SCIENTIFIC INVESTIGATIONS

JCSM
Journal of Clinical Sleep Medicine

pii: jc-00410-14
http://dx.doi.org/10.5664/jcsm.5008

Efficacy of Bilevel-auto Treatment in Patients with Obstructive Sleep Apnea Not Responsive to or Intolerant of Continuous Positive Airway Pressure Ventilation

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Background: Ventilation with continuous positive airway pressure (CPAP) is the gold standard therapy for obstructive sleep apnea (OSA). However, it was recently suggested that a novel mode of ventilation, Bilevel-auto, could be equally effective in treating patients unable to tolerate CPAP. The aim of this study was to investigate the ability of Bilevel-auto to treat OSA patients whose nocturnal ventilatory disturbances are not completely corrected by CPAP.

Methods: We enrolled 66 consecutive OSA patients, not responsive to (group A) or intolerant of (group B) CPAP treatment, after a full night of manual CPAP titration in a laboratory. Full polysomnography data and daytime sleepiness score were compared for each group in the three different conditions: basal, during CPAP, and during Bilevel-auto.

Results: The apnea-hypopnea index decreased significantly during CPAP in both groups; however, in the group A, there was a further significant improvement during Bilevel-auto. The same trend was observed for oxygenation indices, while the distribution and the efficiency of sleep did not differ following the switch from CPAP to Bilevel-auto.

Conclusions: This study confirmed the role of Bilevel-auto as an effective therapeutic alternative to CPAP in patients intolerant of this latter mode of ventilation. Moreover, extending the use of Bilevel-auto to those OSA patients not responsive to CPAP, we showed a significantly better correction of nocturnal respiratory disturbances.

Keywords: sleep apnea, sleep, CPAP, Bilevel-auto, noninvasive ventilation, COPD, obesity

Citation: Carlucci A, Ceriana P, Mancini M, Cirio S, Pierucci P, D'Artavilla Lupo N, Gadaleta F, Morrone E, Fanfulla F. Efficacy of Bilevel-auto treatment in patients with obstructive sleep apnea not responsive to or intolerant of continuous positive airway pressure ventilation. *J Clin Sleep Med* 2015;11(9):981–985.

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of complete or partial upper airway obstruction during sleep.[1] The gold standard therapy for OSA is continuous positive airway pressure (CPAP) delivered through a nasal or facial mask during the night. This treatment has been proven to improve health status, daytime sleepiness, to reduce the risk of cardiovascular events or the consumption of health care resources, as well as to prolong the survival of these patients.[2] It is not, however, always well tolerated, especially by those patients who would benefit from very high pressure levels to compensate for episodes of obstructive apnea-hypopnea.[3–5]

Bilevel-auto was proposed as an alternative treatment of this disorder. Bilevel-auto delivers spontaneous bilevel therapy, automatically adjusting expiratory (EPAP) and inspiratory (IPAP) levels to meet the patient's needs (see below).[6,7] This new therapy was found to be equally effective as standard CPAP therapy, and adherence to the two therapies was comparable.[6] Indeed, in patients who did not tolerate CPAP, this therapy seemed to be associated with better adherence to the treatment.[7]

In our experience there is another group of patients who may benefit from the use of this new mode of ventilation: patients whose nocturnal episodes of apnea-hypopnea are not completely corrected even when treated with high levels of CPAP (up to 20 cm H_2O). To our knowledge, no study has yet evaluated the effect of Bilevel-auto in this group of patients. The aim of this study was, therefore, to confirm and possibly extend the indications for Bilevel-auto therapy in patients with OSA.

BRIEF SUMMARY

Current Knowledge/Study Rationale: CPAP is the gold standard treatment for patients with OSA. However, a small group of patients are not tolerant or not responders to CPAP therapy. The aim of this study was to evaluate in these particular patients the efficacy and tolerance of the Bi-PAP auto, a new ventilator device that is able automatically adjust expiratory and inspiratory pressure level.

Study Impact: The present study demonstrates that Bi-PAP auto enables optimal control of respiratory events during sleep in these patients offering a therapeutic alternative to patients not-compliant or not-responders to CPAP treatment.

METHODS

This study was approved by the Ethical Committee of Salvatore Maugeri Foundation, and written consent was obtained from patients.

From January 2011 to December 2012, we prospectively collected data from all consecutive, treatment-naïve patients admitted to our hospital with a diagnosis of OSA who failed CPAP treatment after manual titration. The diagnosis of OSA was made according to standard criteria[1]: all patients underwent standard sleep evaluation and full polysomnography analyzed according to the American Academy of Sleep Medicine (AASM) 2007 guidelines.[8] After a full-night of manual CPAP titration in a laboratory, performed according to the AASM guidelines,[9] patients were changed to Bilevel-auto if they were not responsive to CPAP (group A) or unable to tolerate CPAP (group B). Non-responsive patients were defined according to AASM guidelines[9]: persistence of respiratory disturbance index above the level of optimal, good, or adequate titration. Non-tolerant patients were those with poor tolerance or compliance to CPAP, recognized during the adaptation period using the effective CPAP level. All treatable causes of poor CPAP tolerance or efficacy (type of mask, presence of leaks, poor humidification) were identified and treated or excluded before the switch to Bilevel-auto.

Patients with diagnosis or radiological evidence of respiratory diseases (i.e. COPD), lung lesions (e.g., previous tuberculosis treated physically, pulmonary abscesses, pneumothorax), neuromuscular disorders (e.g., post-polio lesions), chest-wall defects, bronchopulmonary infection or cardiac or respiratory failure in the preceding 6 months were excluded from the study as were patients with a previous diagnosis of pulmonary arterial hypertension. Other exclusion criteria were: major uncontrolled medical or psychiatric conditions; prior use of CPAP or standard BiPAP ventilation; surgery of the upper airways, nose, sinuses, or middle ears in the 3 months before the study; the presence of any untreated non-OSA sleep disorder (e.g., restless legs syndrome, insomnia); a known history of alcohol or drug abuse within the preceding 3 years.

Demographic information was collected and polysomnographic data were recorded in the basal condition, during CPAP and during Bilevel-auto treatment. Daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS).[10]

Bilevel-auto Setting

Bilevel-auto (Respironics Inc., Murrysville, PA, USA) is an auto-adjusting bilevel ventilator system with different algorithms able to detect and treat obstructive events such as apnea, hypopnea and snoring. Adjustable parameters are: minEPAP (from 4 to [maxIPAP-3]), maxIPAP (from [minEPAP +3] to 25 cm H_2O), and maxPS (from 3 to 8). If 2 consecutive obstructive apneas are detected in a period of 3 minutes, the algorithm increases the EPAP value 1 cm H_2O, maintaining a minimum difference of 3 cm H_2O from the IPAP. If hypopnea or a flow limitation is detected, the algorithm will raise IPAP to eliminate the event until the maximum adjusted level is reached. MaxPS is the maximum difference allowed between IPAP and EPAP. A further increase of IPAP will lead to a same increase of EPAP to maintain the adjusted maxPS constant. In our study Bilevel-auto was set as follows: maxIPAP = 25 cm H_2O and maxPS = 8; the CPAP level that during titration provided correction of obstructive apneas was chosen as reference value for EPAP. We set a minEPAP 2 cm H_2O less than reference CPAP to reach a good accommodation for the patient.

Statistical Analysis

Results are given as the mean ± standard deviation. Patients were classified into 2 groups, according to the reason for the failure of CPAP. The two groups of patients were compared by means of one-way ANOVA. Repeated measures ANOVA was performed to evaluate trends over time (at baseline, during CPAP and Bilevel-auto therapy) in the sleep data from the 2 groups of patients considered. Tukey honest statistical difference test for unequal sample sizes (Spjotvoll and Stoline test) and the Scheffe test were used to compare differences between groups and within groups, respectively. All statistical tests were two-sided, and p values of less than 0.05 were considered statistically significant. Data were analyzed using STATISTICA (data analysis software system), version 10. (StatSoft Inc., 2011, www.statsoft.com).

RESULTS

Of 579 eligible patients who underwent manual standard CPAP titration, 57 patients were excluded since they fulfilled the exclusion criteria. Among the remaining 522, we enrolled 66 patients (18 females): 35 were not responsive to CPAP (group A), while 31 were unable to tolerate this therapy (group B). The mean age of these patients was 57.6 ± 12.1 years, and their mean body mass index was 39.7 ± 9.8 kg/m^2.

Baseline data are shown in **Table 1**, separately for the 2 groups of patients. No differences were found between the 2 groups for any of the variables considered, except for sleep efficiency, which was statistically significantly higher in the group B.

The total sleep time during the manual CPAP titration was 326 ± 74 min in group A versus 351 ± 59 min in group B (p = ns), while the maximum pressure level reached during the manual CPAP titration procedure was 18 ± 3 cm H_2O in group A and 17 ± 2.5 cm H_2O in group B.

The apnea-hypopnea index (AHI), both total and supine, decreased significantly during CPAP, but a further significant reduction was obtained during Bilevel-auto treatment in both groups (**Figure 1A** and **1B**, respectively): as expected, during CPAP the AHI was significantly higher in group A. The same trend was found for arousal index (23.9 ± 10.2 in group A; 11.2 ± 9.9 in group B) and oxygenation indices: there were significant reductions in the oxygen desaturation index (ODI) and percentage of sleep time spent with an oxygen saturation < 90% (T_{90}) from baseline to Bilevel-auto in both groups, but during CPAP these 2 variables were significantly higher in group A (**Figure 1C** and **1D**) than in group B. **Table 2** shows changes in sleep data when patients were switched from CPAP to Bilevel-auto according to the reason for failure of the CPAP. In addition to the aforementioned significant reduction of the AHI, patients in group A also showed further significant improvements in the oxygenation indices: ODI and T_{90} both decreased significantly when patients were switched from CPAP to Bilevel-auto. This difference was not seen in group B.

Two patients did not tolerate the Bilevel-auto treatment and were discharged with CPAP; another 4 patients stopped Bilevel-auto after prescription. Tolerance and adherence to therapy in the remaining 60 patients were good after 6 months: the

mean usage was 5.9 ± 2.1 h/night; no differences were found between group A and B (ANOVA p = ns)

DISCUSSION

This study demonstrates that Bilevel-auto enables optimal control of respiratory events during sleep in those patients not responsive to CPAP and offers a therapeutic alternative for patients not compliant with CPAP, with equal or better control of respiratory events.

Bilevel-auto, a novel mode of ventilation, is able to detect and treat various obstructive events by using different algorithms: detection of apnea and snoring leads to an increase in the EPAP level, while detection of hypopnea or a flow limitation leads to an increase in the IPAP value within a previously set pressure range. Bilevel-auto was proposed as an alternative to CPAP as a rescue therapy in the presence of poor compliance or tolerance.[7,11–13] A validation study performed in OSAS patients naïve to CPAP treatment, compared the efficacy of Bilevel-auto against standard CPAP and subjective and objective compliance over 90 days of use.[6] Authors did not find statistically significant differences in efficacy or compliance between the two treatments, raising the question of whether Bilevel-auto could be considered as an alternative therapy in patients not tolerating CPAP. However, further studies aimed to determine if Bilevel-auto benefit to CPAP treatment in non-compliant patients have yielded conflicting results.

In an observational study in patient with CPAP compliance lower than 4 h/night over 3 months, Gentina et al. found that Bilevel-auto improved compliance to a moderate extent.[7] However, in patients requiring an effective CPAP level higher than 10 cm H_2O there was a greater significant improvement in mean usage/night. In a randomized controlled trial, Ballard et al. found that, changing to flexible bilevel airway pressure therapy improved compliance in patients previously not compliant with CPAP therapy.[11] Powell et al. compared the efficacy of and compliance with CPAP and Bilevel-auto in a group of OSA patients with a poor initial experience of laboratory-based CPAP titration.[13] They did not find a statistically significant difference in adherence to treatment between the groups treated with Bilevel-auto or CPAP, suggesting that the CPAP titration procedure *per se* may be the principal cause of the poor initial tolerance. Finally Ball et al. compared the efficacy of standard BiPAP versus Bilevel-auto in a group of OSA patients not compliant with CPAP therapy, showing the equivalence of both ventilation modalities in normalizing the AHI.[12]

The data collected during the present study indicate new appropriate indications for the prescription of Bilevel-auto therapy. In patients who did not respond to CPAP therapy despite adequate initial tolerance and standardized in-laboratory titration, Bilevel-auto normalized AHI without having negative effects on sleep structure and stability. Similar results were found for the group of patients who were intolerant of CPAP, in which group, differently from previous studies, we

Table 1—Baseline data according to the reason for CPAP failure.

	Group A (n = 35)	Group B (n = 31)	p value
Age (y)	59.2 ± 12.2	55.8 ± 11.9	ns
BMI (kg/m^2)	40.3 ± 8.4	38.9 ± 11.2	ns
Neck-circumference (cm)	43.2 ± 4.7	44.4 ± 5.4	ns
ESS	11.2 ± 5.9	9.8 ± 6.8	ns
VC (% predicted)	87.1 ± 17.9	91 ± 24.3	ns
FEV_1 (% predicted)	88.9 ± 20	88.9 ± 26.5	ns
FEV_1/VC (%)	78.1 ± 8.1	76.9 ± 10.3	ns
PaO_2 (mm Hg)	64.4 ± 9.7	68.2 ± 10.8	ns
$PaCO_2$ (mm Hg)	39.2 ± 3.4	39.5 ± 4.2	ns
pH	7.4 ± 0.29	7.44 ± 0.03	ns
BE	4 ± 2.1	3.9 ± 2.5	ns
SE (%)	78.7 ± 14.2	86.3 ± 8.7	< 0.05
REM (%)	14.1 ± 6.5	17.1 ± 8.6	ns
Arousal index (events/h)	53.7 ± 19.2	57.5 ± 29.6	ns
AHI (events/h)	61.4 ± 25.9	69.1 ± 29.1	ns
AHI_{sup} (events/h)	83.2 ± 39.4	78.6 ± 29.8	ns
ODI (events/h)	64.9 ± 23.2	65.5 ± 12.3	ns
T_{90} (%)	34.2 ± 28.6	27.3 ± 28.9	ns

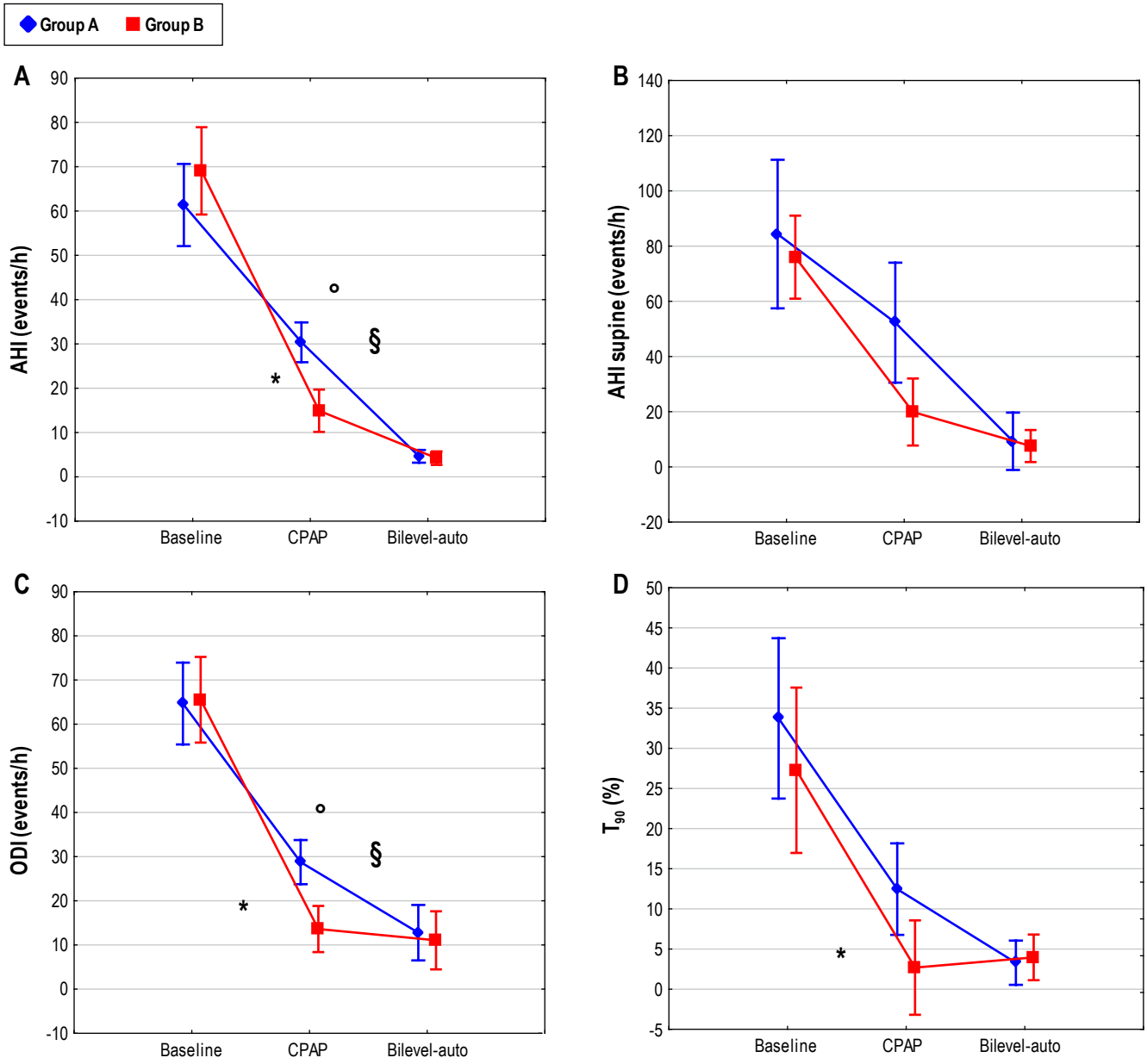
Values given as mean ± standard deviation. Group A = not responsive. Group B = not tolerant. ns, not significant; BMI, body mass index; ESS, Epworth Sleepiness Scale; VC, vital capacity; FEV_1, forced expiratory volume one-second; BE, base excess; SE, sleep efficiency; AHI, apnea-hypopnea index; AHI_{sup}, supine AHI; ODI, oxygen desaturation index; T_{90}, percentage of total sleep time with an oxygen saturation < 90%.

Table 2—Comparison of sleep data recording during CPAP and Bilevel-auto treatment according to the cause of CPAP failure.

	Group A			Group B		
	CPAP	Bilevel-auto	p value	CPAP	Bilevel-auto	p value
SE (%)	74.6 ± 15.3	78.8 ± 8.8	ns	78.5 ± 10.1	82.4 ± 12.2	ns
REM (%)	17.1 ± 10.6	20.5 ± 7.8	ns	19.7 ± 6.6	20.5 ± 8.4	ns
AHI (events/h)	30.4 ± 16.1	4.6 ± 4.9	< 0.0001	14.9 ± 9.1§	4.2 ± 3.3	< 0.0001
ODI (events/h)	29.4 ± 1 8.1	12.9 ± 20.3	0.001	13.8 ± 9.3§	11.2 ± 16.4	ns
T_{90}	12.5 ± 21.9	3.3 ± 6.8	0.01	2.7 ± 6§	3.96 ± 8.9	ns
CPAP (cm H_2O)	18.3 ± 3			17 ± 2.5		ns
IPAP (cm H_2O)		22.3 ± 2§			20.5 ± 2.8§	0.005
EPAP (cm H_2O)		13.6 ± 2.6§			11.8 ± 2.9§	0.009

Values given as mean ± standard deviation. Group A = not responsive. Group B = not tolerant. §Group A vs group B, p < 0.01. ns, not significant; SE, sleep efficiency; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; T_{90}, percentage of total sleep time with an oxygen saturation < 90%.

Figure 1—Changes from baseline to CPAP and Bilevel-auto, according to the cause of CPAP failure (group A = not responsive, group B = not tolerant).



Total or supine apnea-hypopnea index (**A** and **B**, respectively), oxygen desaturation index (ODI) (**C**) and percentage of sleep time spent with an oxygen saturation < 90% (T_{90}) (**D**). Data are expressed as mean ± standard deviation. *p < 0.05 for the comparison between CPAP and baseline in both groups. §p < 0.05 for the comparison between Bilevel-auto and CPAP in both groups. °p < 0.05 for the comparison between group A and group B during CPAP treatment.

also recorded a further significant reduction in AHI during Bilevel-auto, in comparison with the value during CPAP. This better outcome was probably due to the more careful selection of patients shifted to Bilevel-auto therapy, since we included only patients with poor tolerance to high level of CPAP. We hypothesized that in this group of patients, manual titration was interrupted prematurely before reaching the level of pressure required to correct nocturnal ventilatory and oxygenation disturbances.

The mechanism underlying the better efficacy of Bilevel-auto in the group of patients not responsive to CPAP is not completely understood. Usually, as the positive pressure progressively increases during CPAP titration, there is a stepwise resolution of respiratory events starting from apnea to inspiratory flow-limitation.[14] However, in some patients persistent partial inspiratory obstruction can only be controlled at very high pressures (sometimes above the maximum level that can be administered by home CPAP devices) which may not be tolerated. Bilevel-auto enables a dynamic, independent regulation of inspiratory and expiratory positive pressure, providing a more physiological control of the upper airways: inspiratory pressure with Bilevel-auto may increase up to 25 cm H_2O to

correct hypopnea and flow limitations. A similar mechanism could be suggested for the improvement of gas exchanges. An inspiratory pressure that is always higher than the expiratory one may allow recruitment of areas with a low ventilation-perfusion ratio, recognized as one of the cause of nocturnal hypoxia in obese OSA patients.[15]

Long-term follow-up data (at 6 months) demonstrated adequate compliance with Bilevel-auto in both group of patients, which was similar or even better than that reported in previous studies (6% of drop-off).

Limitation of the Study

The main limitation of this study is the lack of randomization or participant blinding. This is a "real life clinical study" we designed to identify a potential alternative approach for those patients not tolerant or "resistant" to CPAP. Ideally, the efficacy of bilevel-auto should have been compared to the standard BiPAP, the second-line therapy for this group of patients in the AASM guidelines. However, it has been demonstrated that the standard BiPAP did not improve tolerance or compliance in patients previously not tolerant to CPAP.[16,17]

In conclusion, Bilevel-auto is a promising technological strategy that provides effective treatment for subgroup of patients who fail CPAP treatment. Our study showed that adherence to nocturnal therapy could be significantly improved in patients intolerant to high levels of CPAP. Moreover we demonstrated that Bilevel-auto can stabilize the respiratory pattern and gas exchange during sleep in OSA patients not responsive to CPAP treatment.

ABBREVIATIONS

CPAP, continuous positive airway pressure
EPAP, expiratory positive airway pressure
IPAP, inspiratory positive airway pressure
OSA, obstructive sleep apnea

REFERENCES

1. American Academy of Sleep Medicine. International classification of sleep disorders, 2nd ed: Diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine, 2005.
2. Engleman HM, Martin SE, Deary IJ, et al. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. Thorax 1997;52:114–9.
3. McArdle N, Devereux G, Heidarnejad H, et al. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999;159:1108–14.
4. 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.
5. Engleman HM, Martin SE, Douglas NJ. Compliance with CPAP therapy in patients with the sleep apnoea/hypopnoea syndrome. Thorax 1994;49:263–6.
6. Blau A, Minx M, Peter JG, et al. Auto bi-level pressure relief-PAP is as effective as CPAP in OSA patients-a pilot study. Sleep Breath 2012;16:773–9.
7. Gentina T, Fortin F, Douay B, et al. Auto bi-level with pressure relief during exhalation as a rescue therapy for optimally treated obstructive sleep apnoea patients with poor compliance to continuous positive airways pressure therapy--a pilot study. Sleep Breath 2011;15:21–7.
8. Iber C, Ancoli-Israel S, Chesson AL, Quan S. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications, 1st ed. Westchester, IL: American Academy of Sleep Medicine, 2007.
9. 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
10. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.
11. Ballard RD, Gay PC, Strollo PJ. Interventions to improve compliance in sleep apnea patients previously non-compliant with continuous positive airway pressure. J Clin Sleep Med 2007;3:706–12.
12. Ball N, Gordon N, Casal E, et al. Evaluation of auto bi-level algorithm to treat pressure intolerance in obstructive sleep apnea. Sleep Breath 2011;15:301–9.
13. Powell ED, Gay PC, Ojile JM, et al. A pilot study assessing adherence to auto-bilevel following a poor initial encounter with CPAP. J Clin Sleep Med 2012;8:43–7.
14. Montserrat JM. Ballester E, Olivi H, et al. Time course of stepwise CPAP titration. Am J Respir Crit Care Med 1995;152:1854–9.
15. Fanfulla F, Grassi M, Taurino AE, et al. The relationship of daytime hypoxemia and nocturnal hypoxia in obstructive sleep apnea syndrome. Sleep 2008;31:249–55.
16. Reeves-Hoché MK, Hudgel DW, Meck R, Witteman R, Ross A, Zwillich CW. Continuous versus Bilevel positive airway pressure for obstructive sleep apnea. Am J Respir Crit Care Med 1995;151:443–9.
17. Haniffa M, Lasserson TJ, Smit I. Interventions to improve compliance with continuous positive airway pressure for obstructive sleep apnoea. Cochrane Database Syst Rev 2004;(4):CD003531.

ACKNOWLEDGMENTS

The authors acknowledge Ms. Rachel Stenner for providing language assistance for the final English revision of the manuscript.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication October, 2014
Submitted in final revised form February, 2015
Accepted for publication March, 2015
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.