



Early View

Research letter

Predictors of One Year Compliance with Adaptive Servo-Ventilation in Patients with Heart Failure and Sleep- Disordered Breathing: Preliminary Data from the ADVENT-HF Trial

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Predictors of One Year Compliance with Adaptive Servo-Ventilation in Patients with Heart Failure and Sleep- Disordered Breathing: Preliminary Data from the ADVENT-HF Trial

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The trial is registered with Current Controlled Trials (www.controlled-trials.com; ISRCTN67500535) and Clinical Trials (www.clinicaltrials.gov; NCT01128816).

See Appendix 1 and 2 for trial personnel and complete list of author affiliations, trial sites and investigators.

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ABSTRACT

Peak flow-targeted adaptive servo ventilation (ASVpf) suppresses both obstructive (OSA) and central sleep apnoea (CSA). Although high hours of positive airway pressure (PAP) use improves quality of life, long-term compliance is problematic. We evaluated ASVpf use in patients with heart failure and reduced ejection fraction with either OSA or CSA to determine the short and long-term predictors of ASVpf compliance.

Of 177 patients randomised to ASVpf, compliance data were available at one and 12 months post-randomisation in 91 with OSA and 45 with CSA. Among patients with OSA, ASVpf use was 4.6 [2.9] h per day at one month but decreased to 4.1 [4.7] h at 12 months ($p=0.04$). Among patients with CSA, median ASVpf use was 5.2 [4.0] h per day at one month and 5.2 [3.5] h per day at 12 months ($p=0.52$). The only predictor of ASVpf use at 12 months was hours of use at one month (OR 2.02; CI 1.58-2.60, $p<0.01$).

These data indicate better compliance with ASVpf than previously reported for other PAP devices in patients with cardiovascular diseases. Hours of daily use at one month predicted compliance at 12 months, indicating that if good short-term compliance is achieved, this effect can be sustained long-term.

To the Editor:

Despite its effectiveness in suppressing sleep-disordered breathing (SDB), positive airway pressure therapy (PAP) is not always well tolerated by patients, and long-term adherence can be problematic. Recently, two multi-centre, randomized clinical trials (RCT) tested the effects of PAP for patients with cardiovascular disease and co-existing SDB on morbidity and mortality with negative outcomes [1, 2]. Relatively poor adherence to PAP therapy (mean 3.7 h/day and 3.3 h/day respectively) in these two trials, might have contributed to their poor results. Indeed, higher PAP use per day is associated with better clinical outcomes than lower use [3].

The “Effect of Adaptive Servo-ventilation on Survival and Cardiovascular Hospital Admissions in Patients with Heart Failure and Sleep Apnoea” (ADVENT-HF) trial is a multinational RCT assessing the effects of treating SDB with peak flow targeted adaptive servo-ventilation (ASVpf) on morbidity and mortality in patients with heart failure (HF) and reduced ejection fraction (HFrEF) [4]. The purpose of this study was to determine the short and long-term predictors of ASVpf adherence in an inception cohort of the ADVENT-HF trial. The trial has been registered (www.clinicaltrials.gov; NCT01128816), and its design, inclusion and exclusion criteria, and methods have been previously described [4].

The analysis included all patients from 38 sites randomised into the ASVpf treatment arm of the ADVENT-HF study before March 31st, 2016, and for whom ASVpf adherence data were available at one and 12 months post-randomisation.

ASVpf compliance, defined as the average hours of use per day, was calculated for all patients and separately for the obstructive (OSA) and central sleep apnea (CSA) groups. At one and 12 months, the percentage of patients compliant with ASVpf treatment, defined as use of more than 50% of the baseline total sleep time per day [4], and the percentage with good compliance, defined as use of 4 or more hours per day were assessed. For patients who withdrew from the study or who discontinued the device, hours of use were evaluated over the time during which the device was used and were imputed to be 0 hours per night after discontinuation.

To define predictors of daily one-month ASVpf use, univariable logistic regression was performed with the following as independent variables: age, body mass index, sex, presence of coronary artery disease, atrial fibrillation or flutter, country of site, baseline values of AHI, Epworth Sleepiness Scale (ESS) score, sleep efficiency, arousal index, New York Heart Association class, N-terminal pro B-type natriuretic peptide, left ventricular ejection fraction, Minnesota Living With Heart Failure Questionnaire scores, as well as type of mask used and leak at one month post-randomisation. A similar analysis was performed for daily 12-month ASVpf with the addition of the independent variables, daily

hours of ASVpf use at one month, as well as AHI, ESS, type of mask and leak at 12 months post-randomisation. To define predictors of daily 12-month ASVpf use, a stepwise multiple regression analysis were performed.

Of 177 subjects randomised to ASVpf, compliance data were available in 136 (91 with OSA and 45 with CSA). Of the remainder, 27 did not attend the scheduled clinic visit and 14 either refused to participate or withdrew consent after randomization. Characteristics of those with OSA and CSA were similar, except for a higher AHI among CSA patients ($37.4 [29.7]$ vs $50.8 [24.2]$, $p=0.050$).

ASVpf was effective in controlling both OSA and CSA. In those with predominantly OSA, while on ASVpf, the AHI decreased from 42.7 ± 19.8 at baseline to 3.9 ± 2.7 one month later to 3.3 ± 2.8 12 twelve months later ($p<0.01$ for both). In those with predominantly CSA, while on ASVpf, the AHI decreased from 50.4 ± 16.7 at baseline to 5.3 ± 3.7 one month later and to 3.9 ± 2.5 twelve months later ($p<0.01$ for both). This compares to a residual AHI of 6.6 (mainly obstructive) 12 months post-randomisation on ASVmv in the SERVE-HF trial.

At one month a nasal mask was used by 93 (68%) of patients: 60 OSA (66%) and 33 CSA (73%). At 12 months the use of a nasal mask did not change: 86 (63%) of patients: 57 OSA (63%) and 29 CSA (64%). The remainder used a full-face mask.

By one month, of the 91 patients with OSA, only 3 (3%), had discontinued ASVpf, while among the 45 with CSA only one patient (2%) had discontinued it. At 12 months, they increased to 18 (20%) and 5 (11%), respectively, or 23 (17%) for all patients. The percentage of patients compliant [4] at 1 month was 86% among OSA and 87% among CSA patients, at 12 months it was 67% and 80%, respectively. The median daily use for all 136 subjects at one month was 4.7 [3.2] h and declined to 4.4 [4.3] h at 12 months ($p < 0.01$). As shown in Figure 1, daily ASVpf use declined from 4.6 to 4.1 hours per day in the OSA group, but remained stable at 5.2 h per day in the CSA group.

Among patients with OSA, 56 (62%) and 48 (53%) used ASVpf at least four hours per day at one and 12 months, respectively, while among patients with CSA, they were 30 (67%) and 27 (60%) at one and 12 months. No variable was a significant predictor of good compliance at one month. Hours of ASVpf use at one month was the only independent predictor of good ASVpf compliance at 12 months in the multivariate analysis of all patients (OR 2.02, CI 1.58-2.60, $p<0.01$) and in the subgroups separately (for OSA, OR 1.94: CI 1.27-2.78, $p<0.01$, for CSA, OR 2.12: CI 1.50-2.98, $p<0.01$).

Both short and long-term ASVpf compliance were good in these patients with HFrEF and SDB enrolled in the ADVENT-HF trial.

The “ASV for CSA in Systolic HF” (SERVE-HF) trial showed that minute ventilation targeted ASV (ASVmv) had no effect on the primary endpoint possibly due, in part, to low ASVmv compliance of 3.4 hours per day at 12 months and 3.7 hours per day over the entire 5 year trial period [5, 6]. Only 48% of patients used ASVmv at least 4 h per day over the trial period [2]. By contrast, ASVpf use in patients with CSA in the present study was higher in terms of hours of daily use and proportion using it at least 4 h per day after 12 months, although the proportion of patients who discontinued ASVpf increased from 2% at one to 11% at 12 months. Factors that might have contributed to better ASVpf compliance in the ADVENT-HF study include the technical characteristics of the ASVpf versus the ASVmv device used in SERVE-HF. ASVmv used relatively high default pressures with a minimum end-expiratory pressure (EPAP) of 5 cmH₂O and minimum inspiratory pressure support of 3 cmH₂O, whereas ASVpf in the present study used lower default pressures with a minimum EPAP of 4 cmH₂O and a minimum pressure support of 0 cmH₂O. These lower pressures might be better tolerated. In addition, unlike ASVmv that did not titrate EPAP to control obstructive events, ASVpf automatically titrates EPAP to control such events. This probably accounts for the lower residual AHI in patients on ASVpf, whether OSA or CSA, in the ADVENT-HF than in the SERVE-HF trial where residual events were mainly obstructive. Centralized versus local interpretation of ASVpf titrations and prescription of

ASVpf settings in ADVENT-HF versus SERVE-HF as well as more frequent interaction with patients due to semi-annual versus annual follow-up visits in ADVENT-HF versus SERVE-HF may also have contributed to better ASVpf compliance. ASVpf compliance was also better in ADVENT-HF than ASVmv compliance in another recent RCT, in which daily use at 6 months was only 2.7 [7].

Daily ASVpf use among patients with OSA in ADVENT-HF was also higher than continuous positive airway pressure use in the “Sleep Apnea Cardiovascular Endpoints [SAVE]” trial (3.5 hours per day 12 months post-randomisation) [1]. However, in contrast to patients with CSA, daily hours of ASVpf use among those with OSA declined at 12 months, in association with an increase in patients discontinuing ASVpf. The reason for the reduction in use over time was not clear. Once the trial is complete, it will be possible to assess outcomes data to determine if any of them are related to ASVpf compliance.

Recent RCTs testing CPAP therapy in non-sleepy OSA patients have demonstrated an absence of any effect on cardiovascular endpoints [1, 8, 9]. However, use of CPAP for >4 h per day was associated with a reduction in the incidence of the primary endpoint [8, 9]. Thus, there is a general tendency for PAP use of ≥ 4 hr per day to be associated with better outcomes. ASVpf has been shown to be more effective in suppressing OSA and CSA in patients with HFrEF than CPAP [5, 10, 11].

The only factor that independently predicted daily hours of good ASVpf compliance 12 months post-randomisation was hours of ASVpf use at one month. These findings are compatible with previous evidence, indicating that patients' initial experience with the treatment may influence their long-term compliance [12, 13].

Whether better adherence of ASVpf therapy in the present study than in previous studies of patients with cardiovascular diseases and SDB [1, 2, 7, 8] will be associated with better clinical outcomes will not be known until completion of the trial.

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REFERENCES

1. McEvoy R, Antic N, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016; 375: 919-931.
2. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015; 373: 1095-1105.
3. Antic NA, Catcheside P, Buchan C, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. *Sleep* 2011; 22: 111-119.
4. Lyons OD, Floras JS, Logan AG, et al. Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: the ADVENT-HF trial. *Eur J heart Fail* 2017; 19: 579-587.
5. Bradley TD, Floras JS. Adaptive Servo-Ventilation for Central Sleep Apnea in Heart Failure. *N Engl J Med* 2016; 374: 689.
6. Javaheri S, Brown LK, Randerath W, et al. SERVE-HF: More Questions Than Answers. *Chest* 2016; 149: 900-904.
7. O'Connor CM, Whellan DJ, Fiuzat M, et al. Cardiovascular Outcomes With Minute Ventilation-Targeted Adaptive Servo-Ventilation Therapy in Heart Failure: The CAT-HF Trial. *J Am Coll Cardiol* 2017; 69: 1577-1587.
8. Peker Y, Glantz H, Eulenburg C, et al. Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Non-Sleepy Obstructive Sleep Apnea: The RICCADSA Randomized Controlled Trial. *Am J Respir Crit Care Med* 2016; 194: 613-620.
9. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA* 2012; 307: 2161-2168.
10. Teschler H, Dohring J, Wang YM, et al. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. *Am J Respir Crit Care Med* 2001; 164: 614-619.
11. Arzt M, Wensel R, Montalvan S, et al. Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. *Chest* 2008; 134: 61-66.
12. Collen J, Lettieri C, Kelly W, et al. Clinical and polysomnographic predictors of short-term continuous positive airway pressure compliance. *Chest* 2009; 135: 704-709.
13. Budhiraja R, Parthasarathy S, Drake C, et al. Early CPAP Use Identifies Subsequent Adherence to CPAP Therapy. *Sleep* 2007; 30: 320-324.

