

Auto-servo ventilation in heart failure with sleep apnea – a randomized controlled trial

Michael Arzt¹, Stephan Schroll^{1*}, Frederic Series², Keir Lewis³, Amit Benjamin³, Pierre Escourrou⁴, Ruth Luigart¹, Victoria Kehl⁵, Michael Pfeifer^{1,6}

Affiliations

¹Department of Internal Medicine II, Division of Respiriology, University Hospital Regensburg, Germany; ²Centre de Recherche, IUCPQ, Universite Laval, Quebec, Canada; ³Department of Respiratory Medicine, Prince Philip Hospital and Swansea College of Medicine, Wales, United Kingdom; ⁴Centrede Medecine du Sommeil ,Hopital Antoine Beclere, Clamart, France; ⁵Institute for Medical Statistics and Epidemiology, Technical University Munich, Munich, Germany; ⁶Center for Pneumology, Donaustauf Hospital, Donaustauf, Germany

Corresponding Author: Michael Arzt, MD, Center for Sleep Medicine, Department of Internal Medicine II, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany Phone: +49 (941) 944 7281, Fax: +49 (941) 944 7282. e-mail: michael.arzt@ukr.de

Word count text (Introduction-Discussion): 3940

*Michael Arzt and Stephan Schroll contributed equally

ABSTRACT

We tested the hypotheses that in patients with congestive heart failure (CHF) and sleep-disordered breathing (SDB) auto-servo ventilation (ASV) improves cardiac function and quality of life.

Between 3/2007 and 9/2009 patients with stable CHF (left ventricular ejection fraction, LVEF \leq 40%) and SDB (apnea-hypopnea index, AHI \geq 20/h) were randomized to either ASV (BiPAP ASV, Philips Respironics, n=37) and optimal medical management or optimal medical management alone (n=35). Outcomes were assessed at baseline and 12 weeks.

The AHI assessed with polysomnography scored in one core-lab was significantly more reduced in the ASV-group (-39 ± 16 vs. -1 ± 13 /hour, $p<0.001$) with an average use of 4.5 ± 3.0 hours/day. Both groups showed similar improvements of the primary endpoint LVEF ($+3.4\pm 5$ vs. $+3.5\pm 6$ %, $p=0.915$) assessed with echocardiography. In the ASV-group reduction of N-terminal pro brain natriuretic peptide (NT-proBNP) was significantly greater (-360 ± 569 versus $+135\pm 625$ ng/ml, $p=0.010$). No differences were observed between the groups in subjective quality of life.

In patients with CHF and SDB ASV reduced NT-proBNP levels, but improvement of LVEF or quality of life was not greater than in the control group. Data support that such patients can be randomized in large scale long-term trials of PAP therapy versus control to determine effects on cardiovascular outcome.

Wordcount Abstract (\leq 200): 200

Keywords: heart failure, sleep, sleep disordered breathing, cardiovascular function, quality of life

INTRODUCTION

Congestive Heart Failure (CHF) is associated with repeated hospitalizations, high morbidity and mortality [1, 2]. The implementation of poly-pharmaceutical and device therapies has resulted in an improved outcome for the patients [3, 4]. However, symptomatic CHF continues to confer a poor prognosis that is equivalent to some malignancies, with a five-year mortality of 20 to 50% [5]. Thus complimentary, non-pharmaceutical, therapies are needed.

One potential therapeutic target in CHF patients is the treatment of any co-existent sleep-disordered breathing (SDB). Recent estimates suggest that SDB affects 51 to 71% of patients with CHF [6, 7]. The consequences of SDB, such as hypoxia, increased sympathetic drive and cardiac after-load may adversely affect heart function and contribute to the increased morbidity and mortality associated with CHF [8-10]. This increased mortality was not reversible in the largest randomized trial of continuous positive airway pressure (PAP) for patients with central sleep apnea (CSA) and CHF [11]. However, a post-hoc analysis of this trial [12] demonstrated that those with suppression of CSA by continuous PAP had marked improvements in LVEF and transplant-free survival compared to control patients who were not treated with continuous PAP. These data suggest that adequate suppression of SDB may play a key role in improving cardiovascular outcome in such patients.

Auto-servo ventilation (ASV) suppresses CSA better than continuous PAP therapy, in patients with and without coexisting obstructive sleep apnea (OSA) [13, 14]. Randomized trials investigating the short-term effects of ASV on cardiac function in patients with CHF and CSA have been small and their findings inconsistent [13, 15-17], with two out of four not showing a significant improvement of LVEF [15, 16].

However, in the absence of a significant change of LVEF, one trial [16] demonstrated a significant fall of plasma brain natriuretic peptide as a surrogate marker of cardiac function [2, 18].

While CHF patients with SDB and SDB-related symptoms usually improve their daytime hypersomnolence and quality of life on treatment with positive airway pressure support [19], it is unknown, whether SDB should be routinely treated in CHF patients with no or mild SDB-related symptoms. Therefore, we performed a multi-centre randomized, open label with blinded and centralized evaluation of outcomes, parallel group trial to test whether in patients with CHF and SDB with no or mild SDB-related symptoms, additional treatment with ASV improves daytime cardiac function and quality of life (QoL) compared to stable optimal medical management alone.

METHODS

Sample size

The sample size for the primary outcome (LVEF) was calculated using analysis of variance, assuming an improvement in left ventricular ejection fraction of 4.0%, a standard deviation of 5.0 and a drop-out rate of approximately 15%. Based on these assumptions, at a 2-sided alpha of 0.05, with 80% power, approximately 35 subjects per group were required.

Patients

Candidates for participation in the trial included patients aged 18-80 years, with CHF (NYHA Class II-III) due to ischemic, non-ischemic or hypertensive cardiomyopathy, a LVEF \leq 40%, stable clinical status and stable optimal medical therapy according to the guidelines of the European Society of Cardiology [2] for at

least 4 weeks and an apnea-hypopnea index (AHI) ≥ 20 per hour of sleep assessed by in-laboratory polysomnography. Patients were excluded if they had unstable angina, myocardial infarction, cardiac surgery or hospital admissions within the previous 3 months, or they had contraindications for PAP therapy, were using oxygen therapy, had severe pulmonary disease, or symptoms of SDB that required immediate treatment. All patients gave written informed consent to participate in the trial. The protocol was approved by the local ethics boards of each participating center. The trial is registered at <http://www.controlled-trials.com> (ISRCTN04353156).

Screening

Polysomnography was performed using the core equipment available at each of the four participating centres (Regensburg, Germany; Laval, Canada; Clamart, France and Swansea, United Kingdom). Thoraco-abdominal effort and airflow were recorded quantitatively by respiratory inductance plethysmography and nasal pressure cannula [20]. Sleep stages, apneas and hypopneas were measured, defined and scored according to standard diagnostic criteria as described previously [20]. The AHI was defined as the number of apneas and hypopneas per hour of sleep. To ensure quality control a blinded analysis of each sleep study was centralized to two experienced sleep technician.

Echocardiography

Transthoracic echocardiographic was performed according to current recommendations for chamber quantification [21]. LVEF was calculated according to a modification of the Simpson's method (end-diastolic minus end-systolic volume

divided by end-diastolic volume). To ensure quality control a blinded analysis of each echocardiogram was centralized to two experienced analysts.

Randomization

Eligible patients were randomly assigned to either the control group, who continued to receive optimal medical management of heart failure, or the ASV group, who in addition, received ASV therapy (1:1). Randomization was performed by computerized schedule in random blocks of 4 and was stratified by type of SDB (e.g. OSA and CSA). Randomization codes were made available by fax-back request after testing for eligibility for the study.

Initiation of Auto-servo Ventilation

By protocol night time pressure settings had to be in the range of tolerated pressure settings during an attended daytime titration with monitoring of blood pressure and heart rate. During the first night CPAP was titrated under polysomnographic monitoring from 4 cmH₂O in 1 cmH₂O increments to the point where any sign of flow limitation was eliminated, or the maximum level the patient could tolerate (≤ 10 cmH₂O).

Before initiating ASV at night a daytime titration with bilevel PAP was performed in order to avoid long term application of ASV with pressure settings that may lead to hemodynamic compromise. First baseline blood pressure (BP) and heart rate (HR) were recorded as described. Expiratory PAP was set at the optimal CPAP level suppressing upper airway obstruction determined by polysomnography. Inspiratory pressure support (IPS) was titrated starting from 1 cmH₂O and increased by 1 cmH₂O up to the maximum of 10 cmH₂O every 5 minutes after BP and HR

reading was taken. Attended daytime IPS titration was stopped when a pressure of 10 cmH₂O was reached or if mean BP <60mmHg or a drop of >15mmHg occurred or the patient did not tolerate IPS.

At the ASV initiation night the expiratory PAP of the ASV device was set to the continuous PAP determined during the titration night. The minimum inspiratory PAP was set to the expiratory PAP level, and the maximum inspiratory PAP to a maximum of 10 cmH₂O above the expiratory PAP level, or not higher than the maximum the patient could tolerate during the daytime test. The default back-up rate of the machine was used. Assessment of hours of ASV use over this period, were obtained from the downloadable SmartCard located in the device.

Measurement of primary and secondary outcomes

Values from the in-laboratory polysomnography and echocardiography tests, performed during screening, were taken as baseline. The primary outcome of the trial was the change in LVEF within twelve weeks of treatment. All secondary outcome measures were performed at baseline and at 12 weeks after randomisation.

Serum samples were stored at -70°C and analysed using standard techniques for measurement of N-terminal pro brain natriuretic peptide (NT-proBNP) and creatinine in one batch at a central laboratory. Glomerular filtration rate was estimated using the four-variable abbreviated modification of diet in renal disease (4vMDRD) formula.

Two questionnaires were used to assess QoL, the SF-36 as a generic QoL questionnaire [22] and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) as a HF specific questionnaire [23]. For the SF-36, a score of 0 represented worst and 100 best possible health. For the MLHFQ, higher scores

indicated more severe impairment. Fatigue was measured using the Fatigue-Severity-Scale [24]. Higher scores suggest indicated worsening symptoms.

Statistical Analysis

The intention to treat (ITT)-analysis set contained all randomized patients (Figure 1). Patients who had a significant change in cardiac medication as a competing treatment during the period of the trial may influence the results. Therefore, the Per-Protocol (PP)-set was also analyzed. It contained all patients in the ITT set, excluding those who had a change in cardiac medication, prematurely withdrew from the study, or received the wrong treatment allocation (Figure 1).

The primary outcome of the trial, change in LVEF within twelve weeks of treatment, was tested with the two-sided independent samples t-test at the 5% significance level. Statistical tests were performed for the between group differences of the week 12 values (adjusted for possible baseline differences with a linear regression) and the change in value within twelve weeks of treatment (independent samples t-test). Changes throughout the study within one group were assessed with the paired samples t-test. All statistical analyses apart from the primary endpoint were performed in an explorative manner and no multiplicity adjustment of the p-values was performed. All primary and secondary endpoint analyses were first performed on the ITT-population and then repeated on the PP-population. In the ITT-population, the change in LVEF was also analyzed by type of SDB. In the PP-analysis all secondary endpoints were analyzed by type of SDB. All statistical tests were two-sided with significance level of 5%. All statistical analyses were performed with SPSS 18.0.

RESULTS

Trial Flow

A total of 194 patients were screened for eligibility (Figure 1). After excluding the majority of them due to $AHI < 20$ per hour of sleep or $LVEF > 40\%$, 72 patients were randomized to ASV ($n = 37$) and the control group ($n = 35$). All patients received the treatment they were allocated, except for one control patient who was treated with ASV.

The ITT-analysis set consists of all 72 randomized patients in the groups they were randomized (Figure 1). The PP-analysis set contained 21 patients in the ASV and 21 patients in the control group. Reasons for exclusion were early withdrawal, one patient from the control group, who was treated with ASV, as well as cardiovascular medication change, in order to avoid bias from competing therapies.

Patients

Table 1 shows the similarity in the baseline characteristics of the two groups. As expected, the majority of the patients were middle-aged males. The only significant difference was in BMI, which was lower in the ASV group (Table 1). The proportion of patients using cardiac medication is shown in Table 1 and did not change significantly during the follow-up period. Only in one patient from the control group a beta-receptor blocker was added and in 2 patients from the ASV group spironolactone was discontinued. The occurrence of serious adverse events was similar between the groups (Table 2).

Intervention

Bilevel PAP daytime test

When IPS in addition to expiratory PAP (mean 8.1 ± 1.7 cmH₂O) was raised from 0 to 10 cmH₂O, neither systolic, diastolic, mean BP nor mean HR changed significantly with expiratory PAP+IPS ($p=0.93$, $p=0.96$, $p=0.92$ and $p=0.88$, Figure E1). Five patients terminated the bilevel PAP daytime test early due to discomfort because of pressure intolerance. In one patient the mean BP dropped to 58 mmHg at an endexpiratory PAP of 15 cmH₂O plus 8 cmH₂O IPS. Until termination of the daytime test none of the patients experienced symptoms of hemodynamic compromise.

Intention-to-Treat-Analysis

Adaptive Servoventilation Settings and Compliance

Daily device use was 4.5 hours on a mean expiratory PAP of 8.1 ± 1.7 cmH₂O and the maximum inspiratory PAP was set at a mean of 14.0 ± 5.3 cmH₂O. Automatic back-up rate was used in all patients.

Primary Outcome

The change in LVEF, the primary endpoint of the study, was similar in the ASV and control patients with both arms showing a modest improvement (2.8 ± 5.5 vs. $2.3 \pm 6.5\%$, $p = 0.767$, Table 3). The primary endpoint was analyzed according to the four participating study centers in order to rule out center or country bias. In all centers the change in LVEF was similar in the ASV and control patients (Regensburg, Germany: $n= 23$, $p=0.964$; Laval, Canada: $n=31$, $p=0.557$; Clamart, France: $n=7$, $p=0.918$; Swansea, United Kingdom: $n=9$, $p=0.472$).

In the subanalyses of patients with OSA (n=36) and CSA (n=32) the change in LVEF was not significantly different between the ASV and the control group (OSA: 3.0±5.4 vs. 1.8±6.9%; CSA: 2.5±5.8 vs. 3.0±6.2%, p>0.05 for both comparisons).

Secondary Outcomes

In the ASV group AHI and central AHI were significantly more decreased compared to the control group (Table 3). Mean SaO₂ increased significantly in the ASV compared to the control group, respectively (Table 3), indicating that ASV effectively suppressed SDB.

There were statistically non-significant trends for a fall of NT-proBNP and a rise of glomerular filtration rate in the ASV-group compared to the control group (-431 ng/ml, p=0.064 and 5.52 ml/min/1.73m², p=0.076, respectively, Table 3). The changes in all other secondary outcomes including general and disease specific QoL and symptoms were similar between the groups (Table 3).

Per-Protocol-Analysis

Primary outcome

There were moderate improvements between baseline and 3 month values of LVEF in both the ASV and control arms, but the between-group differences were again similar (3.8±5.0 vs. 4.1±6.8%, p=0.915; Figure 2C). In the ASV group the change of AHI between baseline and 12 weeks was not significantly related with changes in LVEF (linear regression analysis R²=0.029, p=0.52).

Secondary Outcomes

There were significant reductions in the AHI, central AHI and a rise in mean SaO₂ on ASV therapy (Figure 2A and 2B). There was a significant decrease in NT-pro BNP in the ASV compared to the control group (-372 ± 581 vs. 142 ± 640 , $p=0.010$; Table E1, Figure 2D). P-values were adjusted for baseline differences. GFR was similar between the groups and showed no statistically significant change over time.

Three of the eight subscores of the SF-36 questionnaire (Social Functioning, Bodily Pain and General Health) improved statistically significant in the ASV compared to the control group ($p =0.011$, $p=0.019$ and $p=0.013$, respectively). The change in the physical and the mental component score of the SF-36 was not different between the ASV and control groups (Figure E2).

A larger reduction of MLHFQ total score was observed in the active treatment group (-8.2 ± 16.4) than in the control group (-1.15 ± 15.0 ; Figure E2). This difference was not statistically significant due to the large variation of the scores. While the Epworth Sleepiness Scale Score remained similar in both the ASV and control group, there was a non-significant reduction of the Fatigue Severity Scale on ASV therapy (Figure E2).

Subanalysis in patients with central and obstructive sleep apnea

Of the PP-population 21 patients had predominantly OSA, of whom 10 were randomized to the ASV and 11 to the control group, respectively, and 21 patients had predominantly CSA, of whom 11 were allocated to the ASV and 11 to the control group. The change of LVEF from baseline to 12 weeks was similar in the ASV and control group in both the OSA and the CSA patients, respectively (OSA: 3.6 ± 3.5 versus 4.6 ± 6.9 %, $p>0.05$; CSA: 3.7 ± 6.3 versus 3.4 ± 7.0 %, $p>0.05$). The effects of

ASV on secondary outcomes in the OSA and CSA patients were similar to the results in the entire PP-population.

Effects of treatment adherence to ASV

For this prespecified analysis, the ASV group was stratified into groups with ≥ 4 and < 4 hours use of the ASV device per night, respectively. The control, ASV use < 4 hours and ASV use ≥ 4 groups had an increasing time of intervention per night (0, 0.56 and 4.76 hours). In association with this increasing time of ASV use, there were stepwise trends towards greater improvements in NT-pro BNP, glomerular filtration rate, the Physical Component Score of the SF-36 questionnaire and the Fatigue-Severity-Scale (Figure 3 A-D).

DISCUSSION

The major findings of this randomized, multi-centre, open label, parallel group trial of ASV therapy in patients with CHF and SDB are, that: (1) ASV effectively suppressed SDB (both CSA and OSA) and adherence to this therapy was satisfactory at 4.5 hours per night; (2) ASV was not associated with an improvement of LVEF, the primary outcome, but was associated with a significant fall of NT-proBNP, as a surrogate for cardiac loading conditions and cardiac function in the PP-analysis; (3) ASV did not influence significantly glomerular filtration rate, general and disease specific QoL, or symptoms of fatigue and sleepiness.

In line with previous studies, ASV proved to be an efficient treatment for co-existing CSA and OSA, in patients with CHF [13-15, 17, 20, 25]. In addition, the observed ASV use of 4.5 hours per night is similar to other short and mid-term ASV trials, where the usage range was 4.2 to 5.2 hours per night [13, 15, 17, 25].

Considering the relatively short sleep duration of CHF patients [26], the adherence levels obtained in this trial could be considered satisfactory.

The present trial was powered to detect significant differences in the primary endpoint LVEF, however, neither the ITT nor the PP analysis showed significantly greater improvement of LVEF in the ASV compared to the control group. In the ASV group the change of AHI between baseline and 12 weeks was not significantly related with changes in LVEF. Thus, the data of the present study support previous trials who did not find a significant effect of ASV on LVEF in CHF patients with SDB [15, 16, 27] compared to control interventions (e.g. optimal medical management alone or other forms of PAP therapy). In contrast, Philippe and co-workers [17] found a significant increase in LVEF of 7% in a small subset of 7 CSA patients treated with ASV. Similarly Hastings et al. [25] observed, in a non-randomized trial of ASV in CHF patients with CSA, an increase in LVEF of 6%. Recently, in a 3 months randomized trial comparing the effects of ASV and CPAP in CHF patients with co-existing CSA and OSA, Kasai and colleagues observed a significant improvement of LVEF in patients using ASV (n=16) compared to CPAP (+9.1 versus +1.9%, respectively) [13]. Sharma and colleagues [36] recently studied the effects of ASV on LVEF compared to a control intervention in a meta-analysis including 6 non-randomized and 4 randomized trials. Including all studies ASV did significantly improve LVEF. However, this result is mainly based on the non-randomized trials, while in randomized trials the effects of ASV on LVEF are modest (<2%) [36]. Study design appears to have an influence on effect size, while no specific characteristics of patients, who may have the greatest improvement of LVEF on ASV could be identified [36].

There was a significant reduction of NT-proBNP in the ASV-group and an increase in the control group. Such effects cannot be explained by changes in pharmacological therapy or renal function in the present study, as these potential confounders did not change significantly. One possibility is that ASV improved cardiac pre-load and afterload, which could lead to a reduction of cardiac morbidity [28]. The observed effect size is similar to the 23% reduction of BNP that was found in a previous randomized-cross-over trial after a 4 week ASV treatment period in CHF patients with CSA [16], but less than it has been observed with cardiac re-synchronisation therapy (42% in association with an increase of LVEF) [29].

One potential reason for the finding that ASV does improve NT-proBNP and does not improve LVEF, compared to the control group could be the time of day blood was drawn (morning) and echocardiography (time of day was not predefined) was performed. When observing studies of CPAP in OSA patients, the greatest effects on blood pressure [30] are present in the morning hours. A similar dissociation of effects of ASV on BNP and LVEF in CHF patients and CSA [16] or CSA with coexisting OSA [27] was observed previously.

In accordance with the findings of Pepperell and colleagues [16] we did not observe significant effects of ASV on general and disease specific quality of life. In contrast, Philippe and colleagues [17] demonstrated an improvement in disease specific quality of life as assessed with the Minnesota Living With Heart Failure questionnaire after 6 months of ASV treatment. However, as in the present study, this effect was not observed at 3 months [17].

As reported in the literature, patients in the present study did not report excessive daytime hypersomnolence at baseline [26, 31-33], thus no significant change of this symptom was observed. However, fatigue was observed at baseline,

as indicated by a FSS score of more than 36 [34], and a non-significant fall was observed after 3 months of ASV therapy, bringing this score back into the normal range. Fatigue has not been evaluated in comparable intervention trials.

This trial has several strengths and limitations. To optimize data quality, polysomnography recordings from all centres were centrally scored by two experienced sleep technicians at the University of Pennsylvania who were blinded to the clinical data of the patients. Most other trials in this field have been single centre [16, 19, 25, 27, 32, 35]. In addition, all patients in the present study were on contemporary cardiac medication [2] which has developed considerably in recent years.

One limitation of the study is that some patients had a competitive therapy during the trial period (change in cardiac medication), such patients had to be excluded in the PP-analysis. E.g. after cardiac worsening (n=3 in ASV-group and n=5 in control-group, respectively) patients received intensified diuretic treatment leading to improvement of cardiac function. Thus, although the present study is to date the largest randomized-controlled trial of ASV in CHF patients with SDB assessing cardiac function, the PP-analysis did not comply with the calculated sample size and the trial therefore lacked the necessary power to reliably address the effects on several of the outcome measures and to perform important subanalyses such as whether effect sizes depend of age or cause of heart failure.

However, a stepwise trend towards greater improvements in glomerular filtration rate, general quality of life (physical component score) and fatigue in the group of patients who complied with ASV therapy, suggest that these outcomes should be re-evaluated in larger trials.

In summary, this trial supports the notion that ASV is an effective treatment for both CSA and OSA in patients with CHF. Despite the lack of SDB-related symptoms in this group of patients, adherence to ASV therapy was satisfactory in most patients. ASV in CHF patients with SDB reduces NT-proBNP levels as a surrogate for improvement of cardiac loading conditions and function. These changes were not associated with greater improvement of LVEF in the ASV compared to the control group. There were no significant improvements in QoL or symptoms. The results support that CHF patients with CSA and OSA with no or mild SDB-related symptoms can be randomized in large scale long-term trials of PAP therapy versus control in order to determine whether PAP therapy can improve cardiovascular outcome in such patients.

Acknowledgments

This work was supported by grant support from Philips Home Healthcare Solutions (Murrysville, PA, USA). The sponsor played no role in design, conduct of the study as well as analysis and interpretation of the data. The sponsor played no role in the preparation, review and approval of the manuscript.

Michael Arzt has received grant support from Philips Home Healthcare Solutions (Murrysville, PA, USA), Resmed (Martinsried, Germany) and the German Foundation for Cardiac Research (Deutsche Stiftung für Herzforschung). Michael Arzt is the holder of an endowed professorship from the Free State of Bavaria at the University of Regensburg that was donated by Philips Home Healthcare Solutions (Murrysville, PA, USA) and Resmed (Martinsried, Germany). Michael Arzt has previously received lecture fees from AstraZeneca, Covidien, Philips Home Healthcare Solutions (Murrysville, PA, USA) and Resmed (Martinsried, Germany). Keir Lewis has received grant support from Pfizer Inc and lecture fees and reimbursement for attending conferences from Pfizer, AstraZeneca and Glaxo-Smith Kline. He has participated in advisory boards for MSD, AstraZeneca and Glaxo-Smith Kline. Frederic Series, Amit Benjamin, Pierre Escourrou, Ruth Luigart and Victoria Kehl have no conflicts of interest to disclose. Michael Arzt and Michael Pfeifer had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003; 289: 194-202.
2. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtern U, Silber S, Tendera M, Widimsky P, Zamorano JL, Auricchio A, Bax J, Bohm M, Corra U, della Bella P, Elliott PM, Follath F, Gheorghide M, Hasin Y, Hernborg A, Jaarsma T, Komajda M, Kornowski R, Piepoli M, Prendergast B, Tavazzi L, Vachiery JL, Verheugt FW, Zannad F. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008; 10: 933-989.
3. Jessup M, Brozena S. Heart failure. *N Engl J Med* 2003; 348: 2007-2018.
4. Cubbon RM, Gale CP, Kearney LC, Schechter CB, Brooksby WP, Nolan J, Fox KA, Rajwani A, Baig W, Groves D, Barlow P, Fisher AC, Batin PD, Kahn MB, Zaman AG, Shah AM, Byrne JA, Lindsay SJ, Sapsford RJ, Wheatcroft SB, Witte KK, Kearney MT. Changing Characteristics and Mode of Death Associated with Chronic

Heart Failure Due to Left Ventricular Systolic Dysfunction: A Study Across Therapeutic Eras. *Circ Heart Fail*. 2011; 4: 396-403

5. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; 347: 1397-1402.

6. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, Roselle GA. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation* 1998; 97: 2154-2159.

7. Schulz R, Blau A, Borgel J, Duchna HW, Fietze I, Koper I, Prenzel R, Schadlich S, Schmitt J, Tasci S, Andreas S. Sleep apnoea in heart failure. *Eur Respir J* 2007; 29: 1201-1205.

8. Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol* 2007; 49: 2028-2034.

9. Jilek C, Krenn M, Sebah D, Obermeier R, Braune A, Kehl V, Schroll S, Montalvan S, Riegger GA, Pfeifer M, Arzt M. Prognostic impact of sleep disordered breathing and its treatment in heart failure: an observational study. *Eur J Heart Fail* 2011; 13: 68-75.

10. Wang H, Parker JD, Newton GE, Floras JS, Mak S, Chiu KL, Ruttanaumpawan P, Tomlinson G, Bradley TD. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol* 2007; 49: 1625-1631.

11. Bradley TD, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Tomlinson G, Floras JS.

Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005; 353: 2025-2033.

12. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Ryan C, Tomlinson G, Bradley TD. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation* 2007; 115: 3173-3180.

13. Kasai T, Usui Y, Yoshioka T, Yanagisawa N, Takata Y, Narui K, Yamaguchi T, Yamashina A, Momomura SI. Effect of flow-triggered adaptive servo-ventilation compared with continuous positive airway pressure in patients with chronic heart failure with coexisting obstructive sleep apnea and Cheyne-Stokes respiration. *Circ Heart Fail* 2010; 3: 140-148.

14. Randerath WJ, Galetke W, Kenter M, Richter K, Schafer T. Combined adaptive servo-ventilation and automatic positive airway pressure (anticyclic modulated ventilation) in co-existing obstructive and central sleep apnea syndrome and periodic breathing. *Sleep Med* 2009; 10: 898-903.

15. Fietze I, Blau A, Glos M, Theres H, Baumann G, Penzel T. Bi-level positive pressure ventilation and adaptive servo ventilation in patients with heart failure and Cheyne-Stokes respiration. *Sleep Med* 2007; 9: 652-659.

16. Pepperell JC, Maskell NA, Jones DR, Langford-Wiley BA, Crosthwaite N, Stradling JR, Davies RJ. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. *Am J Respir Crit Care Med* 2003; 168: 1109-1114.

17. Philippe C, Stoica-Herman M, Drouot X, Raffestin B, Escourrou P, Hittinger L, Michel PL, Rouault S, d'Ortho MP. Compliance with and effectiveness of adaptive servoventilation versus continuous positive airway pressure in the treatment of Cheyne-Stokes respiration in heart failure over a six month period. *Heart* 2006; 92: 337-342.
18. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; 347: 161-167.
19. Mansfield DR, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. *Am J Respir Crit Care Med* 2004; 169: 361-366.
20. Arzt M, Wensel R, Montalvan S, Schichtl T, Schroll S, Budweiser S, Blumberg FC, Riegger GA, Pfeifer M. Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. *Chest* 2008; 134: 61-66.
21. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440-1463.
22. Jenkinson C, Gray A, Doll H, Lawrence K, Keoghane S, Layte R. Evaluation of index and profile measures of health status in a randomized controlled trial.

Comparison of the Medical Outcomes Study 36-Item Short Form Health Survey, EuroQol, and disease specific measures. *Med Care* 1997; 35: 1109-1118.

23. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. *Am Heart J* 1992; 124: 1017-1025.

24. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989; 46: 1121-1123.

25. Hastings PC, Vazir A, Meadows GE, Dayer M, Poole-Wilson PA, McIntyre HF, Morrell MJ, Cowie MR, Simonds AK. Adaptive servo-ventilation in heart failure patients with sleep apnea: a real world study. *Int J Cardiol* 2008; 139: 17-24.

26. Arzt M, Young T, Finn L, Skatrud JB, Ryan CM, Newton GE, Mak S, Parker JD, Floras JS, Bradley TD. Sleepiness and sleep in patients with both systolic heart failure and obstructive sleep apnea. *Arch Intern Med* 2006; 166: 1716-1722.

27. Randerath WJ, Nothofer G, Priegnitz C, Anduleit N, Tremel M, Kehl V, Galetke W. Long-term auto servo-ventilation or constant positive pressure in heart failure and co-existing central with obstructive sleep apnea. *Chest* 2012, Epub ahead of print

28. Richards AM, Nicholls MG, Yandle TG, Frampton C, Espiner EA, Turner JG, Buttmore RC, Lainchbury JG, Elliott JM, Ikram H, Crozier IG, Smyth DW. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. *Circulation* 1998; 97: 1921-1929.

29. Fruhwald FM, Fahrleitner-Pammer A, Berger R, Leyva F, Freemantle N, Erdmann E, Gras D, Kappenberger L, Tavazzi L, Daubert JC, Cleland JG. Early and

sustained effects of cardiac resynchronization therapy on N-terminal pro-B-type natriuretic peptide in patients with moderate to severe heart failure and cardiac dyssynchrony. *Eur Heart J* 2007; 28: 1592-1597.

30. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation* 2003; 107: 68-73.

31. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet* 2009; 373: 82-93.

32. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley TD. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med* 2003; 348: 1233-1241.

33. Redeker NS, Muench U, Zucker MJ, Walsleben J, Gilbert M, Freudenberg R, Chen M, Campbell D, Blank L, Berkowitz R, Adams L, Rapoport DM. Sleep disordered breathing, daytime symptoms, and functional performance in stable heart failure. *Sleep*; 33: 551-560.

34. Taylor RR, Jason LA, Torres A. Fatigue rating scales: an empirical comparison. *Psychol Med* 2000; 30: 849-856.

35. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. *Circulation* 2000; 102: 61-66.

36. Sharma BK, Bakker JP, McSharry DG, Desai AS, Javaheri S, Malhotra A. Adaptive servo-ventilation for treatment of sleep-disordered breathing in heart failure: A systematic review and meta-analysis. Epub ahead of print: <http://www.ncbi.nlm.nih.gov/pubmed/22722232>, Chest 2012.

FIGURE LEGENDS

Figure 1 Trial Flow. EF – Ejection Fraction; AHI – Apnoea Hyperpnoea Index; ITT – Intention to Treat; CV - Cardiovascular; ASV – Auto-Servo Ventilation.

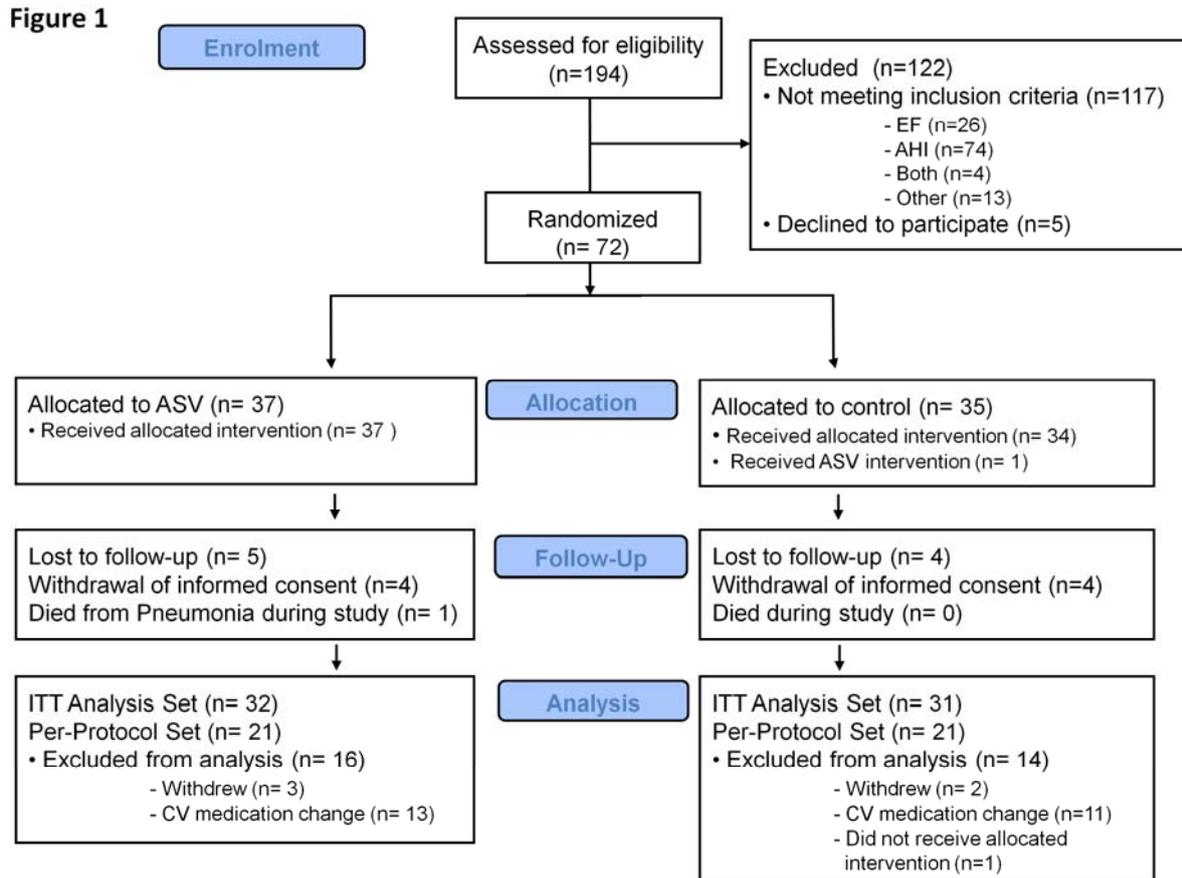


Figure 2 Effects of Auto-Servoventilation on Apnea-Hypopnea Index (A), central Apnea-Hypopnea Index (B), left ventricular ejection fraction (C) and N-terminal pro Brain Natriuretic Peptide (D) in the Per-Protocol data set.

LVEF – Left Ventricular Ejection Fraction; NT-proBNP – N-terminal pro Brain Natriuretic Peptide; ASV – Auto-Servo Ventilation.

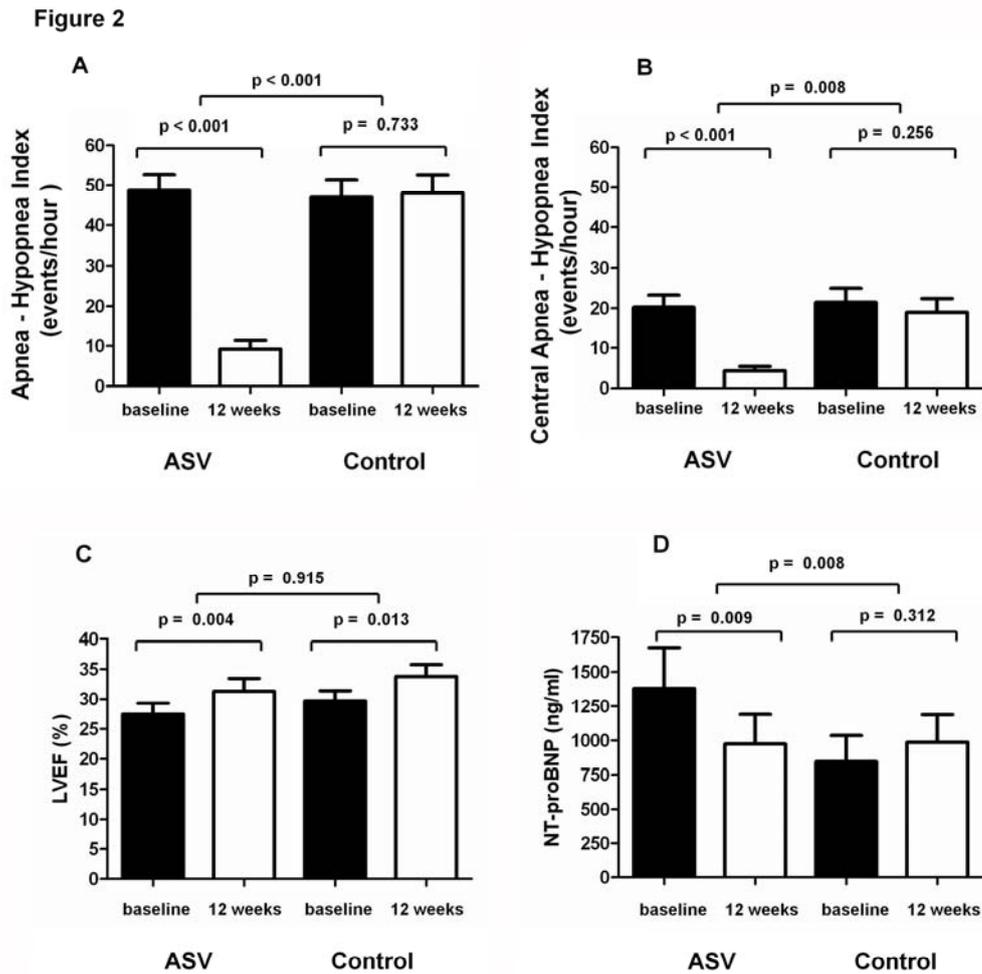


Figure 3 Effects of the duration of Auto-Servoventilation use on changes of outcome measures from baseline to 12 weeks in the Per Protocol data set.

ASV-C – Auto-Servo Ventilation Compliant (defined as ≥ 4 hours device use per night); ASV-NC – Auto-Servo Ventilation Non-Compliant (defined as <4 hours device

use per night); NT-proBNP – N-terminal pro Brain Natriuretic Peptide (A); GFR – Glomerular Filtration Rate (B); SF-36 – Short Form 36 questionnaire (C); FSS – Fatigue Severity Scale (D); CS – Component Score; C – Component.

Figure 3

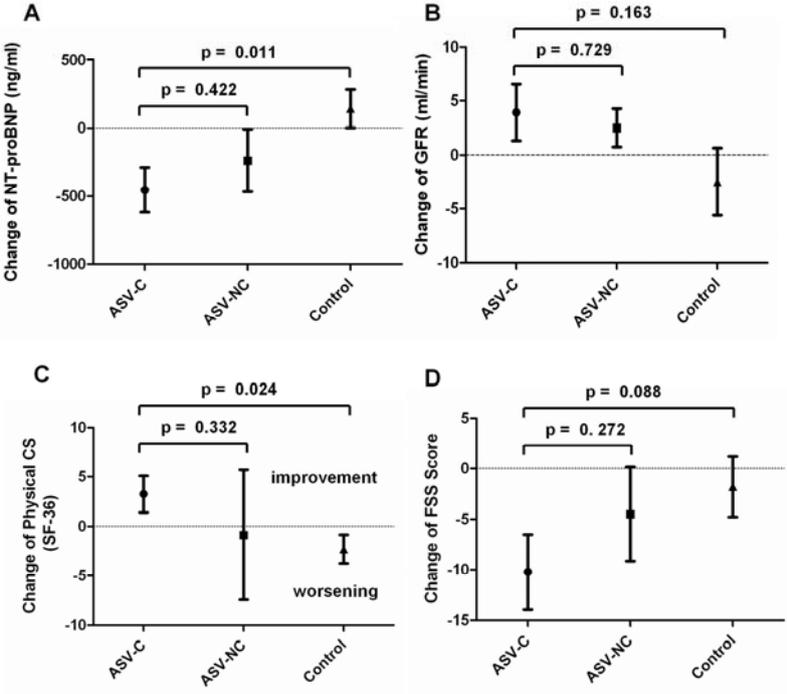


Table 1 Baseline Characteristics

	ASV	Control
n	37	35
Age (years)	64±10	65±9
Male, n (%)	34 (92)	32 (91)
BMI (kg/m ²)*	28.9±4.3	31.6±4.9
Systolic BP (mmHg)	119±15	118±17
Diastolic BP (mmHg)	70±11	70±9
Heart Rate (BPM)	70±11	69±11
NYHA-Class II n (%)	28 (76)	26 (74)
NYHA-Class III n (%)	9 (24)	9 (26)
Cause of Heart Failure		
Ischaemic, n (%)	19 (51)	20 (57)
Non Ischaemic, n (%)	18 (49)	15 (43)
Rhythm & Pacing		
History of Atrial Fibrillation, n (%)	10 (27)	15 (43)
Bi-ventricular Pacemaker, n (%)	3 (8)	6 (17)
Implanted Cardiac Defibrillator, n (%)	16 (43)	17 (49)
Medication		
Diuretic, n (%)	24 (65)	32 (91)
Spironlactone, n (%)	18 (49)	18 (51)
ACE-inhibitor, n (%)	27 (73)	24 (69)
AT-receptor blocker, n (%)	12 (32)	9 (26)
Beta-receptor blocker, n (%)	29 (78)	32 (91)

Data is presented as mean±SD unless otherwise stated. ASV – Auto-Servo Ventilation; n - number; BMI - Body Mass Index; BP – Blood Pressure; NYHA – New York Heart Association; ACE - Angiotensin-Converting Enzyme; AT - Angiotensin. *p=0.017 using an independent samples t-test.

Table 2 Serious adverse events

	ASV	Control
Serious adverse event , n (%)	6 (16)	7 (20)
Cardiac worsening, n (%)	3 (8)	5 (14)
Death during study, n (%)	1 (3) - Pneumonia	0 (0)
Other n (%)	2 (5)	2 (6)
Lung Cancer, n	0	1
DVT/PE, n	1	0
Duodenal Ulcer, n	0	1
Foot Ulcer, n	1	0

Data is presented as n (%). ASV – Auto-Servo Ventilation; n - number; DVT – Deep Vein Thrombosis; PE –Pulmonary Embolism .

Table 3 Outcome Measures – Intention-to-Treat Analysis Set

	ASV		Control		P Value
	Baseline	12 Weeks	Baseline	12 Weeks	
Intervention					
AHI (events/hour)	48 ± 18	11 ±10	47±19	47±22	<0.001
Central AHI (events/hour)	20±16	5±5	19±15	20±15	<0.001
Mean SaO ₂ (%)	93.6±2.3	95.4±1.9	93.5±2.9	93.5±2.6	0.001
Surrogates of Cardiac & Renal Function					
LVEF (%)	29.9±7.2	33.1±8.6	29.4±6.9	31.7±8.9	0.728
NT-pro BNP (ng/ml)	1039±1034	940±1072	1611±2102	1562±1698	0.064
Glomerular Filtration Rate (ml/min/1.73m ²)	65.3±19.1	68.7±20.4	63.2±20.8	63.2±20.8	0.076
General Quality of Life - SF-36					
Physical Component Score	39±10	43±9	40±8	39±10	0.101
Mental Component Score	47±12	47±13	47±12	49±13	0.624
Disease Specific Quality of Life - MLHFQ	32.4±22.8	25.6±22.3	38.2±21.6	33.2±19.9	0.377
Symptoms					
Fatigue Severity Scale Score	42.9±16.9	37.2±17.2	41.2±18.0	37.4±17.2	0.385
Epworth Sleepiness Scale Score	7.5±4.4	8.1±4.2	9.0±5.0	8.4±4.6	0.830

Data is presented as mean±SD. Exclusion was performed per variable. ASV – Auto-Servo Ventilation; AHI - Apnea Hypopnea Index; LVEF – Left Ventricular Ejection Fraction; NT-pro BNP – N Terminal-pro B-type natriuretic peptide; SF-36 – Short Form 36 questionnaire; MLHFQ – Minnesota Living with Heart Failure Questionnaire. P value is for the between group differences, adjusted

for baseline differences using a linear regression. At baseline and 12 weeks all available data from the randomized patients (ASV n=37, Control n=35) and the ITT analysis set (ASV n=32, Control n=31) are shown.