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Original Article

# Titration procedures for nasal CPAP: Automatic CPAP or prediction formula? ☆

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**Abstract**

*Background:* The best method for titration of continuous positive airway pressure (CPAP) therapy in obstructive sleep apnea (OSA) syndrome has not yet been established. The 90th or 95th percentiles of the pressure titrated over time by automatic CPAP (A-CPAP) have been recommended as reference for prescribing therapeutic fixed CPAP (F-CPAP). We compared A-CPAP to F-CPAP, which was determined by a common prediction formula.
*Methods:* Forty-five patients who were habituated to F-CPAP underwent titration polysomnography. In a double-blind, randomized order, each patient used an A-CPAP device in the autotitration and in the fixed pressure mode during one half of the night. Apnea–hypopnea index (AHI) and pressure profiles were primary outcomes. Bias and precision were additionally assessed for both CPAP modes.
*Results:* No significant differences in various sleep parameters or in subjective sleep quality evaluation were found. The AHI was effectively lowered in both CPAP modes (A-CPAP 7.7 [10.8] events/h versus F-CPAP 5.4 [9.0] events/h, $p = 0.061$). Comparison of group means showed that F-CPAP closely paralleled mean (Pmean) and median (P50), but not the 95th percentile (P95) pressure, of A-CPAP. While bias was lowest for Pmean and P50, there was a lack of precision in all A-CPAP pressure categories.
*Conclusions:* We confirm that F-CPAP set by prediction formula is not worse in terms of AHI control than A-CPAP. On average, F-CPAP parallels Pmean and P50 but not P95. However, due to imprecise matching, individual F-CPAP values cannot be derived from Pmean or P50.


*Keywords:* CPAP; Automatic CPAP; Obstructive sleep apnea; Snoring; Prediction formula; Respironics REMstar Auto™

## 1. Introduction

More than two decades after nasal continuous positive airway pressure (CPAP) has become available as a treatment option for obstructive sleep apnea (OSA), the best procedure to determine optimal pressure levels for long-term CPAP therapy remains controversial. While manual CPAP titration has been recommended as a standard operating procedure for this purpose [1], clear directives on how to carry out manual titration

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have never been issued. Therefore, unequivocal pressure titration algorithms that are suitable to treat all patients are still lacking.

In recent years, automatic CPAP (A-CPAP) devices have been developed aiming at safe and efficient pressure adaptation to meet the patient's variable pressure needs [2,3]. A-CPAP can be used for permanent home treatment or to titrate a level of pressure that is suitable for long-term treatment with fixed CPAP (F-CPAP). In previous reports, evidence was provided indicating that an A-CPAP titration procedure is as efficient as manual titration in assuring respiratory control [4], and that the 90th [5,6] or 95th percentiles [7–10] of the pressure titrated by A-CPAP have been suggested as reference pressure levels for F-CPAP treatment at home.

Other research has focused on the prediction of effective CPAP using formulas that include respiratory and/or anthropometric parameters [10,11]. Prediction formulas were found to be useful in simplifying manual CPAP titration [12,13] or even equally efficient as standard titration in finding the required F-CPAP [14,15]. Hukins et al. demonstrated that 'arbitrary' CPAP based on body mass index (BMI) resulted in clinical improvement similar to CPAP determined by manual titration [16]. Another large prospective multi-center trial compared the effects of a prediction formula, A-CPAP and manual titration, and found that these three methods were equally effective in improving subjective sleepiness and the apnea–hypopnea index (AHI) [6]. This was confirmed in a prospective study performed at home, where different methods of CPAP assessment resulted in comparable clinical outcomes [17]. However, despite increasing evidence that alternative methods for assessment of CPAP are effective, manual titration still prevails in official guidelines, although it is the most labour-intensive and expensive procedure.

The goal of the present study was to evaluate whether A-CPAP is superior to 'empirical' CPAP determined by a prediction formula for the assessment of optimal airway pressure. The primary outcome measure of this investigation was the AHI; secondary outcome measures were pressure profiles and subjective appraisal of sleep quality.

## 2. Materials and methods

### 2.1. Study subjects

From May 2005 to December 2005, 62 patients with an AHI > 20/h plus an arousal index > 30/h (i.e., Belgian criteria for reimbursement of nasal CPAP) were considered for participation. Exclusion criteria were a history of prior uvulopalatopharyngoplasty (UPPP), signs of severe nasal obstruction, excessive sleep disruption due to non-respiratory causes, chronic obstructive pulmonary disease (COPD; i.e., forced expiratory volume in 1 s [FEV1]/forced vital capacity [FVC] < 65%), inadequate CPAP compliance at home (average use <3 h per night), central sleep apnea and congestive heart failure. After screening, 10 subjects were excluded because of poor CPAP compliance and another one because of central sleep apnea. After inclusion, six more patients were excluded because of technical problems (i.e., critical loss of data in one or more polysomnographic channels). Finally, 45 patients successfully completed the study. The trial was approved by the Ethical Review Board of our institution and all participants gave written informed consent.

### 2.2. Sleep studies

Polysomnography was carried out using a 19-channel digital polygraph (Morpheus™, Medatec, Brussels, Belgium). During baseline studies, nasal pressure cannulae were used to record airflow; the prongs were connected via flexible tubing 4 mm in diameter to the built-in manometer (Honeywell 164PC01D37, Freeport, IL, USA). The signal was sampled at 200 Hz with appropriate filter settings (TC = 10 s, LP = 20 Hz) and in order to correct for non-linearity the square-root was performed on this pressure signal [18]. During the A-CPAP trial, airflow was evaluated by measuring the respiratory pressure fluctuations in the nasal mask using the same method as described above. This recording closely resembles the signal derived from nasal cannulae and allows reliable detection of apneas, hypopneas and flow-limitation. Respiratory movements were recorded using thoracic and abdominal piezo-sensors (Sleepmate™, Midlothian, VA, USA). Respiratory events were manually scored according to contemporary guidelines [19]. Briefly, an apnea was defined as a total cessation of airflow during at least 10 s; a hypopnea was defined as a decrease in airflow of at least 50% or a clear decrease of less than 50% with an oxygen desaturation >3% and/or an arousal. The AHI was calculated as the sum of apneas and hypopneas divided by total sleep time (h). Inspiratory snores were manually counted and the snoring index was computed as the sum of inspiratory snores divided by total sleep time (h). Sleep stages were identified according to standard criteria [20], arousals were scored based on published guidelines [21] and the arousal index was the sum of arousals divided by total sleep time (h). Sleep stages, respiratory and snoring events and arousals were assessed by polysomnography in epochs of 30 s, and CPAP levels were determined as the average pressure level over the 30-s epoch.

### 2.3. Study design

After the diagnosis of OSA was established, patients were habituated on CPAP treatment at home. The pres-

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sure level was derived from a prediction formula [11] and is referred to as 'F-CPAP' in the results and discussion session. During follow-up consultation after 1 month, it was evaluated whether adjustment was needed based on residual symptoms of sleepiness or snoring. With respect to snoring, the patients were asked to obtain reliable information from bed-partners, relatives, house-mates or occasional travelling companions. None of the patients actually required pressure adaptation. The mean habituation period prior to the titration polysomnography was 89.1 (37.2) days, and the CPAP compliance was 5.7 (1.5) h per night.

After the habituation period, an overnight polysomnography was carried out in the laboratory. In a double-blind, randomized order, two identical REMstar Auto™ devices (Murrysville, PA, USA) were used for each patient during the same night: one in the automatic titration mode and one in the fixed mode. Four hours after the start of polysomnography, the tubing was disconnected from the first device and attached to the second, which was then used for another 4 h. In the auto-titration mode, the pressure was programmed to a range between 4 and 14 cm $H_2O$, whereas in the fixed mode the pressure was set at the predicted level. Both methods were compared regarding their effect on relevant sleep and respiratory variables. In A-CPAP mode, the mean (Pmean), median (P50), maximum (Pmax), 90th (P90) and 95th percentile (P95) of the airway pressure values were computed from the polysomnography data. Statistics on air leakage were obtained from the internal memory of the CPAP devices. Scoring was performed by one skilled technician and reviewed by the first author, both of whom were blinded to treatment conditions.

The morning after the titration study a subjective evaluation of sleep quality was carried out, using a questionnaire and visual analogue scales ranging between 0 (best score) and 10 (worst score). Four questions were asked: (Q1) Did the pressure changes disturb my falling asleep?; (Q2) Did the pressure changes cause awakenings?; (Q3) How did the CPAP device affect my sleep quality?; (Q4) Did the noise of the device disturb my sleep? The questions were duplicated for both halves of the night. In addition, the patients were asked to indicate their preference for one of the devices as if they would have to choose between them for continued use at home. All patients responded affirmatively to the question asked by the technician about whether they had good recall of the treatment effects in the first versus the second half of the night. This subjective preference was compared with objective preference, which was defined in terms of better AHI control: when a (arbitrarily chosen) difference of $>3$ events/h was found, the device with the lowest AHI was considered preferable; a difference $\leqslant 3$ was considered equivocal.

### 2.4. Power calculation and statistical analysis

The estimated number of required subjects was 45, based on the following assumptions: a difference in AHI of 3 or more events/h, standard deviation equal to 5 events/h, statistical power of 0.8 and a two-tailed significance level of 0.05. Analysis of variance (ANOVA) was carried out to assess a potential effect of treatment order (first versus second half of the night) on the AHI and Mann–Whitney *U*-test on the pressure outcomes. The Wilcoxon signed rank test for matched pairs was applied to assess differences between treatment conditions. Bias, precision and maximum errors were calculated for the differences between F-CPAP and the various levels of A-CPAP; bias was defined as the mean and precision as the standard deviation of the individually subtracted values. The McNemar test was used to compare subjective and objective outcomes. SPSS version 12.0 software was used.

## 3. Results

Forty-five patients (36 males and 9 females) successfully completed the study (mean [standard deviation] age 52.4 [10.9] years, BMI 31.1 [7.3] kg/m$^2$, FEV1/FVC 78.0 [4.8]%, AHI 45.8 [25.0] events/h, arousal index 51.0 [20.2] events/h).

Comparison of the two CPAP methods showed no significant differences in various sleep parameters, including time in bed, total sleep time, sleep efficiency, sleep stages and arousal index (Table 1).

As a result of the randomization procedure, 25 patients were started on F-CPAP versus 20 on A-CPAP in the first half of the night. ANOVA did not reveal a significant effect of treatment order on AHI ($p = 0.125$). Comparison of pressure profiles in subjects receiving A-CPAP in the first versus the second half of the night did not show significant differences.

Data on respiratory events and snoring are presented in Table 2. The residual AHI was not significantly different in both treatment conditions; only the central apnea index was significantly higher in A-CPAP than in F-CPAP mode.

The residual AHI was $\geqslant 10$ events/h in six subjects on F-CPAP compared to 10 on A-CPAP, and was $<10$ but $\geqslant 5$ events/h in 11 subjects on F-CPAP compared to seven on A-CPAP. Twenty-eight individuals in each treatment condition had an AHI $< 5$ events/h.

F-CPAP (7.5 [1.6] cm $H_2O$) was compared with different A-CPAP statistics: Pmean was 7.5 [2.2] cm $H_2O$ ($p = 0.973$); P50 was 7.6 [2.7] cm $H_2O$ ($p = 0.946$); P90 was 9.8 [2.5] cm $H_2O$ ($p < 0.001$); P95 was 10.1 [2.4] cm $H_2O$ ($p < 0.001$); Pmax was 10.8 [2.3] cm $H_2O$ ($p < 0.001$) (Fig. 1).

Data on leaks showed no differences (mean leak F-CPAP 30.9 [7.7] versus A-CPAP 30.9 [9.3]).

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Table 1
Sleep parameters in both treatment conditions

| | A-CPAP | F-CPAP | Significance |
|---|---|---|---|
| Time in bed, min | 233.6 (22.2) | 233.1 (21.6) | $p = 0.448$ |
| Total sleep time, min | 176.6 (37.4) | 172.9 (38.5) | $p = 0.550$ |
| Sleep efficiency, % | 75.6 (14.5) | 73.9 (15.2) | $p = 0.611$ |
| Wakefulness, min | 57.1 (34.8) | 60.2 (31.8) | $p = 0.498$ |
| NREM stage 1, min | 15.2 (7.0) | 14.2 (8.1) | $p = 0.296$ |
| NREM stage 1, % TST | 9.4 (5.6) | 8.8 (5.6) | $p = 0.541$ |
| NREM stage 2, min | 95.5 (27.2 | 95.3 (30.4) | $p = 0.919$ |
| NREM stage 2, % TST | 55.2 (14.0) | 53.9 (14.2) | $p = 0.795$ |
| NREM stage 3–4, min | 31.9 (28.5) | 24.6 (22.9) | $p = 0.188$ |
| NREM stage 3–4, % TST | 16.9 (14.9) | 14.8 (13.8) | $p = 0.453$ |
| REM sleep, min | 33.9 (20.4) | 38.8 (27.5) | $p = 0.561$ |
| REM sleep, % TST | 18.7 (10.3) | 22.5 (14.9) | $p = 0.218$ |
| Arousal index, #/h | 32.8 (19.9) | 29.7 (18.8) | $p = 0.183$ |

Table 2
Residual apnea, hypopnea and snoring indexes in both treatment conditions

| | A-CPAP | F-CPAP | Significance |
|---|---|---|---|
| Apnea–hypopnea index, #/h | 7.7 (10.8) | 5.4 (9.0) | $p = 0.061$ |
| Central apnea index, #/h | 2.1 (4.8) | 0.8 (2.0) | $p = 0.031$ |
| Obstructive apnea index, #/h | 0.6 (1.7) | 0.6 (1.5) | $p = 0.715$ |
| Hypopnea index, #/h | 5.0 (7.3) | 3.9 (6.4) | $p = 0.248$ |
| Snoring index, #/h | 13.6 (33.5) | 15.3 (53.2) | $p = 0.350$ |

Table 3 shows the bias, precision and maximum errors for inter-individual differences between F-CPAP and various A-CPAP statistical categories. Pmean and P50 had the least bias compared with F-CPAP, whereas bias increased progressively over P90, P95 and Pmax. All categories of A-CPAP demonstrated considerable imprecision with respect to F-CPAP.

Results of the subjective evaluation are presented in Fig. 2, comprising data of four visual analogue scales. No significant differences in subjective comfort measures were found. Remarkably, as the data in Table 4 illustrate, the disparity between subjective and objective assessments was significant.

Table 3
Difference between F-CPAP and A-CPAP

| Differences, cm $H_2O$ (F-CPAP − A-CPAP) | Pmean | P50 | P90 | P95 | Pmax |
|---|---|---|---|---|---|
| Mean (bias) | 0.02 | −0.05 | −2.29 | −2.58 | −3.30 |
| SD (precision) | 2.22 | 2.61 | 2.51 | 2.44 | 2.35 |
| Minimum | −5.17 | −6.54 | −6.81 | −6.84 | −7.32 |
| Maximum | 4.53 | 4.76 | 3.19 | 2.95 | 2.00 |

Differences between F-CPAP and A-CPAP presented in terms of bias and precision, where bias is the mean and precision is the standard deviation of the individually subtracted values. In addition, the largest errors, either positive or negative, are shown.

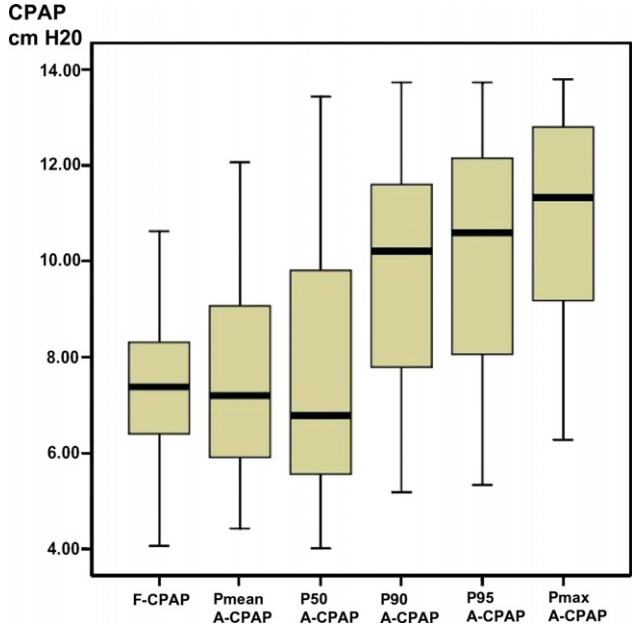


Fig. 1. Pressure profiles. The horizontal black line is median, the box interquartile range and vertical line the min–max range. F-CPAP: 7.5 [1.6] cm $H_2O$. A-CPAP: Pmean: 7.5 [2.2] cm $H_2O$ ($p = 0.973$ versus F-CPAP); P50: 7.6 [2.7] cm $H_2O$ ($p = 0.946$ versus F-CPAP); P90: 9.8 [2.5] cm $H_2O$ ($p < 0.001$ versus F-CPAP); P95: 10.1 [2.4] cm $H_2O$ ($p < 0.001$ versus F-CPAP); Pmax: 10.8 [2.3] cm $H_2O$ ($p < 0.001$ versus F-CPAP).

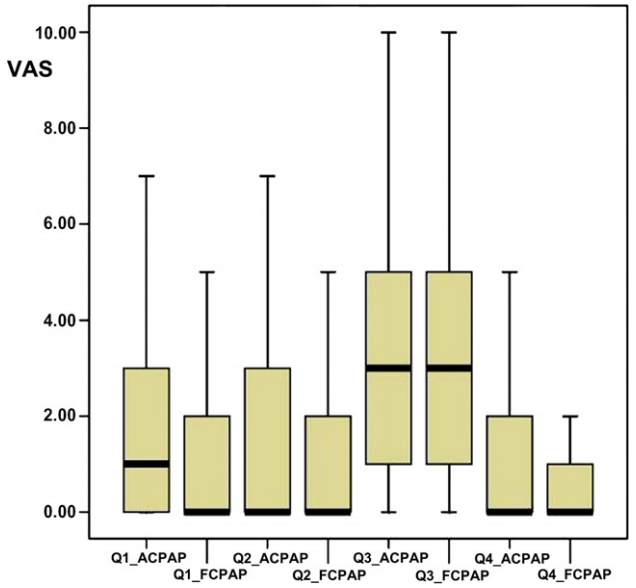


Fig. 2. Sleep quality (VAS). The horizontal black line is median, the box interquartile range and vertical line the min–max range. Comfort of CPAP use in A-CPAP and F-CPAP mode. The questions were duplicated for the first and second half of the night. (Q1) Did the pressure changes disturb my falling asleep? (Q2) Did the pressure changes cause awakenings? (Q3) How did the CPAP device affect my sleep quality? (Q4) Did the noise of the device disturb my sleep? Range of the visual analogue scale (VAS): 0 = best score; 10 = worst score. No statistically significant differences were found.

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Table 4
Subjective versus objective preferences

| | Subjective preference (%) | Objective preference (%) |
|---|---|---|
| A-CPAP | 36 | 7 |
| F-CPAP | 33 | 31 |
| Indifferent | 31 | 62 |

McNemar test: $p = 0.013$.
Subjective preference was indicated by the patients in the post-sleep questionnaire (see Section 2).
Objective preference was derived from the AHI control. If the difference in AHI between the two treatment conditions was >3 events/h, the device corresponding with the lowest AHI was preferred. If the difference was ⩽3 events/h, none of either was preferred.

## 4. Discussion

We report the results of a double-blind, randomized comparative cross-over trial in which predicted F-CPAP was matched against A-CPAP in a CPAP titration setting. While the residual AHI was not significantly different in either CPAP mode, higher pressure in A-CPAP mode was observed. In terms of bias, F-CPAP corresponded best with Pmean and P50 of A-CPAP, suggesting that the use of P90 or P95 as the fixed pressure for chronic treatment could result in over-prescription. However, in terms of precision, the equivalence between F-CPAP and A-CPAP was poor. There was no difference in subjective appreciation of the two CPAP modes, and there was no correspondence between subjective and objective ratings.

No differences were found between the two treatment arms regarding various sleep variables, including total sleep time, sleep efficiency, sleep stages and arousal index. This finding illustrates that randomization was effective and that both treatment options are associated with similar effects on sleep quality. The split-night approach might be considered a limitation of this study, as the individual CPAP exposure is restricted to a period of 4 h in each treatment mode. There are no available data directly comparing half-night with all-night A-CPAP titrations. Factors that affect pressure in A-CPAP mode such as arousals and changes of sleep stage may be different in full versus partial-night studies. However, split-night titration is accepted as a feasible alternative for full-night CPAP titration in certain patients during diagnostic sleep studies [22,23]. Moreover, splitting the night in two halves allows a cross-over design, which adds to the power of the study. At variance with conventional split-night protocols is the fact that in the present trial patients were habituated on F-CPAP for more than 2 months before entering the titration procedure. The lag between the diagnostic and titration sleep study is not unfavourable by itself because sleep architecture may be closer to normal because of the intercurrent habituation to CPAP. Prior acclimatization to CPAP will probably reduce or eliminate the rebound of slow wave and rapid eye movement (REM) sleep, which is often seen as a first-night effect in acute CPAP treatment conditions [24]. Furthermore, it has been shown that sleep efficiency during CPAP titration is significantly higher in subjects who are habituated on CPAP than in CPAP-naive patients [16]. Taking into account these considerations, we believe that the design of the present study was appropriate for the comparative evaluation of both CPAP modes.

Of particular interest is the observation that all included patients tolerated F-CPAP well. The pressure level was calculated according to the prediction formula of Miljeteig et al. [11]. We elected this method over other pressure estimation models because it has been used for the determination of reference pressure by different investigators [6,12,25]. F-CPAP seemed adequate for symptomatic control, as all patients reported satisfactory improvement of subjective sleepiness and snoring. Therefore, no pressure adjustments had to be made during follow-up visits. Moreover, this pressure level proved sufficient for reducing AHI to less than 10 events/h in 39/45 subjects, which is a criterion for an acceptable treatment result [26]. A-CPAP did not improve this outcome any further; in only 35/45 subjects was the same criterion fulfilled. Starting F-CPAP based on either predicted or arbitrary pressure has likewise been found to be a feasible treatment modality in three recent clinical trials [6,16,17]. In the most recent study by West et al., 98 patients were randomized into three groups: A-CPAP throughout, F-CPAP based on P95 and F-CPAP based on prediction formula [17]. While there was no significant difference in any of the clinical outcome measures after 6 months, the P95 subgroup received higher pressures than the predicted pressure or A-CPAP cohorts. The authors suggested that administration of lower pressure is equally effective to improve AHI and reduce symptoms. This finding is in keeping with the results of the present study.

Using the 90th or 95th percentile of an A-CPAP pressure range is still regarded by many as an appropriate and efficient method to assess the level of F-CPAP for long-term treatment [4,7,8]. Since patients seem to do equally well with lower average pressure levels, the question must be raised whether assessment of P95 really yields the 'optimal' pressure. In a recent report, it was pointed out that significant differences in P95 exist between different brands of A-CPAP devices, with considerable bias (3.0 cm $H_2O$) and wide limits of agreement (ranging from +9.3 to −3.2 cm $H_2O$) [9]. In an earlier study, insignificant changes in group means were found when P95 was re-assessed with A-CPAP after 1 and 6 months of treatment [27]. However, large standard deviations were disclosed, which were indicative of considerable individual variability in pressure requirement, in positive or negative direction. The

results of the present study cast further doubt on the validity of the P95 for F-CPAP determination. Among the different A-CPAP statistical variables, we found that F-CPAP levels corresponded best with Pmean and P50 but not with P90, P95 or Pmax. Using the P95 for setting of F-CPAP in this group of patients would have resulted in over-prescription of airway pressure by an average of 2.58 cm $H_2O$. Further studies are needed to clarify the issue of the validity of P95 assessment for subsequent F-CPAP treatment. The observed imprecision of the P95 could reflect random variation in CPAP requirements by the patients on the one hand, but also intrinsic variability of the A-CPAP methodology on the other hand.

A poor agreement between F-CPAP and Pmean or the different percentiles of A-CPAP was found in the present study. The standard deviations of the differences were large and fluctuated around 2.50 cm $H_2O$. Accordingly, the correspondence between the individual F-CPAP and A-CPAP values was not precise. For instance, if Pmean would have been used to decide on the level of fixed CPAP, 40% of the individuals would have been more than 2.22 cm $H_2O$ away from the value determined by the prediction formula. Although the group means for F-CPAP and Pmean were identical in this study (7.5 cm $H_2O$), substituting F-CPAP by Pmean values would be at risk for substantial individual error up to 5.17 cm $H_2O$ in the negative and 4.53 cm $H_2O$ in the positive direction. From the present data, Pmean or P50 values cannot be recommended for setting the level of fixed pressure in the context of permanent CPAP usage at home. The same applies to P90, P95 and Pmax values which, in addition, have considerable bias regarding F-CPAP. The lack of precision observed in the present investigation is in agreement with results from other clinical trials [10,27]. The data from our current study seem to support the conclusion of these studies that there probably is a range of CPAP over which adequate control of OSA and associated symptoms can be maintained. In this respect, predicted pressure might have similar accuracy and clinical outcome to pressure derived from A-CPAP titration.

In conclusion, it was demonstrated in the current study that F-CPAP and A-CPAP resulted in similar control of the AHI but with higher pressure in A-CPAP mode. The patients showed no subjective preference for one of both treatment modes. In terms of bias, F-CPAP corresponded best with Pmean and P50, not with P90, P95 and Pmax of the pressure titrated over time by A-CPAP. However, there was a considerable lack of agreement between the two CPAP modes. This would preclude extrapolation of individual A-CPAP titration data to predicted pressure values. Finally, it seems that there is no additional advantage in performing an A-CPAP titration procedure if patients are stable under predicted F-CPAP.

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