N = 66)

Demographic variables	
Age, years	49.4 (36/64.3)
Body mass index, kg/m ²	25.1 (21.2/30.4)
Epworth Sleepiness Scale	9.9 (3.0/15.6)
Polysomnographic variables	
Apnea-hypopnea index, episodes/h	33.9 (19.5/59.9)
Lowest SpO ₂ , %	77.2 (62.7/87.3)
PnCPAP, cm H ₂ O	7.9 (5.0/10.0)
Cephalometric variables	
Bony structure	
SNA, degrees	79.5 (74.6/84.7)
SNB, degrees	76.7 (71.1/82.6)
ANB, degrees	2.8 (0.0/6.7)
Soft tissues	
PNS-P, mm	43.4 (38.0/48.2)
Soft palate area, cm ²	3.85 (3.10/4.63)
Hyoid bone position	
MP-H, mm	21.3 (13.2/29.6)
Anatomical balance	
Tongue area, cm ²	36.7 (31.3/42.7)
Lower face cage, cm ²	65.3 (56.1/74.0)
TG/LFC	0.557 (0.487/0.623)

Values reported as median (10th/90th percentile). SpO₂, oxygen saturation; PnCPAP, optimal nasal continuous positive airway pressure; SNA, angle of the sella-nasion-maxilla; SNB, angle of the sella-nasion-mandible; ANB, angle of the maxilla-nasion-mandible; PNS-P, distance from the posterior nasal spine to the tip of the soft palate; MP-H, perpendicular distance from the anterosuperior point of the hyoid bone to the mandibular plane; TG/LFC, ratio between tongue area (TG) and the lower face cage (LFC).

was checked to ensure the assumptions of no multicollinearity, linearity, or homoscedasticity. In these analyses, statistical significance was indicated by $p < 0.05$.

RESULTS

The demographic, polysomnographic, and cephalometric variables of the 66 subjects are shown in **Table 1**. AHI was 33.9 (19.5/59.9) episodes/h, BMI was 25.1 (21.2/30.4) kg/m², and the PnCPAP was 7.9 (5.0/10.0) cm H₂O.

The Pearson product moment correlation coefficients between the PnCPAP and demographic, polysomnographic, and cephalometric variables are summarized in **Table 2**. Results were expressed as correlation coefficients (r) and p -values (p). Among these variables, BMI ($r = 0.379$, $p = 0.002$), AHI ($r = 0.456$, $p < 0.001$), MP-H ($r = 0.311$, $p = 0.011$), tongue area ($r = 0.340$, $p = 0.005$), and TG/LFC ($r = 0.395$, $p = 0.001$) showed significant and positive correlation with the PnCPAP. Meanwhile, lowest SpO₂ ($r = -0.321$, $p = 0.007$) showed a significantly negative correlation with PnCPAP. In addition, there was a significant correlation between TG/LFC and AHI ($r = 0.317$, $p = 0.009$).

The angle between Cd-A and Cd-Pog (angle A-Cd-Pog) ($r = 0.492$, $p = 0.001$),¹⁷ SNA ($r = 0.590$, $p < 0.001$), and ANB ($r = 0.626$, $p < 0.001$) were significantly and positively correlated with LFC.

In order to identify the explanatory variables that can determine the PnCPAP, stepwise multiple regression analysis was conducted with BMI, lowest SpO₂, AHI, MP-H, tongue area,

and TG/LFC, all of which were independent variables with significant correlation with the PnCPAP according to the Pearson product moment correlation coefficient (**Table 2**). Of these variables, only AHI and TG/LFC were significantly associated with PnCPAP (**Table 3**, model 2).

The PnCPAP was determined by the following equation:

$$\text{PnCPAP} = 1.000 + 0.043 \times \text{AHI} + 9.699 \times \text{TG} / \text{LFC}$$

This equation accounted for 28.0% of the total variance in the PnCPAP. ($R^2 = 0.280$, $p < 0.01$)

DISCUSSION

This is the first study to investigate whether the anatomical balance created by cephalometric analyses contributes to PnCPAP in Japanese OSAS patients. The study demonstrated

Table 2—Correlation between PnCPAP and other descriptive variables (N = 66)

	Correlation coefficient (r)	p-value
Demographic variables		
Age	0.106	0.398
Body mass index	0.379	0.002
Epworth Sleepiness Scale	-0.021	0.869
Polysomnographic variables		
Apnea-hypopnea index	0.456	< 0.001
Lowest SpO ₂	-0.321	0.009
Cephalometric variables		
Bony structure		
SNA	0.108	0.390
SNB	-0.056	0.656
ANB	0.170	0.173
Soft tissue		
PNS-P	0.143	0.253
Soft palate area	0.043	0.733
Hyoid bone position		
MP-H	0.311	0.011
Anatomical balance measures		
Tongue area	0.340	0.005
Lower face cage	0.159	0.203
TG/LFC	0.399	0.001

PnCPAP, optimal nasal continuous positive airway pressure. SpO₂, oxygen saturation; SNA, angle of the sella-nasion-maxilla; SNB, angle of the sella-nasion-mandible; ANB, angle of the maxilla-nasion-mandible; MP-H, perpendicular distance from the anterosuperior point of the hyoid bone to the mandibular plane; PNS-P, distance from the posterior nasal spine to the tip of the soft palate; TG/LFC, ratio between tongue area (TG) and the lower face cage (LFC).

that both anatomical imbalance (increased TG/LFC) and AHI were positively and independently correlated with the PnCPAP, suggesting that both the frequency of respiratory events before treatment and anatomical balance act to increase the PnCPAP.

Watanabe et al. and Isono demonstrated that obesity and craniofacial abnormalities contribute synergistically to the increase in collapsibility of the pharyngeal airway in OSAS patients.^{17,18} Tsuiki and colleagues reconfirmed the above concept with the use of cephalometry.¹⁹ Specifically, the luminal size of the airway was determined by the transmural pressure responsible for the balance between the size of the surrounding rigid bony enclosure and the amount of soft material inside the bony enclosure. Therefore, obesity could be described as a condition in which an excess of soft material was present inside a given maxillomandibular size. If this is the case, then the transmural pressure decreases, and the airway narrows. Using this concept, we further investigated the relationship between the anatomical balance and PnCPAP.

The results of the present study are consistent with those from previous reports in that AHI was a significant independent contributor to PnCPAP.^{5,6,8,9,11} This finding is also compatible with our previous study, in which greater PnCPAP was required to suppress OSAS when a patient had higher AHI.²⁴ Of note, the present study demonstrated that the balance between the amount of oropharyngeal soft tissue and the craniofacial bony size could predict PnCPAP. Physiologically, anatomical imbalance increases the upper airway collapsibility,²⁵⁻²⁷ possibly leading to an increased PnCPAP in patients with OSAS. Thus, it is likely that the upper airway anatomical balance has a significant influence on PnCPAP. In contrast to AHI, BMI was not a significant variable for PnCPAP in the present study. Obesity is widely recognized as a risk factor for OSAS, and a pattern of fat distribution around the neck, torso, and abdominal viscera is strongly linked to the pathophysiological mechanisms of OSAS.²⁸ Recently, Basoglu and Tasbakan proposed a new equation for PnCPAP prediction and validated its use in a clinical setting.¹² Interestingly, the equation included a local demographic (neck circumference) rather than a general factor (BMI), which was in line with our results. We speculate that excessive soft tissue contributing to increased neck circumference may increase TG/LFC. In other words, fat deposition in the neck region might be partially interpreted as excessive oropharyngeal soft tissue that is not encircled by the maxilla and mandible, leading to anatomical imbalance. In Asian OSAS patients, craniofacial bony restriction might be a stronger contributor to PnCPAP than BMI. OSAS develops at a lower BMI level in Asian populations than in Western populations,²⁹ and the contribution of

Table 3—Stepwise multiple regression analysis with PnCPAP as a dependent variable (N = 66)

Model	R ²	Predictors	B (95% CI)	β	T	p value
1	0.208	Constant	6.046 (5.071/7.022)	0.456	12.379	< 0.001
		AHI	0.054 (0.027/0.080)		4.102	< 0.001
2	0.280	Constant	1.000 (-3.138/5.138)	0.367	0.483	0.631
		AHI	0.043 (0.017/0.070)		3.252	0.002
		TG/LFC	9.699 (1.952/17.446)		2.502	0.015

PnCPAP, optimal nasal continuous positive airway pressure; B, Unstandardized Coefficients; CI, confidence interval; β, standardized coefficients; AHI, apnea-hypopnea index; TG/LFC, ratio between tongue area (TG) and the lower face cage (LFC).

Asian cephalometric characteristics, such as smaller maxilla and mandible, retrognathia, and a shorter and steeper anterior cranial base, to the development of OSAS have been invoked to explain the ethnicity-related differences.^{15,16,30}

This study demonstrated the importance of vertical dimension on cephalometric variables. CPAP increased the airway volume, reduced lateral wall thickness,³¹ and increased lung volume, which culminated in enhanced upper airway size and promoted stability. These factors result from the caudal traction effect on upper airway size.^{32,33} Previously, the hyoid bone position (MP-H) was included in a described predictive equation of PnCPAP.¹¹ In the present study, MP-H was positively correlated with PnCPAP, but the variable did not appear to be significant on stepwise regression analysis. A previous report demonstrated that the hyoid bone was located more caudally in OSAS patients.³⁴ Because the human hyoid bone is mobile and has no connection to other bones, caudal expansion of excessive soft tissue within the maxillomandibular enclosure may be responsible for the shift of the hyoid bone to the caudal direction.³⁵ Thus, MP-H may be affected by both obesity and TG/LFC, thereby possibly being confounded in the stepwise regression analysis. Conversely, LFC did not correlate with AHI, but angle A-Cd-Pog,¹⁷ SNA, and ANB positively correlated with LFC. We speculate that LFC was associated with both longitudinal and vertical dimensions in terms of the development of the bony structures: maxilla and mandible.

The present study has several limitations. First, we did not measure neck circumference, which is associated with a high risk of OSAS.³⁶ Further study would be of benefit to investigate the correlation between neck circumference, cephalometric variables, and AHI. Second, all investigations were performed in only one dental division of a single sleep disorder center, which may cause some sampling bias. The PnCPAP in the present study were slightly lower than those in a previous study of male Japanese OSAS patients.³⁷ However, AHI was decreased to < 5 episodes per hour on titration PSG of all the subjects, their adherence to CPAP was good, and the effectiveness of nCPAP was maintained through the follow-up period. Thus, we were able to verify that the PnCPAP determined by nCPAP titration in this study were appropriate. Third, the subjects in the present study were all male. Since regional distribution of fat deposition differs between genders,³⁸ future research evaluating PnCPAP in female OSAS patients is needed. Finally, our structural analyses were two-dimensional and did not include three-dimensional analysis of the whole upper airway structure that can be achieved by MRI.³⁹ Future study would be desirable to evaluate the correlation between PnCPAP and anatomical imbalance with volumetric analyses of the constituents of the upper airway by using three-dimensional MRI.

The present study yielded several findings with clinical implications. For example, our two-dimensional cephalometric approach has the advantage of easier applicability in general clinical settings. Recently, the American Academy of Sleep Medicine suggested that autotitrating CPAP with a self-adjusting mode can be used to treat patients with moderate to severe OSAS.⁴⁰ However, autotitrating CPAP can overcompensate for mask or mouth leaks with inadequately high CPAP pressure. Therefore, results from the present study may help set the adequate pressure range for autotitrating CPAP.

In conclusion, anatomical balance of the upper airway in addition to the severity of OSAS can contribute to the PnCPAP.

REFERENCES

1. American Thoracic Society. Indications and standards for use of nasal positive airway pressure (CPAP) in sleep apnea syndromes. *Am J Respir Crit Care Med* 1994;150:1738-45.
2. Antic NA, Catchside P, Buchan C, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. *Sleep* 2011;34:111-19.
3. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046-53.
4. Kushida CA, Chediak A, Berry RB, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. *J Clin Sleep Med* 2008;4:157-71.
5. Choi JH, Kim EJ, Kim KW, et al. Optimal continuous positive airway pressure level in Korean patients with obstructive sleep apnea syndrome. *Clin Exp Otorhinolaryngol* 2010;3:207-11.
6. Loredó JS, Berry C, Nelesen RA, et al. Prediction of continuous positive airway pressure in obstructive sleep apnea. *Sleep Breath* 2007;11:45-51.
7. Stradling JR, Hardinge M, Paxton J, et al. Relative accuracy of algorithm-based prescription of nasal CPAP in OSA. *Respir Med* 2004;98:152-4.
8. Lin IF, Chuang ML, Liao YF, et al. Predicting effective continuous positive airway pressure in Taiwanese patients with obstructive sleep apnea syndrome. *J Formos Med Assoc* 2003;102:215-21.
9. Miljeteig H, Hoffstein V. Determinants of continuous positive airway pressure level for treatment of obstructive sleep apnea. *Am Rev Respir Dis* 1993;147:1526-30.
10. Akashiba T, Kosaka N, Yamamoto H, et al. Optimal continuous positive airway pressure in patients with obstructive sleep apnoea: role of craniofacial structure. *Respir Med* 2001;95:393-7.
11. Akahoshi T, Akashiba T, Kawahara S, et al. Predicting optimal continuous positive airway pressure in Japanese patients with obstructive sleep apnoea syndrome. *Respirology* 2009;14:245-50.
12. Basoglu OK, Tasbakan MS. Determination of new prediction formula for nasal continuous positive airway pressure in Turkish patients with obstructive sleep apnea syndrome. *Sleep Breath* 2012;16:1121-7.
13. Schiza SE, Bouloukaki I. Prediction formulas for nasal continuous positive airway pressure in patients with obstructive sleep apnea syndrome. *Sleep Breath* 2012;16:941-3.
14. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230-5.
15. Li KK, Kushida C, Powell NB, et al. Obstructive sleep apnea syndrome: a comparison between Far-East Asian and white men. *Laryngoscope* 2000;110:1689-93.
16. Sakakibara H, Tong M, Matsushita K, et al. Cephalometric abnormalities in non-obese and obese patients with obstructive sleep apnea. *Eur Respir J* 1999;13:403-10.
17. Watanabe T, Isono S, Tanaka A, et al. 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* 2002;165:260-5.
18. Isono S. Contribution of obesity and craniofacial abnormalities to pharyngeal collapsibility in patients with obstructive sleep apnea. *Sleep Biol Rhythms* 2004;2:17-21.
19. Tsuiji S, Isono S, Ishikawa T, et al. Anatomical balance of the upper airway and obstructive sleep apnea. *Anesthesiology* 2008;108:1009-15.
20. Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep* 2007;30:711-9.
21. Rechtschaffen A, Kales A. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Los Angeles, CA: Brain Information Service/Brain Research Institute, University of California, 1968.
22. EEG arousal: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992;15:173-84.
23. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999;22:667-89.

24. Tsuiki S, Kobayashi M, Namba K, et al. Optimal positive airway pressure predicts oral appliance response to sleep apnoea. *Eur Respir J* 2010;35:1098-105.
25. Smith PL, Wise RA, Gold AR, et al. Upper airway pressure-flow relationships in obstructive sleep apnea. *J Appl Physiol* 1988;64:789-95.
26. Schwartz AR, Smith PL, Wise RA, et al. Induction of upper airway occlusion in sleeping individuals with subatmospheric nasal pressure. *J Appl Physiol* 1988;64:535-42.
27. Kuna S, Remmers JE. Anatomy and physiology of upper airway obstruction: In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*, 3rd edition. Philadelphia, PA: WB Saunders: 2000;840-58.
28. Schwartz AR, Patil SP, Laffan AM, et al. Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc* 2008;5:185-92.
29. Yamagishi K, Ohira T, Nakano H, et al. Cross-cultural comparison of the sleep-disordered breathing prevalence among Americans and Japanese. *Eur Respir J* 2010;36:379-84.
30. Lee RW, Vasudavan S, Hui DS, et al. Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. *Sleep* 2010;33:1075-80.
31. Schwab RJ, Pack AI, Gupta KB, et al. Upper airway and soft tissue structural changes induced by CPAP in normal subjects. *Am J Respir Crit Care Med* 1996;154:1106-16.
32. Heinzer RC, Stanchina ML, Malhotra A, et al. Effect of increased lung volume on sleep disordered breathing in patients with sleep apnoea. *Thorax* 2006;61:435-9.
33. Tagaito Y, Isono S, Remmers JE, et al. Lung volume and collapsibility of the passive pharynx in patients with sleep-disordered breathing. *J Appl Physiol* 2007;103:1379-85.
34. Ferguson KA, Ono T, Lowe AA, et al. The relationship between obesity and craniofacial structure in obstructive sleep apnea. *Chest* 1995;108:375-81.
35. Yu X, Fujimoto K, Urushibata K, et al. Cephalometric analysis in obese and nonobese patients with obstructive sleep apnea syndrome. *Chest* 2003;124:212-8.
36. Flemons WW, Whitelaw WA, Brant R, et al. Likelihood ratios for a sleep apnea clinical prediction rule. *Am J Respir Crit Care Med* 1994;150(Pt1):1279-85.
37. Yukawa K, Inoue Y, Yagyu H, et al. Gender differences in the clinical characteristics among Japanese patients with obstructive sleep apnea syndrome. *Chest* 2009;135:337-43.
38. Simpson L, Mukherjee S, Cooper MN, et al. Sex differences in the association of regional fat distribution with the severity of obstructive sleep apnea. *Sleep* 2010;33:467-74.
39. Schwab RJ, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. *Am J Respir Crit Care Med* 2003;168:522-30.
40. Morgenthaler TI, Aurora RN, Brown T, et al. Practice parameters for the use of autotitrating continuous positive airway pressure devices for titrating pressures and treating adults patients with obstructive sleep apnea syndrome; an update for 2007. An American Academy of Sleep Medicine report. *Sleep* 2008;31:141-7.

ACKNOWLEDGMENTS

The authors are grateful to Masato Matsuura, M.D. (Department of Life Sciences and Bio-informatics, Division of Biomedical Laboratory Sciences, Graduate School of Health Care Sciences, Tokyo Medical and Dental University, Tokyo, Japan), Jun Kodama, and Keiko Maeda, D.D.S. (Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan) for performing data collection and statistical analysis. Part of the present study was supported by Grants-in-Aid for Scientific Research (25461180 to E. Ito, 25515010 to S. Tsuiki, and 25515009 to Y. Inoue) from the Japanese Society for the Promotion of Science.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication May, 2013

Submitted in final revised form October, 2013

Accepted for publication October, 2013

Address correspondence to: Yuichi Inoue, M.D., Ph.D., Japan Somnology Center, Neuropsychiatric Research Institute, 1-24-10 Yoyogi, Shibuya-ku, Tokyo 151-0053, Japan; Tel: +81-3-3374-9112; Fax: +81-3-3374-9125; E-mail: inoue@somnology.com

DISCLOSURE STATEMENT

This was not an industry supported study. Part of the present study was supported by Grants-in-Aid for Scientific Research (25461180 to E. Ito, 25515010 to S. Tsuiki, and 25515009 to Y. Inoue) from the Japanese Society for the Promotion of Science. The sponsor had no role in the design of the study, the collection and analysis of the data, or in the manuscript preparation. The authors have indicated no financial conflicts of interest. This work was performed at the Neuropsychiatric Research Institute, Tokyo, Japan.