NEW RESEARCH

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A Novel Adaptive Servoventilation (ASVAuto) for the Treatment of Central Sleep Apnea Associated with Chronic Use of Opioids

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SCIENTIFIC INVESTIGATIONS

Study Objectives: To compare the efficacy and patient comfort of a new mode of minute ventilation-targeted adaptive servoventilation (ASVAuto) with auto-titrating expiratory positive airway pressure (EPAP) versus bilevel with back-up respiratory rate (bilevel-ST) in patients with central sleep apnea (CSA) associated with chronic use of opioid medications.

Methods: Prospective, randomized, crossover polysomnography (PSG) study. Eighteen consecutive patients (age ≥ 18 years) who had been receiving opioid therapy (≥ 6 months), and had sleep disordered breathing with CSA (central apnea index [CAI] ≥ 5) diagnosed during an overnight sleep study or positive airway pressure (PAP) titration were enrolled to undergo 2 PSG studies—one with ASVAuto and one with bilevel-ST. Patients completed 2 questionnaires after each PSG; Morning After Patient Satisfaction Questionnaire and PAP Comfort Questionnaire.

Results: Patients had a mean age of 52.9 ± 15.3 years. PSG prior to randomization showed an apnea hypopnea index (AHI) of 50.3 ± 22.2 and CAI of 13.0 ± 18.7. Titration with ASVAuto versus bilevel-ST showed that there were significant differences with respect to AHI and CAI. The AHI and CAI were significantly lower on ASVAuto than bilevel-ST (2.5 ± 3.5 versus 16.3 ± 20.9 [p = 0.0005], and 0.4 ± 0.8 versus 9.4 ± 18.8 [p = 0.0002], respectively). Respiratory parameters were normalized in 83.3% of patients on ASVAuto versus 33.3% on bilevel-ST. Patients felt more awake and alert on ASVAuto than bilevel-ST based on scores from Morning After Patient Satisfaction Questionnaire (p = 0.0337).

Conclusions: The ASVAuto was significantly more effective than bilevel-ST for the treatment of CSA associated with chronic opioid use.

Keywords: ASV, adaptive servoventilation, central sleep apnea, CSA, opioids, sleep apnea, positive airway pressure, bilevel, bilevel-ST

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Opioid medications have become one of the most highly prescribed medications for the treatment of chronic non-terminal pain and are associated with serious adverse effects such as sleep disordered breathing, respiratory depression, and death. The purpose of this study was to determine the effectiveness of the minute ventilation-targeted adaptive servoventilation (ASVAuto) with auto-titrating expiratory positive airway pressure versus bilevel with back-up respiratory rate (bilevel-ST) in treating central sleep apnea induced by chronic use of opioid medications on patients who may frequently vary their opioid intake depending on daily severity of pain.

Study Impact: Results showed that ASVAuto was significantly more effective than bilevel-ST for the treatment of central sleep apnea induced by chronic opioid use. Clinicians should consider the ASVAuto as a primary treatment modality in this particular group of patients. Further studies are needed to clarify long-term effectiveness of therapy in improving morbidity and mortality.

Chronic pain affects at least 116 million adults in the United States.[1] A joint statement issued in late 1990s by the American Pain Society and the American Academy of Pain Medicine highlighting the importance of effectively treating chronic pain has resulted in an increase in opioid prescribing for chronic non-terminal pain in the United States.[2,3] The introduction of sustained-release opioids and the expanded use of methadone have contributed to this increase, with the therapeutic use of oxycodone and methadone growing by more than 6-fold and 8-fold, respectively, over the period 1997-2003.[4] Due to national quality improvement initiatives implemented in the late 1990s, prescriptions for opioids such as methadone and oxycodone for pain control have increased substantially in emergency room visits.[5] Opioids are very effective and widely prescribed analgesics, but their use is limited by a number of problematic side effects, most notably sleep disordered breathing, respiratory depression, and death.[6-9]

Sleep disordered breathing (SDB) describes a specific group of disorders characterized by repeated interruptions of breathing during sleep resulting in ventilatory disturbances, disrupted sleep, neurocognitive impairment, and long-term cardiovascular morbidity. Obstructive sleep apnea (OSA), a subset of SDB, is thought to be due to a narrow upper airway, obesity, and ventilatory control instability. In contrast, central sleep apnea (CSA) is characterized by disruption of central neurologic control on the drive to breathe leading to respiratory pauses. In contrast to OSA, respiratory effort is abolished in central sleep apnea.

One adverse effect of opioid use that is gaining increased recognition is the influence of therapy on respiratory control

during sleep, and the occurrence of SDB, particularly CSA.[10-12] Estimates of the occurrence of SDB during chronic opioid use have varied. Several studies indicated a high prevalence of CSA in patients using opioids on a chronic basis.[7,10-12] Retrospective data reported that the proportion of patients with OSA, CSA, or a combination of both was 36%, 24%, and 21%, respectively.[13] Similar findings were documented in a larger cohort of patients, with corresponding values of 39%, 24%, and 8%.[14] In another study, ataxic breathing and central apneas occurred during NREM sleep in 70% of patients receiving chronic opioid therapy compared with 5% of controls, and there also appeared to be a relationship between opioid dose or blood concentration and the occurrence of central apneas during sleep.[6,7] Farney and associates showed that SDB (obstructive and central apneas) and nocturnal hypoxemia were present in 44 of 70 patients on buprenorphine/naloxone, a partial μ-opioid agonist with limited respiratory toxicity used for the treatment of opioid dependency and chronic pain.[15]

There is a paucity of data on treatment options and the effectiveness of these options for patients with SDB associated with chronic opioid use. Furthermore, there is no clear consensus on how best to manage opioid-induced SDB, apart from using the lowest effective opioid dose. The results of studies utilizing continuous positive airway pressure (CPAP) therapy to treat CSA in opioid users have been disappointing.[16-20] Bilevel positive airway pressure (PAP) with back-up respiratory rate (bilevel in spontaneous-timed mode [bilevel-ST]) appeared to be a more promising strategy.[20,21] A relatively newer approach being investigated in chronic opioid users with SDB is the use of adaptive servoventilation (ASV). This PAP device uses a breath-by-breath algorithm to analyze minute ventilation and adjusts pressure support and respiratory rate with each respiratory cycle to meet a minute ventilation target. Preliminary results have been promising,[16,18] but there is a lack of long-term data for any PAP therapies in opioid-induced SDB with respect to efficacy as well as effects on morbidity and mortality.

The current study compared two different PAP therapies—bilevel-ST versus enhanced minute ventilation-targeted ASV (ASVAuto) with auto titrating expiratory positive airway pressure (EPAP)—in patients with CSA secondary to chronic opioid use. We hypothesized that ASVAuto would be superior to bilevel-ST in treating CSA induced by chronic opioid use.

METHODS

This prospective, randomized, blinded, 2-period crossover comparative study was conducted at a single center in the USA (Stanford Sleep Medicine Center, Redwood City, CA).

Participants

Participants (age ≥ 18 years) who had been receiving chronic opioid therapy (≥ 6 months), and had SDB with CSA (central apnea index [CAI] ≥ 5) diagnosed during a sleep study or PAP titration using 2007 American Academy of Sleep Medicine (AASM) criteria were enrolled.[22] All 18 participants had been using bilevel-ST ≥ 4 weeks, and compliance to therapy (≥ 4 h of nocturnal sleep time) was verified using device data or patient report.

All participants gave written informed consent to participate in the study. The study protocol was approved by the Stanford University institutional review board. Exclusion criteria were the presence of severe or unstable heart or lung disease such as congestive heart failure, chronic obstructive pulmonary disease, neurological disease such as stroke, neuromuscular disease, narcolepsy, evidence of Cheyne-Stokes respiration (CSR) during sleep study, acute upper respiratory tract infection, and pregnancy.

Study Design and Protocol

This was a prospective, randomized, blinded, crossover study to evaluate the clinical and polysomnographic (PSG) effectiveness of a novel minute ventilation-targeted adaptive servoventilation (ASVAuto) as a primary modality for the treatment of patients who have central sleep apnea secondary to chronic opioid use. Participants were randomized to one of 2 groups, utilizing a crossover design to evaluate the 2 modes with the participant as his or her own control. All 18 participants were on treatment with bilevel-ST as determined by their treating physician, and demonstrated usage of bilevel equipment for ≥ 4 weeks prior to randomization. Participants were asked to undergo 2 PSG studies; one with usage of ASVAuto, and one with usage of bilevel-ST set at their usual home values as determined by prior titration in the sleep laboratory or by their treating physician. The study was comprised of 2 visits. Participants were also asked to complete 2 patient satisfaction questionnaires on the morning after their PSG studies:

Group 1: Undergo bilevel-ST overnight recording with crossover to ASVAuto overnight recording on a separate night.

Group 2: Undergo ASVAuto overnight recording with crossover to bilevel-ST overnight recording on a separate night.

After each experimental night, participants went back home and used their bilevel-ST device as prescribed by their treating physician. Home bilevel settings and opiate medication dosages were requested not to be changed during patient's participation in the study.

Participants underwent full PSG assessment in the sleep laboratory on both nights of the study; the second overnight study was conducted within 2 weeks of the first assessment. PSG measurements included all standard PSG leads as recommended by the AASM. Sleep staging and respiratory events were scored according to AASM criteria[22] by an independent PSG technologist unaware of treatment. An apnea was defined as a reduction in airflow > 90% relative to baseline ≥ 10 seconds. An obstructive apnea was defined as the absence of airflow associated with continued thoraco-abdominal excursions. An obstructive hypopnea was defined as a reduction in airflow ≥ 30% and associated with either 4% drop in oxygen saturation or 3-s electroencephalographic (EEG) arousal. A central apnea was defined as the absence of airflow with absence of thoraco-abdominal excursions.

PSG data included total recording time, total sleep time (TST), sleep efficiency (%), % slow wave sleep (SWS), % rapid eye movement (REM) sleep, sleep architecture (% TST Stage 1, 2, 3, REM), average oxygen saturation (%), minimum oxygen saturation (%), apnea-hypopnea index ([AHI] obstructive apneas plus obstructive hypopneas plus central apneas), apnea

Table 1—Demographic/baseline characteristics

Baseline Characteristics	Result (N = 18)
Gender, % Males	67.7% (12/18)
Age (years)	
Mean ± SD	52.9 ± 15.3
Min, Max	24, 76
BMI (kg/m^2)	
Mean ± SD	30.9 ± 6.7
Min, Max	23.7, 48.8

BMI, body mass index.

index ([AI] obstructive apneas plus central apneas), hypopnea index (HI), central apnea index (CAI), total arousal index, and respiratory arousal index. Flow and pressure data from the PAP device were converted to a DC signal using the ResMed Tx Link module to allow it to be recorded by the PSG system.

All participants completed 2 questionnaires after each PSG. The Morning After Patient Satisfaction Questionnaire consisted of a number of open-ended and multiple choice questions relating to the patient's sleep quality on the preceding night; it is designed to measure sleep quality and patient satisfaction. The PAP Comfort Questionnaire used a 100-mm visual analog scale (VAS) to determine subjective tolerance of PAP therapy.

The PAP flow generator used in the study for the ASVAuto was the VPAP Tx (ResMed Ltd, Sydney, Australia). The bilevel-ST used for the study was the VPAP III ST-A (ResMed Ltd, Sydney, Australia). In the bilevel mode, the technologist alters the inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) in order to maintain upper airway patency and provide respiratory support. The flow generator augments any breath initiated by the patient by detecting the onset of inspiration or expiration and delivering the set IPAP or EPAP pressures. The bilevel-ST mode supplies additional breaths should the patient's own respiratory rate falls below the clinician's set "back-up" respiratory rate.

The ASVAuto algorithm maintains a targeted minute ventilation (MV) and attempts to provide synchrony between patient initiated breathing and pressure support provided by the device. It continually monitors the patient's MV and calculates a target MV at 90% of patient's recent MV. Pressure support and EPAP are adjusted in response to whether the instantaneous MV is below or above the target MV. If ventilation decreases from target, then pressure support is increased and monitored for its effect on minute ventilation. The synchrony is maintained through constant breath phase mapping, which predicts inspiratory and expiratory times as well as expiratory pauses to maintain synchrony with the patient's respiratory cycle. The ASVAuto mode allows EPAP level to auto-adjust, responding to the occurrence of an obstructive apnea, airflow limitation, and snoring.

Study Endpoints

The primary endpoint was to determine the efficacy of ASVAuto at improving PSG variables in participants with CSA secondary to chronic use of opioid medications. The secondary endpoint was to compare ASVAuto versus bilevel-ST mode with respect to patient comfort and satisfaction on the night of the study in the sleep laboratory.

Table 2—Opiate usage

Medication *	Dosage (range)/day
buprenorphine	20 mg
buprenorphine/naloxone	8-12 mg
fentanyl	50-150 mcg
fentanyl pop	1600 mcg
hydrocodone	325 mg
hydromorphone	0.7-8 mg
methadone	4-50 mg
morphine	15-60 mg
oxycodone	5-80 mg
oxymorphone	10-20 mg

* Many participants were taking a combination of opiates.

Statistical Analysis

This is a crossover study design where participants were randomly assigned to one of 2 treatment groups: ASVAuto/bilevel-ST (ASVAuto first, bilevel-ST second) or bilevel-ST/ASVAuto (bilevel-ST first, ASVAuto second). The effect of treatment order was assessed using the student t-test and Wilcoxon rank sum test, as appropriate, comparing PSG results for participants in the ASVAuto/bilevel-ST group to bilevel-ST/ASVAuto group. Since all treatment order effects were not statistically significant, the primary endpoints were summarized by treatment (ASVAuto versus bilevel-ST) and treatment groups were compared using paired t-test statistics or Wilcoxon test, depending on the distribution of the data. Descriptive statistics, including mean, standard deviation, and range were presented for continuous data. All p-values were based on a 2-sided test with a type I error rate of 0.05. Analyses were conducted using SAS version 9.2 software (SAS Institute, Inc., Cary, NC).

RESULTS

A total of 60 participants were screened: 21 met inclusion criteria, 1 dropped out, 2 participants were not monitored according to protocol and were excluded, leaving data from 18 participants available for inclusion in the analysis.

Participant Characteristics

Participants (12 male, 6 female; age 24-76 [mean 52.9] years) had body mass index ranging from 23.7 to 48.8 (mean 30.9) kg/m^2 (**Table 1**). Indications for opioid therapy were back surgery (n = 1), back pain (n = 9), knee pain (n = 1), neuropathy (n = 1), motor vehicle accident pain (n = 1), full body pain (n = 1), left flank pain (n = 1), pelvic pain (n = 1), restless leg syndrome (n = 1), and complex regional pain syndrome (n = 1). **Table 2** lists opiate medications used and dosage range. Some participants were taking more than one opiate medication.

Respiratory Parameters

As no treatment order effects were identified, ASVAuto and bilevel-ST data from the 2 treatment groups were combined. PSG results are detailed in **Table 3**. The pre-entry baseline PSG showed an overall AHI and CAI of 50.3 ± 22.2 (45.4) and 13.0 ± 18.7 (5.3), respectively (mean ± SD [median]). There

were significant differences on study nights between ASVAuto and bilevel-ST with respect to total AHI, AI, and CAI, all of which were lower with ASVAuto treatment. The total AHI was significantly lower on ASVAuto versus bilevel-ST (2.5 ± 3.5 [0.3] versus 16.3 ± 20.9 [6.6], p = 0.0005). Similar findings were found with CAI for ASVAuto versus bilevel-ST (0.4 ± 0.8 [0.0] versus 9.4 ± 18.8 [1.5], p = 0.0002). **Figure 1** shows the AHI and CAI for ASVAuto versus bilevel-ST. The apnea index (AI) was significantly lowered on ASVAuto than bilevel-ST (0.4 ± 0.8 [0.0] versus 11.0 ± 19.6 [1.8], p < 0.0001). The respiratory arousal index was significantly lowered with ASVAuto versus bilevel-ST (1.1 ± 1.7 [0.3] versus 4.8 ± 4.8 [3.3], p = 0.0055). Respiratory parameters were normalized in 83.3% of participants on ASVAuto versus 33.3% on bilevel-ST. There were no significant differences in the average oxygen saturation (%) or minimum oxygen saturation (%).

There was no significant difference in the 95th percentile pressure (cm H_2O) for ASVAuto versus bilevel-ST (ASV-IPAP 16.5 ± 2.6 [16.0] versus bilevel-IPAP 15.4 ± 3.1 [16.0], p = 0.22; ASV-EPAP 9.3 ± 2.5 [8.1] versus bilevel-EPAP 10.5 ± 3.0 [11.0], p = 0.14; **Table 4**). The mean back-up respiratory rate during bilevel recording was 9.1 ± 2.9.

Total sleep time was significantly higher with bilevel-ST compared to ASVAuto (**Table 3**). Sleep efficiency (%), slow wave sleep, and REM sleep were not significantly different between the 2 treatment modalities.

Patient Comfort and Satisfaction

Despite longer total sleep time with bilevel-ST, on the Morning After Patient Satisfaction Questionnaire, participants felt more awake and alert after a night of ASVAuto therapy than bilevel-ST therapy, p = 0.0337 (**Table 5**). There were no significant differences with ASVAuto versus bilevel-ST therapy on the PAP Comfort Questionnaire (**Table 6**).

DISCUSSION

The present study compared two PAP modalities for the treatment of opioid induced central sleep apnea; the ASVAuto versus bilevel-ST during one night of recording in

Table 3—PSG results

	ASVAuto (N = 18)		Bilevel-ST (N = 18)		p-value
Polysomnographic Results	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**	**(Paired t-test)**
Total sleep time	356.3 ± 82.9	360.5	388.3 ± 75.2	413.5	0.0291 *
Sleep efficiency (%)	82.8 ± 15.3	84.4	87.1 ± 8.8	89.2	0.5509
Slow wave sleep (%)	17.0 ± 15.6	11.8	22.9 ± 21.9	16.8	0.1633
REM sleep (%)	11.5 ± 7.0	10.3	10.7 ± 6.1	9.4	0.6637
AHI, Total	2.5 ± 3.5	0.3	16.3 ± 20.9	6.6	0.0005 *
AHI, REM	1.0 ± 2.1	0.0	5.0 ± 8.5	0.0	0.0117 *
AHI, NREM	2.6 ± 3.8	0.4	17.3 ± 21.7	7.1	0.0005 *
AI, Total	0.4 ± 0.8	0.0	11.0 ± 19.6	1.8	< 0.0001 *
AI, REM	0.1 ± 0.5	0.0	3.5 ± 7.6	0.0	0.0625
AI, NREM	0.5 ± 0.9	0.0	11.6 ± 20.4	2.0	< 0.0001 *
HI, Total	2.0 ± 3.3	0.3	5.3 ± 6.5	3.5	0.0518
HI, REM	0.9 ± 1.8	0.0	1.5 ± 2.3	0.0	0.4805
HI, NREM	2.1 ± 3.5	0.4	5.7 ± 7.0	3.5	0.0417 *
CAI, Total	0.4 ± 0.8	0.0	9.4 ± 18.8	1.5	0.0002 *
CAI, REM	0.0 ± 0.0	0.0	2.4 ± 6.1	0.0	0.2500
CAI, NREM	0.5 ± 0.9	0.0	10.0 ± 19.5	1.6	< 0.0001 *
Average O_2 saturation (%)	95.7 ± 1.4	96.0	96.1 ± 1.7	96.0	0.1215
Lowest O_2 saturation (%)	90.4 ± 3.7	91.0	88.9 ± 4.9	91.0	0.1304
Total arousal index	24.4 ± 14.9	21.3	30.7 ± 18.0	26.7	0.0304 *
Respiratory-arousal Index	1.1 ± 1.7	0.3	4.8 ± 4.8	3.3	0.0055 *

Treatment Order: 9 Participants ASVAuto/bilevel-ST, 9 Participants bilevel-ST/ASVAuto. All treatment order effects for the following results were not statistically significant. * p < 0.05. REM, rapid eye movement; AHI, apnea hypopnea index; NREM, non rapid eye movement; AI, apnea index; HI, hypopnea index; CAI, central apnea index.

Table 4—Comparison of 95th percentile pressures for ASVAuto to bilevel-ST pressure settings

	ASVAuto 95th percentile (N = 18)		Bilevel-ST (N = 18)		p-value
Pressure during PSG (cm H_2O)	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**	**(Paired t-test)**
IPAP	16.5 ± 2.6	16.0	15.4 ± 3.1	16.0	0.2166
EPAP	9.3 ± 2.5	8.1	10.5 ± 3.0	11.0	0.1411

PSG, polysomnography; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure.

the sleep laboratory. We found that compared to bilevel-ST, the ASVAuto successfully suppressed all abnormal respiratory events including obstructive and central apneas, oxygen desaturations, and respiratory related arousals during initial treatment. The ASVAuto uses breath-by-breath algorithms to analyze the patient's ventilatory status with corresponding adjustments. Unlike the bilevel-ST mode, it has the advantage of adapting to changes in severity of breathing abnormalities in real time, such as minute-to-minute and night-to-night variability. On the other hand, the bilevel-ST setting is typically determined by one night of titration in the sleep laboratory. Because the bilevel-ST delivers pre-programmed settings, it cannot adjust to the variability in sleep-disordered breathing severity induced by opioid use, as well as the potential variation in pain threshold and physiologic response to pain level, even if the participant's dosage of opiates taken on each study night was kept constant.

Adaptive servoventilation was first introduced by Teschler and associates.[23] ASV has been shown to improve respiratory parameters as well as heart function in patients with central sleep apnea secondary to systolic heart failure (Cheyne-Stokes respiration).[24-26] Studies have also shown that ASV is effective in the treatment of complex sleep apnea, defined as the emergence of central apneas during PAP treatment (e.g., CPAP).[16,19] In a study by Dellweg and colleagues, after 6 weeks of treatment, ASV continued to be superior in treating complex sleep apnea compared to bilevel therapy in spontaneous-timed mode (total AHI 7.4 ± 4.2 versus 16.5 ± 8 [p = 0.027], CAI 1.5 ± 1.7 versus 10.2 ± 5.1 [p < 0.0001], respectively).[27]

There are limited studies, however, evaluating the use of ASV for the treatment of CSA secondary to chronic opioid use. Farney and associates conducted a retrospective study with ASV to treat comorbid OSA and CSA in chronic opioid users with disappointing results.[17] Twenty-two patients on chronic opioids referred for suspected SDB did not respond to CPAP and were subsequently placed on ASV. In this study, default settings were used (EPAP of 5.0 cm H_2O, minimum pressure support of 3.0 cm H_2O, maximum pressure support of 10.0 cm H_2O). With EPAP set at 5 cm H_2O, it was likely below the pressure required to maintain upper airway patency, and therefore residual apneas remained.

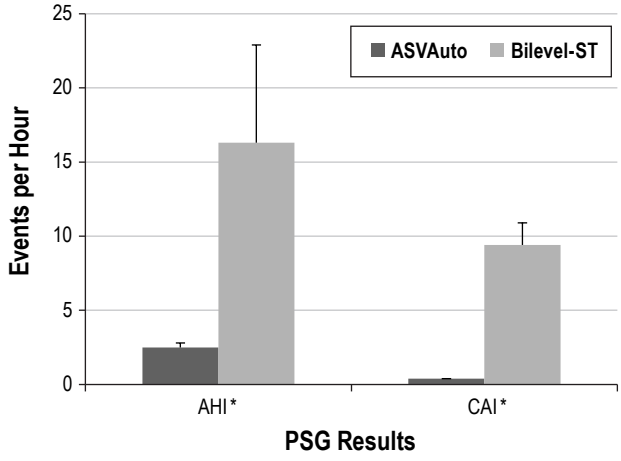
In contrast, two studies have shown promising results with ASV in treating SDB associated with chronic opioid use.[16,18] Javaheri and associates evaluated five consecutive patients with SDB on chronic opioid therapy and found that ASV effectively eliminated central apneas (AHI decreased from 70 to 20, CAI of 0).[18] In contrast to the study by Farney et al.,[17] EPAP was adjusted to effectively eliminate obstructive events. EPAP titration with appropriate adjustment of both inspiratory and expiratory pressures is critical in treating comorbid OSA and CSA. Compared to CPAP, bilevel in spontaneous mode, and bilevel in spontaneous-timed mode, Allam and associates showed that ASV was superior in the treatment of complex sleep apnea (CSA) in systolic heart failure, and CSA induced by chronic use of opioids.[16] Sixty-four participants had a mean AHI < 10 with ASV compared to other modalities, and majority of participants reported improvements in sleep quality.[16]

Table 5—Morning After Questionnaire

	ASVAuto (N = 18)	Bilevel-ST (N = 17)	p-value (Paired t-test *)
How do you feel right now?			
Alert and Awake	33.3% (6)	5.9% (1)	
Rested	50.0% (9)	52.9% (9)	0.0337 *
Barely awake	11.1% (2)	11.8% (2)	
Tired and Sleepy	5.6% (1)	29.4% (5)	
Quality of Sleep			
Restful	70.6% (12)	47.1% (8)	0.4805
In-between	11.8% (2)	35.3% (6)	
Restless	17.7% (3)	17.7% (3)	

Values are presented as % (N). * Signed rank test based on scored data.

Figure 1—Comparison of AHI and CAI with ASVAuto and bilevel with back-up rate in the total patient group.



There was a significant reduction in total number of abnormal breathing events during sleep (AHI and CAI) with ASVAuto compared to bilevel with back-up respiratory rate. PSG, polysomnography; AHI, apnea hypopnea index; CAI, central apnea index. * p < 0.001.

Table 6—PAP Comfort Questionnaire

	ASVAuto (N = 18) Mean ± SD	Bilevel-ST (N = 17) Mean ± SD	p-value (Paired t-test)
Satisfaction with PAP 0 = Very Dissatisfied, 100 = Very Satisfied	76.0 ± 27.2	67.8 ± 28.0	0.4450
Refreshed after waking in the morning 0 = Exhausted, 100 = Very Refreshed	71.4 ± 22.6	60.5 ± 25.6	0.1324
Discomfort from Pressure 0 = No Discomfort, 100 = Severe Discomfort	14.8 ± 24.1	31.4 ± 33.2	0.1249

The significant difference seen in this study with regards to respiratory parameters between the ASVAuto and bilevel-ST deserves further discussion. All 18 participants were on treatment with bilevel-ST that was determined by prior titration in the sleep laboratory or by their treating physician. One possible explanation for this difference could be that participants were not optimally titrated during prior titration study with respect to pressure and respiratory rate. Some participants also had changes made to their bilevel-ST during clinic visits for reasons as determined by treating physician (e.g., pressure discomfort, unacceptable leak values, elevated AHI, or patient request). Some of these changes could have resulted in suboptimal treatment of sleep disordered breathing.

Another possible explanation for the difference in respiratory parameters between ASVAuto and bilevel-ST could be related to the specific algorithm of each device and its effectiveness in normalizing abnormal breathing. Data from studies using polysomnograms suggests that opioid-induced SDB is characterized by several respiratory patterns. One pattern is characterized by irregular breathing with a mixture of central apneas of variable duration, along with variable amplitude in tidal volume and breathing rate, also known as ataxic breathing.[28] Camille Biot first described this irregular ataxic breathing pattern in 1897 in a 16-year-old patient with tuberculous meningitis.[28] Javaheri and associates described a second pattern of cluster breathing characterized by cycles of deep breaths in which the amplitude of tidal volume is relatively stable with interspersed central apneas of variable duration.[18] Guilleminault and associates described a third pattern characterized by obstructive apneas with progressive decrease in inspiratory effort (rather than an expected increase), and mixed apneas with unusually long expiratory pauses that may or may not meet AASM[22] criteria for a central apnea.[20] Unlike other types of CSA in which central apneas are clearly seen (e.g., complex sleep apnea), or the breathing pattern is distinctly characterized as periodic breathing with crescendo-decrescendo changes in tidal volume alternating with central apneas (e.g., Cheyne-Stokes Respiration), the respiratory pattern seen in opioid induced CSA is rather variable and irregular, and central apneas can be difficult to discern.

Because the bilevel-ST delivers fixed IPAP, EPAP, and back-up respiratory rate, it cannot adjust to the variability of abnormal breathing induced by opioids. This is particularly important for patients on chronic opioid therapy, as—in addition to the breathing irregularity as described above—levels of opioid medications change during the half-life of the active ingredient and may change over time since last titration sleep study. Also, there may have been fluctuations in weight since titration sleep study. These factors may have accounted for some of the differences seen in respiratory parameters between ASVAuto versus bilevel-ST.

Noninvasive positive pressure ventilation such as bilevel has been shown to lower carbon dioxide levels in patients with sleep apnea and hypercapnea.[29,30] Dellweg and associates compared bilevel-ST versus ASV in complex sleep apnea and found that respiratory indices were comparably lowered with both devices on initial titration night; however, after 6 weeks of treatment bilevel-ST was significantly inferior to ASV in terms of suppressing respiratory events (AHI: [16.5 ± 8 versus 7.4 ± 4.2], CAI: [10.2 ± 5.1 versus 1.5 ± 1.7]), respectively.[27] The authors speculate that long-term use of bilevel-ST may decrease the carbon dioxide reserve as well as lower the apnea threshold, with consequent emergence of central apneas. The carbon dioxide reserve (the difference between eupneic carbon dioxide and apnea threshold) is the major determinant of ventilatory instability and development of a central apnea; the narrower the reserve, the more likely a central apnea will occur. Because bilevel is considered a ventilatory assist mode, it lowers the carbon dioxide level and may potentially decrease carbon dioxide below the apneic threshold. The authors, however, did not measure carbon dioxide levels in order to confirm these hypotheses. In our study, participants had been on bilevel-ST for at least four weeks or longer prior to randomization. It may be that long-term use of bilevel resulted in changes in carbon dioxide levels with propensity for central apneas to occur. Further studies are needed to confirm this hypothesis.

Central Sleep Apnea and Opioids

CSA associated with chronic opioid use has unique characteristics but also shares characteristics with other types of CSA.[31] One such type of CSA is CSR secondary to systolic heart failure. This type of CSA is secondary to instability of the ventilatory system due to increased chemoresponsiveness to arterial partial pressure of oxygen and carbon dioxide.[31] In both conditions, central and obstructive events are present during sleep, and therapy with CPAP effectively treats obstructive events in both. While central apneas are partly responsive (50% of the patients) to CPAP in heart failure, with opioids, central apneas persist despite CPAP therapy. Studies have shown that opioid induced CSA is unresponsive to CPAP and requires advanced PAP modes for effective treatment.[16-18,20,21]

The results of this study showed that ASVAuto is significantly more effective than bilevel-ST for the treatment of CSA secondary to chronic opioid use. Although bilevel-ST and ASVAuto both deliver positive pressure to improve upper airway patency, provide ventilatory assist, and are capable of providing back-up breaths, their underlying algorithms substantially differ. The ASVAuto has several advantages over the bilevel-ST mode; it provides variable and real time breath-by-breath pressure support to eliminate obstructive and central hypopneas. With this platform, dynamic pressure support is applied during the "undershoot period" and reduced during the "overshoot period," maintaining synchrony with the patient's own respiratory cycle. The ASVAuto provides an adaptive back-up respiratory rate based on the patient's breathing to abort impending central apneas, and offers auto-adjusting expiratory positive airway pressure (auto EPAP) to treat upper airway obstruction such as an obstructive apnea, airflow limitation, or snoring. The auto-adjusting EPAP capability maintains upper airway patency at all times, allowing pressure support to respond to periods of reduced ventilatory drive, and providing back-up breaths when respiration is not detected. Hence ASVAuto stabilizes the instability in respiration due to changes in tidal volume, periodic apneas, and irregularities in respiratory cycles and seen in opioid-induced sleep disordered breathing. Finally, ASVAuto assures that if patients with chronic pain change their daily intake of opiate medication, there will be an adapted response to this abrupt change and the associated sleep disordered breathing severity.

This is the first study to compare ASVAuto versus bilevel-ST in this population, and to show the treatment efficacy of ASVAuto versus bilevel-ST device. The study provides evidence for the successful treatment of patients with CSA secondary to chronic opioid use by ASVAuto by both objective (AHI and CAI) and subjective measures. A limitation of this study is the small sample size; however, we believe that this sample is representative of a chronic opioid use population. The study also compared one night of treatment with ASVAuto versus bilevel-ST. It is unclear why participants had a signficantly longer total sleep time while on bilevel-ST. This could reflect a need for longer sleep due to poorer quality sleep and more abnormal breathing events while on bilevel-ST versus ASVAuto, or habituation and familiarity on bilevel-ST versus first-night effect on ASVAuto.

Summary

In this randomized crossover study, the ASVAuto was superior to bilevel-ST in suppressing sleep disordered breathing, specifically CSA secondary to chronic opioid use. Similar to obstructive sleep apnea, it is conceivable that CSA secondary to chronic opioid use may contribute to increased morbidity and mortality. Large comparative clinical trials are needed to determine long-term efficacy, advantages, and disadvantages, as well as improvements in morbidity and mortality. In the absence of long-term randomized clinical trials and guidelines, we recommend ASVAuto therapy for the treatment of CSA associated with chronic opioid use.

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