# The Treatment of Complex Central Sleep Apnea (CompCSA)

## Including Cheyne-Stokes Breathing (CSB), with Respironics' BiPAP autoSV Advanced therapy system

**Authors:** Shahrokh Javaheri, MD[1], Mark Goetting, MD[2], Rami Khayat, MD[3], Jamie Goodwin, PhD[4] and Paul Wylie, MD[5]

**Introduction:** This study was conducted to evaluate the therapeutic performance of a new servo-ventilation device (BiPAP autoSV Advanced, Philips Respironics) for the treatment of Complex Central Sleep Apnea (CompCSA), Periodic Breathing (i.e., Cheyne Stokes Breathing).

**Study design:** A prospective multicenter randomized controlled trial.

**Setting:** Professional sleep laboratories – five (5) sites within the United States (US).

**Participants:** Thirty-two (32) participants with CompCSA, including Cheyne-Stokes Breathing (CSB).

**Measurements and results:** Qualifying subjects were randomly assigned to complete two full-night attended polysomnograms (PSG) while treated with either the currently marketed device (BiPAP autoSV, Philips Respironics) or the BiPAP autoSV Advanced device. The BiPAP autoSV Advanced includes an automatic EPAP adjustment and a modified auto backup rate. Standard sleep and breathing endpoints were evaluated and analyzed.

Both interventions successfully treated sleep-disordered breathing events as compared to previous clinical diagnostic and CPAP titration nights. Values for apnea hypopnea index, obstructive apnea index, central apnea index, and mixed apnea index were significantly lower with the BiPAP autoSV Advanced compared to the BiPAP autoSV device.

**Conclusions:** The results of this study indicate that recent improvements to Philips Respironics' current autoSV technology successfully reduce or eliminate both CompCSA and CSB in patients presenting with these conditions.

**Abbreviations:** PSG – polysomnogram; PAP – Positive Airway Pressure; EPAP – Expiratory PAP; IPAP – Inspiratory PAP; CPAP – Continuous PAP; BiPAP – Bi-level PAP; autoSV Advanced – BiPAP autoSV Advanced; autoSV – BiPAP autoSV; SDB – Sleep-Disordered Breathing; OSA – Obstructive Sleep Apnea; CSA –- Central Sleep Apnea; CSR – Cheyne-Stokes Respiration; CompCSA – Complex Central Sleep Apnea (SDB inclusive of Central, Obstructive, Mixed Apneas and CSR); AHI – Apnea Hypopnea Index; Complex Sleep Apnea Syndrome (CSAS).

**Key words:** Bi-level Positive Pressure Ventilation, Servo-Ventilation, Auto EPAP, Pressure Support

[1]Sleepcare Diagnostics, Mason, Ohio
[2]Sleep Health, Portage, Michigan
[3]Ohio State University, Columbus, Ohio
[4]University of Arizona, Tucson, Arizona
[5]Arkansas Center for Sleep Medicine, Little Rock, Arkansas

PHILIPS
RESPIRONICS

## Introduction

Complex Central Sleep Apnea (CompCSA), including: Cheyne-Stokes Respiration (CSR), idiopathic CSA, Periodic Breathing (PB or altitude induced CSA), narcotic-induced CSA and CPAP-emergent Central Sleep Apnea has been and continues to be of significant interest to the sleep community. Cheyne-Stokes Respiration (CSR) is well known and has long been characterized as a cyclic waxing and waning pattern of respiration lasting approximately 50-70 seconds, resulting from ventilatory instability related to increased "loop gain." Similarly, idiopathic CSA and periodic breathing have also been reviewed and characterized in the literature for some time and may lack the crescendo / decrescendo pattern of CSR and are shorter in duration, typically 30-40 seconds. Narcotic-induced CSA has been suspected for some time, but until recently has received limited exposure in the literature. Recent publications by Javaheri et al. and Webster et al. highlight this condition and explore the prevalence, respectively.[i,ii] Characterization of narcotic-induced CSA is ongoing, but is typically highly variable and less cyclic.[iii]

CPAP-emergent Central Sleep Apnea was first reported by Gilmartin et al. in 2005[iv] as Complex Sleep Disordered Breathing, and then as Complex Sleep Apnea Syndrome (CSAS) in 2006 by Morganthaler et al.[v] Lehman et al.[vi] again noted this condition and the specific development and effects of treatment with CPAP. This area continues to receive significant attention in the literature and throughout the sleep community. Recently, Javaheri et al. published "The Prevalence and Natural History of Complex Sleep Apnea,"[vii] which concluded that approximately 6.5 percent of patients with a primary diagnosis of OSA have central sleep apnea during CPAP titration. Of the total population of patients prescribed CPAP for long-term use, approximately 1.5 percent showed persistent central sleep apnea, i.e., their SDB was not corrected with CPAP alone. Although bi-level therapy, with or without a backup rate, may be a recommended therapy, this too has been shown to be insufficient based on data from Morganthaler et al.[viii]

As aptly pointed out by Eckert et al., "While the precise precipitating mechanisms involved in the various types of CSA may vary considerably, unstable ventilatory drive during sleep is a principal underlying feature."[ix] Characterization of the physiology and potential phenotyping of patients exhibiting these types of SDB have not been completely elucidated and are not the focus of this paper. The intent of this current study was to evaluate two auto servo-ventilation devices on patients who demonstrated some form of persistent complex central sleep apnea, including Cheyne-Stokes Breathing (CSB), that was not successfully treated with standard CPAP therapy. This study included participants with the following medical diagnoses: Heart disease (including CHF, A-fib, s/p MI, pacemaker, CAD, HTN, and Dysrhythmias), CVA, pain (including neuropathic, arthritic, and cancer), COPD, GERD and diabetes. Frank CSR was identified in at least seven of the 32 participants and some indication of heart disease was present in nearly half of the evaluated population (15/32).

## BiPAP autoSV Advanced

This study evaluated the performance of the BiPAP autoSV Advanced device. Servo-ventilation devices provide a mode of pressure support to treat obstructive and complex central sleep apnea disorders.

The main features of the BiPAP autoSV include:

- Normalization of ventilation by automatically adjusting IPAP pressure to achieve a target peak flow.
- Response to central apneas and hypopneas, and periodic breathing by increasing the magnitude of ventilation.
- Timed, backup breaths during central apneas. The optimal backup rate is automatically determined by the device (based on the patient's sleep-disordered breathing presentation).

An enhanced form of the BiPAP autoSV device, the BiPAP autoSV Advanced, was developed to provide the following enhancements:

- Improved timed backup breath delivery during central apnea.
- Automatic control of EPAP pressure to treat obstructive events.

## Methods

Participants were enrolled after completing either an in-lab or home diagnostic PSG. Portable testing was permitted as part trial inclusion, however, all participants completed an in-lab PSG. Randomization was contingent upon the results of a CPAP titration night. Only participants that exhibited continued CompCSA and met all criteria for participation after their CPAP titration night were randomized into the study. All randomized subjects had prior PAP use for more than four weeks and continued to have persistent CSA.

Five sites in the United States studied 32 participants with CompCSA. Subjects were recruited if they demonstrated an Apnea Hypopnea Index (AHI) ≥ 10 and a Central Apnea Index (CAI) ≥ 5 on their full-night diagnostic polysomnogram (PSG) and continued in the study if on their full-night CPAP titration they had a CAI ≥ 5. Qualifying subjects underwent two additional full-night in-lab PSGs, one with the BiPAP autoSV, and the other with the BiPAP autoSV Advanced device. The order of treatment was randomized and participants were blinded as to which device they received during their study nights.

**Table 1: Inclusion / exclusion criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Pre-study inclusion criteria:<br>• Age 21-80<br>• Ability to provide consent<br>• Documentation of medical stability by investigator | • Participants who are acutely ill, medically complicated, or medically unstable. |
| Enrollment inclusion criteria:<br>• Participants who, during the ambulatory PSG study (Stardust) or in-lab diagnostic PSG, demonstrated an AHI ≥ 10 and CAI ≥ 5<br>or<br>• Participants who previously demonstrated CSA, with a CAI ≥ 5 on CPAP titration | • Pregnancy (confirmed absence of pregnancy with a urine or serum pregnancy test in women of child bearing potential).<br>• Participants in whom PAP therapy is otherwise medically contraindicated.<br>• Participants who are unwilling to wear CPAP.<br>• Participants who are currently prescribed oxygen therapy.<br>• Participants with previously diagnosed respiratory failure or respiratory insufficiency and who are known to have chronically elevated arterial carbon dioxide levels while awake ($PaCO_2$ ≥ 45mmHg).<br>• Participants who have had surgery of the upper airway, nose, sinus, or middle ear within the previous 90 days.<br>• Participants with untreated, non-OSA/CSA sleep disorders, including but not limited to insomnia, periodic limb movement syndrome, or restless legs syndrome (PLM Arousal Index > 15).<br>• Participants who are unwilling to participate in the study. |

Device settings for both groups in the investigation are listed in Table 2. The BiPAP autoSV Advanced device automatically adjusted the level of Pressure Support (PS), EPAP, and respiratory rate. In the BiPAP autoSV, EPAP was set to, and remained at, the best CPAP setting determined previously on the CPAP titration night. If indicated, the protocol allowed for additional EPAP titration within the first two hours of the test night with BiPAP autoSV. Pressure Support (PS) and respiratory rate were automatically adjusted by the device.

**Table 2: Device settings**

| Device setting | BiPAP autoSV | BiPAP autoSV Advanced |
|---|---|---|
| EPAP | Determined from CPAP titration | Not available |
| EPAPmax | Not available | 16 cm $H_2O$ |
| EPAPmin | Not available | Determined from CPAP titration<br>Set to EPAP - 2 |
| IPAPmax | 30 cm $H_2O$ | Not available |
| IPAPmin | Set equal to EPAP | Not available |
| PSmax | Not available | 20 cm $H_2O$ |
| PSmin | Not available | 0 cm $H_2O$ |
| Backup rate | Determined automatically | Determined automatically |

## Results – demographic data

Sixty-two patients were screened for participation, and 35 participants were randomized. Data are presented from the completed-cases population which consisted of 32 participants (5 females and 27 males) with an average age of 63.7 ± 11.2 (S.D.) years, and an average BMI of 31.2 ± 5.3. Three participants were excluded from the completed-cases analysis. One subject who completed both randomized nights failed to meet the required minimum Total Sleep Time (as defined in the protocol).

The second participant also completed both randomized nights, but the BiPAP autoSV device was set up in error with the min and max EPAP settings fixed on the BiPAP autoSV Advanced night. Although data were available for this participant on both nights, the comparison to the predicate device was not appropriate due to this error and thus these data were excluded from the completed-cases analysis. The third participant withdrew from the study prior to completing either randomized night.

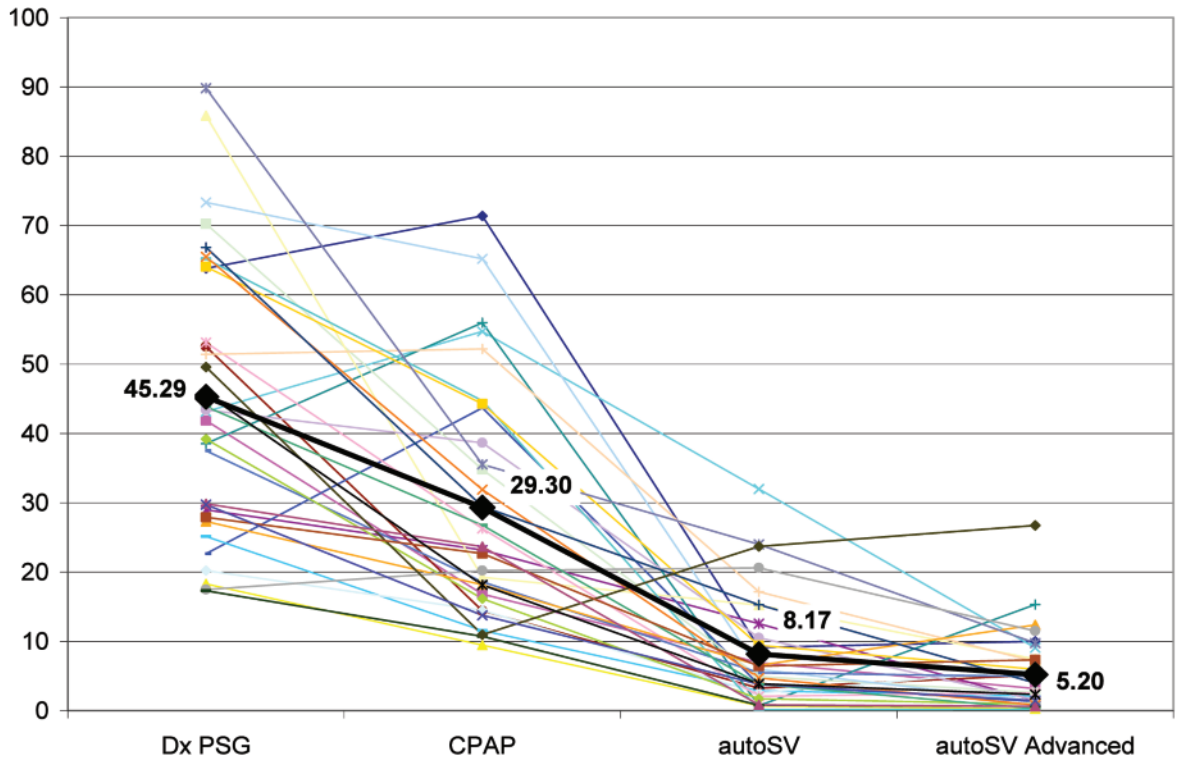
Table 3 presents the summary statistics and significance levels for the completed-cases analysis comparing the Dx PSG, CPAP titration (CPAP), BiPAP autoSV (autoSV), and the BiPAP autoSV Advanced (autoSV Advanced). Figure 1 presents the AHI data graphically, with mean values indicated in bold. Compared to the diagnostic PSG and CPAP titration, treatment with the BiPAP autoSV Advanced resulted in a statistically significant reduction in AHI and CAI ($p < 0.001$).

**Table 3: Comparison across four PSG nights (Dx PSG vs. CPAP vs. autoSV vs. autoSV Advanced; N=32)**

| | Variable | Mean | Std. deviation | Median | Min | Max | Overall p-value* |
|---|---|---|---|---|---|---|---|
| AHI | Dx PSG | 45.29 | 20.15 | 43.28 | 17.29 | 89.81 | ≤0.0001 |
| | CPAP | 29.30 | 16.90 | 23.42 | 9.47 | 71.39 | |
| | autoSV | 8.17 | 8.00 | 5.20 | 0.15 | 31.98 | |
| | autoSV Advanced | 5.20 | 5.66 | 2.89 | 0.19 | 26.74 | |
| CAI | Dx PSG | 9.94 | 11.20 | 8.22 | 0.00 | 54.39 | ≤0.0001 |
| | CPAP | 15.14 | 15.76 | 9.77 | 4.98 | 66.08 | |
| | autoSV | 2.11 | 3.32 | 1.13 | 0.00 | 14.15 | |
| | autoSV Advanced | 0.50 | 0.76 | 0.27 | 0.00 | 2.91 | |
| OAI | Dx PSG | 10.71 | 16.50 | 5.78 | 0.00 | 73.31 | ≤0.0001 |
| | CPAP | 0.73 | 1.16 | 0.41 | 0.00 | 5.52 | |
| | autoSV | 1.69 | 2.38 | 1.02 | 0.00 | 12.89 | |
| | autoSV Advanced | 1.10 | 1.71 | 0.51 | 0.00 | 8.83 | |
| MAI | Dx PSG | 4.57 | 9.94 | 0.51 | 0.00 | 48.81 | 0.0019 |
| | CPAP | 0.51 | 1.23 | 0.00 | 0.00 | 6.21 | |
| | autoSV | 0.33 | 0.67 | 0.13 | 0.00 | 3.65 | |
| | autoSV Advanced | 0.19 | 0.39 | 0.00 | 0.00 | 2.03 | |
| HI | Dx PSG | 20.08 | 13.59 | 18.61 | 1.35 | 55.24 | ≤0.0001 |
| | CPAP | 12.93 | 10.76 | 10.31 | 0.85 | 40.76 | |
| | autoSV | 4.00 | 4.41 | 2.19 | 0.00 | 15.35 | |
| | autoSV Advanced | 3.41 | 4.58 | 1.72 | 0.00 | 20.87 | |

*Overall p-values per the Friedman Test. Post-hoc comparisons showed a significant reduction in all respiratory indices with autoSV Advanced compared to the diagnostic night, as well as a significant reduction in AHI, CAI, and HI compared to CPAP.

**Figure 1: AHI comparative data across all nights**




BiPAP autoSV Advanced exhibited superior treatment to BiPAP autoSV, with respect to the AHI, the CAI, the Obstructive Apnea Index (OAI), and the Hypopnea Index (HI) ($p<0.05$). Other key variables, including Arousal Index (AI), Mixed Apnea Index (MAI), Total Sleep Time (TST), Sleep Efficiency (SE%), Wake After Sleep Onset (WASO), and Baseline $SpO_2$ and Low $SpO_2$, did not differ significantly between devices. There were no significant differences between the two devices with respect to sleep stage measures.

## Discussion

These data indicate that recent improvements made to the current auto servo-ventilation technology (automatically adjusted EPAP and enhanced auto backup rate) will likely lead to a more successful reduction or elimination of CompCSA in patients presenting with this condition. With both autoSV devices there were clinically and statistically significant reductions in the AHI, CAI, OAI, MAI, and the HI from diagnostic and CPAP titration nights ($p<0.002$ for all). While both the current BiPAP autoSV and the new BiPAP autoSV Advanced provided clinically effective significant treatment, as revealed by an AHI < 10, the new autoSV Advanced demonstrated statistical superiority in all of the key endpoints including AHI, CAI, OAI, and HI ($p < 0.05$ for all).

Additional long-term studies are necessary to determine if the short-term benefits are maintained over time and whether the reduced apnea would result in less comorbidities or better quality of life. Although some patients were not completely treated with these devices (AHI < 15), an overwhelming majority of patients (84 percent) were. Recognizing the challenges in treating the comprehensive condition known as CompCSA, sleep clinicians and technicians can be confident that the new BiPAP autoSV Advanced will aid caregivers in providing optimal therapy that is tailored to these specific patients' needs.

## Conclusion

This paper reports the findings of a recent randomized, controlled comparative clinical trial of the BiPAP autoSV device versus the BiPAP autoSV Advanced. These data indicate that both devices provide therapeutic benefit in patients diagnosed with Complex Central Sleep Apnea (CompCSA) including those with Cheyne-Stokes Breathing (CSB).

## References:


[i] Javaheri et al., Adaptive pressure support servoventilation: a novel treatment for sleep apnea associated with use of opioids. *J Clin Sleep Med.* 2008 Aug 15;4(4): 321-3.

[ii] Webster et al., Sleep-disordered breathing and chronic opiod therapy. *Pain Medicine* 2008; 9(4): 425-432.

[iii] Walker et al., Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med.* 2007 Aug 15;3(5): 455-61.

[iv] Gilmartin, et al., Recognition and management of complex sleep-disordered breathing. *Curr Opin Pulm Med* 2005; 11: 485-93.

[v] Morganthaler, et al., Complex sleep apnea syndrome: is it a unique clinical syndrome? *Sleep* 2006; 29(9): 1203-9.

[vi] Lehman, et al., Central sleep apnea on commencement of continuous positive airway pressure in patients with a primary diagnosis of obstructive sleep apnea-hypopnea. *J Clin Sleep Med* 2007; 3(5): 462-6.

[vii] Javaheri, et al., The prevalence and natural history of complex sleep apnea. *J Clin Sleep Med* 2009; 5(3): 205-11.

[viii] Morganthaler, et al., Complex sleep apnea syndrome: is it a unique clinical syndrome? *Sleep* 2007; 30(4): 468-75.

[ix] Eckert, et al., Central sleep apnea: pathophysiology and treatment. *Chest* 2007; 131: 595–607.

Respironics, autoSV, BiPAP and Stardust are trademarks of Respironics and its affiliates. All rights reserved.


©2009 Koninklijke Philips Electronics N.V. All rights are reserved.

Philips Healthcare reserves the right to make changes in specifications and/or to discontinue any product at any time without notice or obligation and will not be liable for any consequences resulting from the use of this publication.

CAUTION: US federal law restricts these devices to sale by or on the order of a physician.

Hoech KW 09/14/09 MCI 4102517 PN 1064783

Philips Healthcare is part of Royal Philips Electronics

Respironics Asia Pacific
+65 6298 1088
Respironics Australia
+61 (2) 9666 4444
Respironics Europe, Middle East, Africa
+33 1 47 52 30 00
Respironics United Kingdom
+44 800 1300 845

Philips Respironics
1010 Murry Ridge Lane
Murrysville, PA 15668

Customer Service
+1 724 387 4000
+1 800 345 6443 (toll free, US only)
www.philips.com/respironics