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New Predictive Equation for Optimal Continuous Positive Airway Pressure in Adult Patients with Obstructive Sleep Apnea

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Abstract:

Objective: This study aimed to develop and validate a new continuous positive airway pressure (CPAP) prediction equation and compare it with other formulas.

Material and Methods: We retrospectively included patients with obstructive sleep apnea who underwent a CPAP titration study between January 2012 and December 2016. All clinical and polysomnographic data were collected. The new prediction equation was developed using the first data set, and the predictability performance was validated using the second data set.

Results: Among the 266 enrolled patients, 73.7% were male, and the mean body mass index (BMI) was 30.8±7.4 kg/m^2. Five variables, namely age, BMI, neck circumference (NC), apnea–hypopnea index (AHI), and minimum pulse oxygen saturation (Min SpO_2), highly correlated with the optimal titration pressure, and were therefore included in the equation, as stated below:

$$\text{Predicted pressure (cm } H_2O) = 2.26 + (0.02 \times \text{Age}) + (0.04 \times \text{BMI}) + (0.11 \times \text{NC}) + (0.04 \times \text{AHI}) - (0.04 \times \text{Min } SpO_2)$$

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This equation accounted for 54.4% of the variance in predicting the optimal titration pressure (R^2=0.544, p-value <0.001). Its optimal estimation was 62.0% in the validated group. The equation-derived predicted pressure correlated with good agreement with the laboratory-derived optimal titration pressure (r=0.70, 95% CI=0.6335–0.755, p-value<0.001) according to Bland–Altman analysis.

Conclusion: Our equation is highly consistent with the CPAP titration study in predicting fixed CPAP pressure, and is thereby beneficial for sleep technicians in establishing a starting pressure for such studies at a sleep laboratory.

Keywords: continuous positive airway pressure, obstructive sleep apnea, optimal pressure, predictive equation, sleep apnea

Introduction

Obstructive sleep apnea (OSA) is a common sleep problem with estimated prevalences among adults from 30 to 70 years of age; approximately 14.0% of men and 5.0% of women have an apnea–hypopnea index (AHI) of more than 5 events/hour with symptoms of daytime sleepiness.[1] OSA not only affects sleep quality but also causes cardiovascular morbidity and mortality.[2,3] The primary treatment for moderate to severe OSA is continuous positive airway pressure (CPAP), which provides pneumatic splinting of the collapsed upper airway. It effectively reduces AHI, improves sleepiness and quality of life, and may prevent cardiovascular complications.[4] The laboratory-conducted full-night CPAP titration study is still generally preferred to determine the minimum pressure required to prevent the patient's respiratory events.[5] This procedure requires at least two overnight sleep studies, and is therefore time consuming, and the split-night CPAP titration study, which includes initial diagnostic polysomnography (PSG) followed by a manual CPAP titration study on the same night is an alternative choice. However, this technique also requires time-consuming titration and often fails to obtain the optimal titration pressure (P-titrated). Practical issues related to the limitations of laboratory CPAP titration are widely solved by unattended automatic positive airway pressure (APAP) titration with using 90th or 95th percentile of CPAP pressure. According to some guidelines, only certain APAP devices can be used in determining the treatment pressure for patients without significant comorbidities suffering from OSA.[6] The issue of predicting effective CPAP levels has also been studied. In addition, various predictive formulas for optimal pressure are based on differences in clinical variables or PSG parameters.[7-13] In this study, we aimed to develop and validate a new CPAP prediction equation to help establish the starting pressure for CPAP titration study at a sleep laboratory and to compare it with other formulas in estimating the CPAP.

Material and Methods

This retrospective study included patients with OSA who were at least 20 years old and had undergone a CPAP titration study at the Sleep Laboratory Center of Songklanagarind Hospital, a university hospital in Southern Thailand, between January 2012 and December 2016. All enrolled subjects had to have obtained the optimal P-titrated level before admission to the study. We collected all clinical and PSG data for each patient including age, gender, Epworth Sleepiness Scale (ESS)[14,15], body mass index (BMI), neck circumference (NC), Friedman tongue position (FTP), AHI, minimal pulse oxygen saturation (Min SpO_2), oxygen desaturation index (ODI), and optimal P-titrated. The NC was measured at the Adam's apple level, and

the FTP was assessed in the upright position with the mouth open without tongue protrusion.[16,17] The ODI was the average number of desaturation episodes per hour of recording in which the oxygen saturation decreased by 3.0%. Patients with incomplete data were excluded from the study.

PSG and CPAP titration studies

Type 1 PSG (Compumedics E series, Compumedics, Abbotsford, Australia), which consisted of electro-encephalometry, electro-oculography, chin and leg electromyography, electrocardiography, thermistors and a nasal pressure transducer for oronasal airflow, thoracic and abdominal belts for respiratory efforts, pulse oximetry for oxyhemoglobin concentration, a tracheal microphone for snoring, and sensors for assessing sleeping position, was conducted for each patient. Data from the recordings of each parameter were scored manually using standard criteria.[18] An apnea event was scored when the thermistor signal decreased by ≥90.0% of the pre-event baseline for ≥10 seconds. We scored hypopnea when the nasal pressure signals decreased by 30.0% for ≥10 seconds associated with ≥3.0% oxygen desaturation or an arousal. The AHI was calculated by the number of apnea and hypopnea events per hour of total sleep time.[19] In cases in which the AHI was at least 40 during a minimum of 2 hours of diagnostic PSG, split-night studies were performed. Certified sleep technicians in the sleep laboratory manually performed the CPAP titration studies. The pressure was started at 4 cm H_2O and then increased by at least 1 cm H_2O at an interval of ≥5 minutes. If 2 obstructive apneas, 3 hypopneas, or 5 respiratory-effort-related arousals, or at least 3 min of loud or unambiguous snoring occurred, the CPAP was increased. The optimal P-titrated was defined as the lowest effective pressure that reduced AHI <5 for at least 15 minutes, a minimum SpO_2 level above 90.0% at the selected pressure, and included supine rapid eye movement (REM) sleep at the selected pressure that was not continually interrupted by spontaneous arousals or awakenings.[20]

All baseline data are presented as means (standard deviation (S.D.)) for continuous variables, numbers (%) for categorical variables, or medians (interquartile range (IQR)) for original variables. In comparing between groups, we used chi-square or Fisher's exact test for nominal variables and Mann–Whitney U test for original variables. Two data sets, the prediction equation development and validation phases, were the source of the independent data.

In developing an equation that could predict the optimal pressure, all variables from the first data set with p-value<0.050 on univariate analysis were used to identify the independent predictive variables through stepwise multiple linear regression analysis. The relationships between the baseline data (e.g., anthropometric and PSG variables) and the optimal P-titrated derived from the titration studies were explored using Pearson correlation coefficients. For the validation phase, we used all variables from the second data set to assess the mean differences between the optimal P-titrated and predicted pressures (P-predicted) from our prediction equation using a Bland–Altman plot, and to compare this equation with the formulas of Hoffstein, Lin, Luo, Lee, and Wu.[7-12] The prediction performances were classified into optimal estimation (difference between P-titrated and P-predicted) of ≤1 cm H_2O), >1 cm H_2O increment, or >1 cm H_2O decrement. These estimations would determine how well P-predicted approximated P-titrated in individual subjects. Normality was checked by the Shapiro–Wilk test, and the mean pressure differences were analyzed by the Student's t-test or Wilcoxon rank sum test. All statistical analyses were performed using Epidata software (version 3.1) and R (version 3.5.1). A p-value< 0.050 was considered to be statistically significant.

Results

Most of the enrolled subjects were males with obesity who suffered from severe OSA with significant oxygen desaturation and daytime sleepiness. Age, BMI, NC, AHI, and Min SpO_2 of both data sets demonstrated no statistically significant differences (Table 1).

Prediction equation development

Of the 266 enrolled patients, 73.7% were male. The mean BMI was 30.8±7.4 kg/m^2, while the mean NC was 39.4±3.8 cm. The mean ESS score was 10.0±4.4, and a majority of the patients had FTP class 3–4 (80.4%). The mean AHI was 51.1±29.5 events/hour with a minimum oxygen saturation of 78.6%±8.7%. The mean P-titrated was 7.7±2.1 cm H_2O. According to the univariate analysis, age, BMI, NC, AHI, Min SpO_2, and ODI were significantly correlated with optimal P-titrated, and they were considered in the multiple linear regression analysis (Table 2). In the multiple linear regression analysis, only five variables, namely age, BMI, NC, AHI, and Min SpO_2, had a high correlation with optimal P-titrated, and were therefore included in the equation (Table 3). This equation accounted for 54.4% of the variance in optimal P-titrated (R^2=0.544, adjusted R^2=0.535, p-value<0.001). The prediction equation was then created as follows:

P-predicted (cm H_2O) = 2.26 + (0.02xAge) + (0.04x BMI) + (0.11xNC) + (0.04xAHI) – (0.04xMin SpO_2)

where BMI=body mass index, NC=neck circum-ference, AHI=apnea–hypopnea index, and Min SpO_2=minimum pulse oxygen saturation.

Table 1 Baseline characteristics and polysomnographic data of study patients

Variable	Prediction equation development set (n=266)	Validation set (n=274)	p-value
Age (years), mean (S.D.)	49.6 (13.0)	48.6 (14.1)	0.369
BMI (kg/m^2), mean (S.D.)	30.8 (7.4)	31.2 (7.4)	0.580
NC (cm), mean (S.D.)	39.5 (3.8)	39.8 (4.1)	0.313
ESS scores, median (S.D.)	10.0 (7.0,12.0)	9.0 (6.0,12.0)	0.032
AHI (events/hour), mean (S.D.)	51.1 (29.5)	49.4 (27.0)	0.494
Min SpO_2 (%), mean (S.D.)	78.6 (8.7)	77.2 (11.1)	0.095
ODI (events/hour), mean (S.D.)	41.4 (29.0)	35.6 (28.1)	0.018
FTP scale, number (%)			0.044
1–2	26 (19.5)	29 (21.8)	
3–4	107 (80.4)	104 (78.2)	
Optimal titration pressure (cm H_2O), mean (S.D.)	7.7 (2.1)	7.4 (1.8)	0.048

BMI=body mass index, NC=neck circumference, ESS=Epworth Sleepiness Scale, AHI=apnea–hypopnea index, Min SpO_2=minimum pulse oxygen saturation, ODI=oxygen desaturation index, FTP=Friedman tongue position, kg/m^2= kilograms per square meter, cm H_2O= centimeters water, SD=standard deviation, IQR=interquartile range

Table 2 Relationship of variables and optimal titration pressure by univariate analysis (n=266)

Variable	Coefficient (SE)	R^2	p-value
Age	−0.010 (0.010)	0.004	<0.001
BMI	0.108 (0.016)	0.140	<0.001
NC	0.272 (0.030)	0.238	<0.001
AHI	0.048 (0.003)	0.443	<0.001
Min SpO_2	−0.104 (0.014)	0.182	<0.001
ODI	0.049 (0.003)	0.444	<0.001

BMI=body mass index, NC=neck circumference, AHI=apnea–hypopnea index, Min SpO_2=minimum pulse oxygen saturation, ODI=oxygen desaturation index, SE=standard error

Table 3 Multiple linear regression analysis to predict the optimal titration pressure (n=266)

Variable	Coefficient	SE	p-value
Age	0.024	0.007	0.001
BMI	0.036	0.015	0.018
NC	0.112	0.030	<0.001
AHI	0.037	0.003	<0.001
Min SpO_2	−0.041	0.011	<0.001

BMI=body mass index, NC=neck circumference, AHI=apnea–hypopnea index, Min SpO_2=minimum pulse oxygen saturation, SE=standard error

Validation of prediction equation

After developing the equation, we validated it by using the second data set of the subjects (N=274). The mean BMI and NC were 31.2±7.4 kg/m^2 and 39.8±4.1 cm, respectively. The mean AHI was 49.4±27.0 events/hour, with the mean Min SpO_2 of 77.2%±11.1%. The mean P-titrated of the second data set was 7.4±1.8 cm H_2O, while that from our equation was 7.7±1.6 cm H_2O. The correlation coefficients between the laboratory-derived pressure and the equation-derived pressure were r=0.6995, 95% CI=0.6335–0.755, and p-value<0.001. In addition, Bland–Altman analysis showed good agreement between the two methods with a mean difference of −0.4 ±1.3 cm H_2O (95% limits of agreement −2.95 to 2.15 cm H_2O). Only 13 of the 274 patients (4.7%) were outside the limits of agreement.

Comparison between our equation and other formulas

The optimal estimation of our equation was 62.0% (170 in 274), whereas that of the Hoffstein's formula was 45.6%, and the optimal estimations of Lin, Luo, Lee, and Wu's formulas, which were acquired from Asian studies,

Table 4 Predictive performance of our prediction equation in comparison with that of five previously reported formulas (n=274)

Prediction formula	Mean P-predicted (S.D.), cm H_2O	Mean difference between P-titrated and P-predicted (S.D.)	Difference between P-titrated and P-predicted Number (%)		
			±1 cm H_2O	>1 cm H_2O decrement	>1 cm H_2O increment
Our prediction equation	7.7 (1.6)	−0.4 (1.3)	170 (62.0)	75 (27.4)	29 (10.6)
Hoffstein et al.	7.3 (2.1)	0.1 (1.7)	125 (45.6)	67 (24.5)	82 (29.9)
Lin et al.	8.0 (2.0)	−0.6 (1.7)	135 (49.3)	106 (38.7)	33 (12.0)
Luo et al.	8.1 (2.2)	−0.7 (1.8)	132 (48.2)	108 (39.4)	34 (12.4)
Lee et al.	8.9 (2.3)	−1.6 (1.7)	85 (31.0)	170 (62.0)	19 (6.9)
Wu et al.	8.1 (2.2)	−0.7 (1.7)	138 (50.4)	104 (38.0)	32 (11.7)

P-titrated=optimal titration pressure, P-predicted=predicted pressure, cm H_2O=centimeters water, S.D.=standard deviation

were 49.3%, 48.2%, 31.0%, and 50.4%, respectively. However, Lee's formula clearly showed a pressure difference of >1 cm H_2O decrement, which was up to 62.0% (Table 4).

Discussion

The present study examined a large group of patients with OSA who underwent CPAP titration studies, which data were used to develop a new equation for predicting CPAP for Asian patients, which was then compared with five previously reported formulas in a separate validation group. The Hoffstein formula was the first widely used equation for predicting CPAP in Caucasian populations. The four remaining formulas were based on studies in Asian populations, using different parameters. Regarding our equation, CPAP prediction was determined by a combination of age, BMI, NC, AHI, and Min SpO_2. This equation accounted for 54.0% of the total variance. The P-predicted derived from our equation positively correlated with the optimal P-titrated derived from the sleep laboratory ($r=0.7$, p-value<0.001), showing a good agreement between the two pressure-identifying methods. Moreover, the optimal estimation of our formula was 62.0%, whereas that of Wu formula was only 50.0%. The Lee formula, which only uses the ESS score, tended to show a lower CPAP pressure in our patients (62.0%). In contrast, the Hoffstein formula

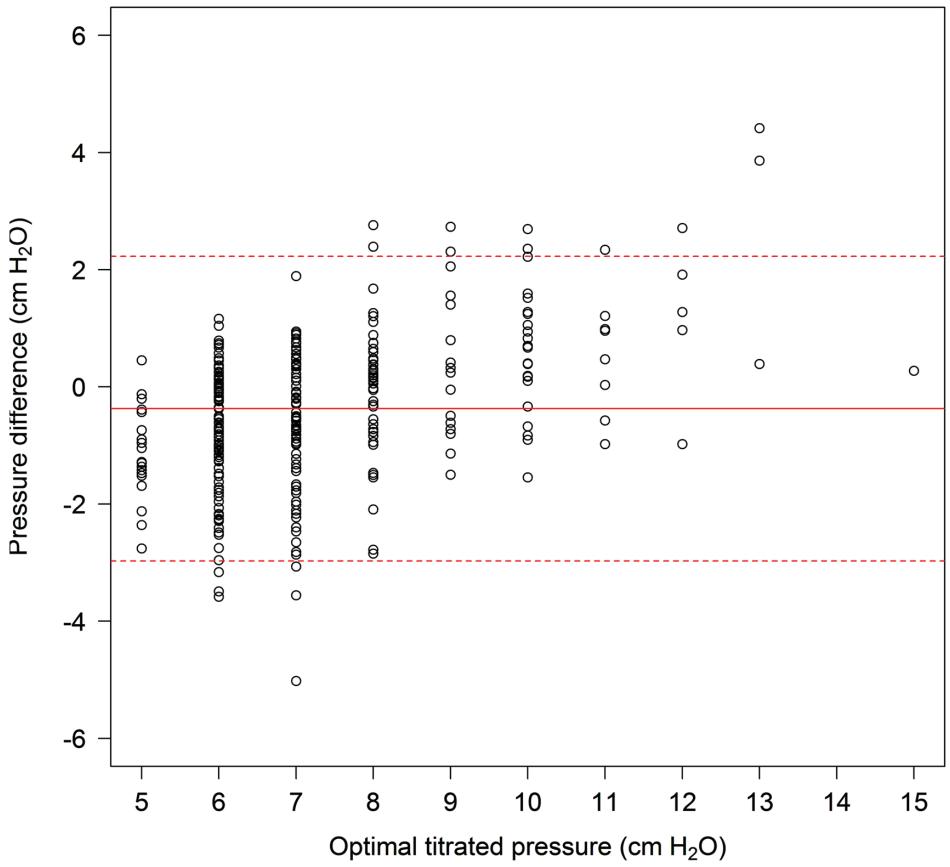

Figure 1 Bland–Altman plot showing the differences against the mean of the optimal titration pressure (P-titrated) and predicted pressure (P-predicted).

tended to show a higher pressure, reaching up to 30.0%, for Asian patients.

According to the multivariate analysis in this study, age was significantly related to the optimal P-titrated. The presence of this variable in our equation differentiates our formula from all other proposed formulas. The variable NC was also related to the optimal P-titrated in our study, consistent with the study of Kirgezen et al., which reported that the NC was one of the major factors affecting the optimal P-titrated of a CPAP device.[21] The remaining variables such as BMI, AHI, and Min SpO_2 were significantly related to the optimal P-titrated, similar to the majority of the formulas.[7-13] However, we found that the ESS scores and sex were not significantly associated with the optimal P-titrated.

The effect of race on CPAP prediction should also be considered. Generally, Asian and Caucasian patients have different craniofacial and body structures. In addition, Asian patients are typically less obese and have a smaller neck size than Caucasians, as reported in several previous studies.[9-12] However, in this study, the Hoffstein formula could predict CPAP at an optimal estimation of only 45.0%, similar to other Asian-derived formulas. This might be due to a slightly higher mean BMI in the patients with OSA included our study (31.2±7.4 kg/m^2) similar to the BMI of 34.0±8.0 kg/m^2 in the Hoffstein study. Surprisingly, the optimal estimation of the Lee formula in predicting pressure was only 31.0%; hence, it mostly tended to predict CPAP pressure at a lower level (62.0%). Also, the ESS scores are subjective and thus somewhat unreliable with various possible biases.

PSG is an important tool for diagnosing sleep apnea. Unfortunately, the full procedure is quite costly, thus making the diagnostic PSG followed by a second CPAP titration study less accessible for many institutions. One alternative option is to use the split-night PSG procedure, which includes both a diagnostic portion and a CPAP titration portion, if OSA is found. This approach is both cost effective and convenient for patients. Long-term CPAP use has no difference between this technique and the standard full-night PSG.[22,23] However, there are still some concerns regarding the split-night study in terms of an inadequate time for proper titration, which should last at least 3 hours. Moreover, PSG during the CPAP titration portion should include respiratory event elimination during both REM and non-rapid eye movement sleep. If the respiratory events are not eliminated, then the CPAP has not obtained optimal titration. Split-night titration studies are more commonly associated with unsuccessful CPAP titration than full-night titration (50.0% vs. 35.5%).[24] Our formula provides an optimal estimation of CPAP of as high as 62.0%. Therefore, this formula might improve the manual CPAP titration success by predicting the starting pressure, especially in split-night studies with limited time. In addition, it may be beneficial in some resource-limited settings to help determine the fixed CPAP for adult patients with OSA. Although the PSG titration is still the standard method for obtaining a fixed pressure for CPAP, titration with an automatic CPAP device or predictive formula is being increasingly used in many developed countries. Some previous studies have shown that home CPAP titrations repeated over multiple nights or various predictive equations can determine an appropriate therapeutic prescription for fixed CPAP in most patients.[25,26] Moreover, recent data have supported that pressures differing by only a few cm H_2O from the standard titrated level may be reasonably effective in reducing respiratory events and somnolence.[25-30] However, an inappropriate CPAP pressure can cause undesirable side effects and affect treatment adherence. Thus, long-term CPAP compliance and clinical consequences should be further studied in patients using this pressure-derived formula.

For the study limitations, this study did not include parameters from clinical anatomical evaluation (FTP, tonsil

sizes, etc.). Some predicted formulas have proposed a potential benefit from using anatomical evaluation parameters, such as FTP and hyomental distance. However, performing upper-airway anatomical evaluation in all patients is not practical in some multidisciplinary sleep centers.[13] In addition, this formula was developed and compared with other formulas at only one center. The subjective variables could be interpreted differently between examiners among different sleep centers, which might give rise to different outcomes.

Conclusion

Our equation is highly consistent with the CPAP titration study in predicting the optimal CPAP pressure. It might help sleep technicians establish a starting pressure for CPAP titration studies at a sleep laboratory. Furthermore, it may be useful in some resource-limited settings to determine the CPAP pressure for adult patients with OSA.

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Conflict of interest

None

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