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Paper:

Hetzenecker, A., Escourrou, P., Kuna, S., Series, F., Lewis, K., Birner, C., Pfeifer, M. & Arzt, M. (2015). Treatment of sleep apnea in chronic heart failure patients with auto-servo ventilation improves sleep fragmentation: a randomized controlled trial. *Sleep Medicine*, 17, 25-31.

<http://dx.doi.org/10.1016/j.sleep.2015.08.020>

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Title: Treatment of sleep apnea in chronic heart failure patients with auto-servo ventilation improves sleep fragmentation: a randomized controlled trial

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PII: S1389-9457(15)00924-7
DOI: <http://dx.doi.org/doi: 10.1016/j.sleep.2015.08.020>
Reference: SLEEP 2883

To appear in: *Sleep Medicine*

Received date: 12-3-2015
Revised date: 17-8-2015
Accepted date: 21-8-2015

Please cite this article as: Andrea Hetzenecker, Pierre Escourrou, Samuel T Kuna, Frederic Series, Keir Lewis, Christoph Birner, Michael Pfeifer, Michael Arzt, Treatment of sleep apnea in chronic heart failure patients with auto-servo ventilation improves sleep fragmentation: a randomized controlled trial, *Sleep Medicine* (2015), <http://dx.doi.org/doi: 10.1016/j.sleep.2015.08.020>.

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**Treatment of sleep apnea in chronic heart failure patients with Auto-Servo Ventilation
improves sleep fragmentation:
a randomized controlled trial**

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Short title: Sleep quality in CHF-patients treated with ASV

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1 Highlights

- Treatment of sleep disordered breathing in chronic heart failure patients with auto-servo ventilation (ASV) reduced sleep fragmentation measured by polysomnography.
- Sleep fragmentation and sleep efficiency, measured by actigraphy at home, significantly improved after 12 weeks of ASV therapy.
- The effects of ASV were similar in predominantly central or obstructive sleep apnea.

ABSTRACT

Background: Impaired sleep efficiency is independently associated with worse prognosis in patients with chronic heart failure (CHF). Therefore, we tested whether auto-servo ventilation (ASV, BiPAP-ASV, Philips Respironics) reduces sleep fragmentation and improves sleep efficiency in CHF patients with central sleep apnea (CSA) or obstructive sleep apnea (OSA).

Methods: In this multi-center, randomized, parallel group trial 63 CHF patients (age 64 ± 10 y; left ventricular ejection fraction $29\pm 7\%$) with CSA or OSA (Apnea-Hypopnea Index, AHI $47\pm 18/h$; 46% CSA) referred to sleep laboratories of the four participating centers were studied. Participants were randomized to either ASV ($n=32$) or optimal medical treatment alone (control, $n=31$).

Results: Polysomnography (PSG) and actigraphy at home (home) with centralized blinded scoring were obtained at baseline and 12 weeks. ASV significantly reduced sleep fragmentation (total arousal index_{PSG}: -16.4 ± 20.6 versus $-0.6\pm 13.2/h$, $p=0.001$; sleep fragmentation index_{home}: -7.6 ± 15.6 versus $4.3\pm 13.9/h$, $p=0.003$, respectively) and significantly increased sleep efficiency assessed by actigraphy (SE_{home}) compared to controls (2.3 ± 10.1 versus $-2.1\pm 6.9\%$, $p=0.002$). Effects of ASV on sleep fragmentation and efficiency were similar in patients with OSA and CSA.

Conclusions: In CHF patients with either CSA or OSA, ASV treatment modestly improves sleep fragmentation as well as sleep efficiency at home.

Key words: heart failure, sleep disordered breathing, auto-servo ventilation, sleep quality, NT-pro BNP

Clinical Trial Registration: <http://www.controlled-trials.com/ISRCTN04353156>

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2 INTRODUCTION

Chronic heart failure (CHF) affects 1-2% of the adult population and prevalence increases up to 4-16% in patients over 55 years [1–4]. Central sleep apnea (CSA) and obstructive sleep apnea (OSA) are reported in 25–40% and 49-72% of CHF patients respectively [5–8]. Patients with CHF have a significantly shorter sleep duration and reduced sleep efficiency (SE) assessed by polysomnography (PSG) compared to individuals from a community sample whether or not they have OSA [9]. There are two reasons, why sleep fragmentation and sleep may be important treatment targets in CHF patients with sleep disordered breathing (SDB). First, patients with CHF have poor SE and SE assessed by PSG is a strong predictor for mortality in CHF patients, independent of other known risk factors for mortality [10]. Secondly, high SE early after initiation of continuous positive airway pressure (CPAP) in patients with OSA without known heart disease is an important factor in determining their subsequent use of this treatment modality [11,12].

In patients with CHF, concomitant sleep disorders such as insomnia, periodic limb movement disorder, sleep disturbances either as a consequence of depression or due to the presence of CHF per se are often difficult to manage [13,14]. Therefore, CSA or OSA which can be treated with positive airway pressure (PAP) are promising targets for improving sleep fragmentation and sleep quality in CHF [15].

It remains unclear if treatment of CSA with PAP in patients with CHF can improve sleep fragmentation and sleep quality. In OSA patients with normal cardiac function, PAP-therapy leads to a significant reduction of sleep fragmentation and an increase of the time in sleep stage N3 as well as REM sleep [16]. In CHF patients with sleep apnea, especially with CSA, the effects of PAP therapy on sleep structure are rather unclear. There are only a few randomized studies addressing this issue in patients with CHF and CSA and/or OSA. In the largest trial, a subanalysis of the CANPAP study with 205 HF patients, the effects of CPAP on CSA were determined. Apnea-hypopnea-index (AHI) was significantly reduced, but neither arousal frequency nor sleep structure changed significantly [17]. Studies of auto-servo ventilation (ASV) in CHF patients with CSA and/or OSA report conflicting

effects on sleep fragmentation and sleep quality, assessed by polysomnography. Whilst two studies reported a reduction of arousal frequency and restoration of sleep structure within the first night of ASV treatment in CHF patients with CSA [9,18], another study showed that treatment of CSA with ASV in CHF patients significantly improved CSA and OSA, but had no effect on arousal frequency [19]. In these studies, sleep quality was assessed by PSG in a sleep laboratory when CPAP or ASV were used throughout a single night. This does not reflect the time of use of the PAP device and effects on sleep fragmentation and SE at home over a longer period of time.

We tested if ASV (BiPAP-ASV, Philips Respironics) reduces sleep fragmentation and improves SE as assessed by in-lab PSG and also home actigraphy in patients with severe CSA or OSA.

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3 METHODS

3.1 Design and participants

We analyzed in a multi-center, randomized, rater-blinded, open label, parallel group trial (ISRCTN04353156), the effects of ASV on arousals, sleep efficiency and sleep stages (assessed by PSG) and sleep fragmentation and sleep efficiency (assessed by actigraphy) [20]. Such analyses were not pre-specified. The pre-specified primary and secondary outcomes of the trial (ISRCTN04353156) were previously published [20]. In patients with CHF and SDB, ASV reduced NT-proBNP levels, but improvement of left ventricular ejection fraction (LVEF) or quality of life was not greater than in the control group [20].

The study complies with the Declaration of Helsinki. The protocol was approved by the local ethics committees, and all patients provided written informed consent. Inclusion criteria were a medical history of CHF due to ischemic, non-ischemic or hypertensive cardiomyopathy, age 18-80 years, impaired exercise capacity (New York Heart Association, NYHA, Class II or III), impaired LVEF \leq 40%, stable clinical status, and stable optimal medical therapy according to the guidelines of the European Society of Cardiology [21] for at least 4 weeks and an AHI \geq 20 per hour of sleep assessed by in-laboratory PSG [22,23].

Exclusion Criteria were unstable angina, myocardial infarction, cardiac surgery or hospital admissions within the previous 3 months, NYHA Class I or IV, pregnancy, contraindications for BiPAP AutoSV, patients receiving oxygen therapy, severe restrictive and obstructive airways disease, CHF due to primary valve disease, patients awaiting heart transplant, inability or unwillingness to provide written informed consent, and diurnal symptoms of OSA requiring immediate treatment e.g. falling asleep while driving.

3.2 Randomization and Intervention

Eligible patients were randomized 1:1, either to receive optimal medical management or optimal medical management plus ASV therapy (BiPAP-ASV, Philips Respironics). Randomization was

performed by a computerized schedule in random blocks of four and was stratified by type of sleep apnea (e.g. OSA and CSA) [20]. Details of the initiation of ASV have been described previously [20].

3.3 Outcome measures

3.3.1 Polysomnography (PSG)

PSG was performed at a screening visit, at ASV initiation to ensure abolition of the AHI and after 12 weeks follow up. At follow up patients in the control group received diagnostic PSG, whereas patients in the ASV group received PSG during ASV treatment [20]. Airflow and thoraco-abdominal effort were recorded quantitatively by nasal pressure cannula and respiratory inductance plethysmography [9]. Sleep stages, apneas, hypopneas and arousals were measured, defined and scored by two experienced sleep technicians who were blinded to group status according to standard diagnostic criteria. Apneas were defined as absence of airflow ≥ 10 second (measured reduction of airflow to less than 10% peak 'nominal' airflow). Hypopneas were defined as a $\geq 50\%$ reduction in airflow from baseline for ≥ 10 seconds or with a discernable reduction in airflow, if it was in association with a 4% oxygen desaturation or an arousal. Apneas and Hypopneas had to be classified obstructive if out-of-phase thoraco-abdominal motion or airflow limitations were present. Mixed apneas were classified as central through the study. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. Patients with $\geq 50\%$ of all apneas and hypopneas being central in nature were classified as having CSA. Patients with a proportion $< 50\%$ of central apneas and hypopneas were classified as having OSA. Arousals were defined as a cortical response to stimulus characterized by at least a 3 second increase in EEG frequency: the appearance of alpha or beta rhythm, an obvious change to an ascending sleep stage, in REM sleep as an increase in submental EMG or the appearance of a K-complex, regardless of sleep stage. The arousal was classified as a respiratory arousal, when it occurred during or 1 second after an apnea or hypopnea. The arousal was classified as a movement arousal, when it occurred 1 second before or after the leg movement. Total arousals contained respiratory arousals, movement arousals and spontaneous arousals [24]. For subanalyses of arousals data from one study site were available (n=18). SE assessed by PSG (SE_{PSG}) was defined as the ratio

of total sleep time to time in bed. To ensure quality control, a blinded analysis of each sleep study was centralized and performed by two experienced sleep technicians at the University of Pennsylvania.

3.3.2 Actigraphy

Compared to the “gold standard” polysomnography in sleep laboratory, wrist actigraphy was shown to be a reliable method to evaluate sleep fragmentation and sleep quality in the patients` natural environment at home [25]. The participants were asked to wear an Actiwatch® (Model AW64; Cambridge Neurotechnology Ltd, Cambridge, UK) on their non-dominant wrist for 5 days prior to therapy titration and during the last 7 days of their 12 weeks of therapy. Participants also used the event marker of their Actiwatch® to mark sleep times.

The Actiwatch® measured activity with a piezo-electric accelerometer that recorded intensity, amount and duration of movement in all directions. All movements over 0.05g were recorded with a sampling frequency of 32 Hz. Actigraph data from 1-min epochs were collected and automatic scoring of sleep was performed using a validated algorithm. This algorithm analysed recorded activity counts in each epoch according to the level of activity in the surrounding 2 min (± 2 min) to give a final activity count for each epoch. The total value was used to decide if the epoch was scored as wake or sleep. A threshold of >40 counts/epoch was used to define wake.

Time in bed, sleep latency, SE assessed by actigraphy (SE_{home}) and sleep fragmentation index_{home} were all calculated by the actigraphy sleep–wake algorithm. To ensure quality control, the final blinded analysis of each participant’s actigraphy recording was centralised to one investigator.

3.4 Statistical Analysis

The intention to treat (ITT)-analysis set contained all randomized patients. For all statistical analysis we used the ITT set. Only to analyse the association of the change of SE, sleep fragmentation and the changes in cardiac function (NT-pro BNP) the Per-Protocol (PP)-set was used. In the PP-set, patients

with changes in cardiac medication and patients who prematurely withdrew from the study were excluded [20].

The baseline characteristics were tested with the two-sided independent samples t-test at the 5% significance level. Further statistical tests were performed for the between group differences of the change in value within twelve weeks of treatment using analysis of covariance (ANCOVA) accounting for possible baseline differences. Changes throughout the study within one group were assessed with the paired samples t-test. All statistical analyses were performed with SPSS version 18.0.

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4 RESULTS

4.1 Trial Flow

A total of 194 patients were screened for eligibility as described previously [20]. Most of them were excluded because they did not fulfil the inclusion criteria of $AHI \geq 20$ per hour of sleep or $LVEF \leq 40\%$. 72 patients were randomized, 37 patients to the ASV group and 35 patients to the control group. In the ASV and control groups 5 of 37 patients and 4 of 35 patients were lost to follow-up (11% versus 14%, $p=0.252$), respectively. Therefore, the ITT-analysis set contained 32 patients in the ASV and 31 patients in the control group (Figure 1). The PP-set contained 21 patients in the ASV and 21 patients in the control group.

4.2 Participants

Table 1 shows the baseline characteristics of the ASV and the control group. There was a predominance of males with an average age of 64 years. Body Mass Index (BMI) in the control group was significantly higher than in the ASV group. Resting blood pressure and heart rate, LVEF, NYHA-Classification and NT-pro BNP concentrations, as well as the proportion of ischemic heart failure, were similar.

In the ASV group the EPAP was 8.1 ± 1.5 cmH₂O, the minimum IPAP was 8.7 ± 2.2 cmH₂O and the maximum IPAP was 17.0 ± 2.7 cmH₂O. Average usage of ASV per night was similar during the first night at the sleep lab, the 12 week treatment period “at home” as well as during the follow-up PSG at 12 weeks (4.33 ± 3.25 hours versus 4.45 ± 2.90 hours versus 4.72 ± 3.28 hours, $p=0.751$).

4.3 Polysomnography

Patients in both groups had severe sleep apnea (Table 2). The proportion of CSA was 47% in the ASV and 45% in the control group. There was no significant difference in AHI, cAHI and time in Cheyne Stokes Respiration in the control and the ASV group at baseline ($p=0.572$, $p=0.777$ and $p=0.616$, respectively). After 12 weeks, patients in the ASV group showed a significantly greater reduction of AHI, central AHI and obstructive AHI compared to the control group. The duration of Cheyne Stokes Respiration was significantly reduced with ASV (Table 2). Mean oxygen saturation significantly improved in the ASV group compared to the control group ($p=0.001$). Furthermore the total arousal index was significantly improved in the ASV group compared to the control group (Table 2, Figure 2A). There was no difference in the change in SE_{PSG} between baseline and 12 weeks neither in the ASV group nor in the control group (Table 2, Figure 2B). There was no linear correlation between average ASV usage and changes of total arousal index or SE_{PSG} (Pearson correlation $R=0.313$, $p=0.498$ and $R=0.093$, $p=0.631$, respectively). Even when distinguishing between “compliant” patients (usage of the ASV more than 4 hours per night) and “non-compliant patients” (usage less than 4 hours) there was no significant difference in change of arousal index ($-14/h$ vs. $-19/h$, $p=0.538$) or SE_{PSG} (0.5% vs. -0.9% , $p=0.755$).

Analysis of sleep stages at baseline and after 12 weeks showed a significant reduction of time in sleep stage N1 paralleled by a statistically non-significant increase of sleep stage N2 and REM sleep in the ASV group compared to the control group. The control group had no significant change in the distribution of sleep stages (Table 2, Figure 3).

Changes in PSG parameters in the ASV group were independent of the type of sleep apnea. Patients with OSA ($n=17$) showed similar reductions of total arousal index and SE_{PSG} as patients with CSA ($n=15$, $p=0.792$, $p=0.224$, respectively).

Subanalyses of arousals from one study site showed the effects of ASV on respiratory, movement and spontaneous arousals, respectively. The majority of arousals fulfilled the criteria of respiratory arousals. ASV significantly reduced respiratory arousal index and total arousal index (Table 3).

4.4 Actigraphy

At baseline there were no significant differences between the ASV group and control group in sleep onset latency ($p=0.693$), total sleep time ($p=0.792$), time in bed ($p=0.480$), sleep fragmentation index ($p=0.770$) and SE_{home} ($p=0.372$, Table 4). After 12 weeks, participants randomized to ASV therapy showed a significantly greater reduction of sleep fragmentation index and a significantly better SE_{home} at night than patients in the control group (Table 4, Figure 2). Change of sleep onset latency and total sleep time were similar in both groups (Table 4). The changes of sleep fragmentation and SE_{home} in the ASV group were not associated with changes in the Epworth Sleepiness Scale ($p=0.338$ and $p=0.645$, respectively). There was no linear correlation between average ASV usage and changes of sleep fragmentation or SE_{home} (Pearson correlation $R=0.092$, $p=0.630$ and $R=-0.072$, $p=0.704$, respectively). And there was no significant statistical difference between “compliant” patients and “non-compliant patients” regarding changes of sleep fragmentation ($-8/h$ vs. $-8/h$, $p=0.971$) or SE_{home} (1.7% vs. 3.2%, $p=0.686$).

4.5 NT-pro BNP

NT-pro BNP tended to decrease more in the ASV group compared to the control group ($p=0.062$ after adjustment for baseline differences). The change of NT-pro BNP in the ASV group from baseline to 12 weeks was not associated with the change in AHI neither in the ITT-analysis ($R^2=0.024$) nor in the PP-analysis ($R^2=0.073$). Using the PP-set the change of NT-pro BNP was significantly associated with

changes in surrogates of sleep quality in the home environment such as actigraphically assessed sleep fragmentation index ($R^2=0.395$, $p=0.002$) and SE_{home} ($R^2=0.418$, $p=0.002$).

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5 DISCUSSION

The current subanalysis of the trial “ASV in CHF with sleep SDB - a randomized controlled trial” (ISRCTN04353156) [20] dealt with the effects of ASV on sleep quality and leads to several novel observations. First, CHF patients treated with ASV had a significant decrease of sleep fragmentation compared to the control group, indicated by a reduction of total arousal frequency assessed by PSG. Second, sleep fragmentation and SE, measured by actigraphy at home, also significantly improved after 12 weeks of ASV therapy. Third, the effects of ASV on measures of sleep fragmentation and efficiency assessed by PSG were similar in CHF patients with predominantly CSA or OSA. In a post-hoc analysis, the changes of surrogates of sleep fragmentation and quality in the home environment were significantly associated with an improvement of NT-proBNP concentrations in patients with ASV therapy.

The data of the present analysis have to be interpreted in the light of the preliminary results of the SERVE-HF study [26] (ISRCTN19572887), a multinational, multi-center, randomized controlled trial designed to assess whether treatment of predominantly CSA with ASV therapy reduces mortality and morbidity in patients with CHF. The preliminary primary results showed a statistically significant 2.5 percent absolute increased annual risk of cardiovascular mortality for those randomized to ASV therapy compared to the control group [27,28]. Mechanism explaining this unexpected result remain unclear. Malhotra et al remark in their comment that the new results should not be seen as a disappointment, they strongly support further investigation in this area [29].

In our study, treatment of sleep apnea in CHF patients with ASV reduced total arousal frequency by approximately 39%, while there was no change in the control group. This magnitude of improvement is similar to other randomized trials [30,31]. Randerath et al showed in a long term study of ASV in patients with CHF and coexisting CSA and OSA a reduction of arousal frequency of 35% after 12 month ASV treatment [30]. Yoshihisa et al, also found a reduction of arousal frequency of 37% in patients with CHF and CSA treated with ASV [31].

In our study, SE measured by PSG did not change after 3 month of ASV treatment. There are no other randomized trials of ASV evaluating its effects on SE after more than one night of treatment. Arzt and Teschler observed an improvement of SE after treatment of severe CSA in 14 CHF patients with ASV [9,18]; while other studies showed no significant change in SE [32,33]. In the ASV group, there was a decrease of sleep stage N1 and a shift to sleep stage N2 and REM sleep after 12 weeks, while there was no significant change in sleep stages in the control group. This is consistent with other studies evaluating ASV treatment in CHF patients with CSA. Most of them reported a decrease of sleep stage N1 and N2, as well as an increase of sleep stage N3 and REM sleep [9,18,30,31,34].

The results of actigraphy at home showed a significant improvement of sleep fragmentation in the ASV group compared to the control group. This is in line with our overnight laboratory PSG findings, where a significant decrease of total arousal frequency in the ASV group was observed. Those receiving ASV therapy had no changes in SE as measured by PSG, whereas wrist actigraphy showed a significant improvement of SE after 12 weeks may be due to discrepancy between the 2 measuring devices.

Studies in patients with OSA without overt heart disease showed that wrist actigraphy has a high agreement with PSG results [28,35], although a few studies report an overestimation of TST and therefore SE in actigraphy [36]. Laboratory PSG measures only one night of sleep and in an artificial environment whereas less intrusive actigraphy, measures sleep over several days/nights and in the patient's home. The changes in sleep quality in the ASV group were not associated with changes in the Epworth sleepiness scale. This may be due to the fact, that both groups had no excessive sleepiness at baseline, as prescribed previously [23].

Until now, there are no studies comparing the effects of ASV treatment in CHF patients with either CSA or OSA. In our study 15 patients in the ASV group had OSA while 14 patients had predominantly CSA. The improvements with ASV in CHF patients on sleep fragmentation and SE were similar in those with predominantly CSA or OSA. Regardless of the type of sleep apnea the reduction in arousal frequency on ASV treatment in our participants was less than that reported in studies of PAP therapy in patients without cardiac disease. In contrast to OSA patients without cardiac

disease [16,37] PAP or ASV treatment does not normalize sleep architecture, e.g. slow wave sleep remains significantly reduced. Therefore other factors may contribute to reduced sleep quality in CHF patients, such as medication side effects (e.g. beta blockers), pulmonary congestion or higher rates of concomitant comorbidities including periodic leg movement disorder, insomnia or depression [13,14,38].

Consistent with other randomized trials of ASV in CHF patients with SDB, we showed a greater reduction of NT-proBNP compared to the control intervention [9,30,39,40]. Using the PP-set, in the ASV group the reduction of NT-proBNP was significantly associated with a reduction of sleep fragmentation and an increase of SE assessed with actigraphy.

Patients in the control group had a significantly higher BMI and higher use of diuretics than patients in the ASV group. In the context of findings that nocturnal rostral fluid can contribute to the pathogenesis of both OSA and central sleep apnea [41] in patients with heart failure by accumulation in the neck or in the lungs, respectively, this difference may have an influence on the severity and type of SDB. However, in the present study the AHI, the central AHI as well as the time in Cheyne Stokes Respiration were similar between groups.

6 CONCLUSIONS

In summary, we showed that ASV therapy in patients with CHF and severe CSA or OSA can reduce sleep fragmentation and may improve sleep quality. The effects of ASV on sleep fragmentation and sleep quality are modest. Whether such effects translate in improved subjective sleep quality and quality of life, merits further investigation.

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Acknowledgements

The authors thank Ruth Luigart and Astrid Braune for excellent technical assistance.

Guarantor statement

Michael Arzt takes responsibility for the content of the manuscript, including the data and analysis.

Authors Contributions

Michael Arzt, Michael Pfeifer, Pierre Escourrou, Keir Lewis and Frederic Series were involved in the conception, hypotheses delineation, and design of the study, acquisition of the data, the analysis and interpretation of such information, writing the article and in its revision prior to submission.

Samuel T Kuna was substantially involved in analysis of the data, interpretation of such information, and in critical revision of the article.

Andrea Hetzenecker and Christoph Birner were substantially involved in the interpretation of the data, writing the article and in its revision prior to submission.

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Figure 1. Flow chart. Abbreviations: CV - Cardiovascular; ASV – Auto-Servo Ventilation. *Figure 1.5 column fitting*

Figure 2. Effects of Auto-Servo Ventilation (ASV) in patients with CHF and severe CSA or OSA on sleep fragmentation and sleep efficiency (SE). (a) ASV (white) significantly reduced the total arousal index assessed by PSG (Arousal Index_{PSG}) and the sleep fragmentation index assessed by actigraphy at home (Sleep Fragmentation Index_{home}) compared to the control group (black). (b) While ASV had no significant effect on SE assessed by PSG, ASV significantly increased SE assessed at home by actigraphy compared to the control group. *Each figure single column fitting.*

Figure 3. Percent changes in the distribution of sleep stage in the control group (black) and the ASV-group (white). In the control group the distribution of sleep stages remained similar after 12 weeks. In the ASV group there was a significant reduction of sleep stage 1 (N1) and a redistribution to sleep stage N2 and rapid eye movement sleep (REM) was observed. Abbreviations: N1= sleep stage N1, N2=sleep stage N2, N3=sleep stage N3, REM=rapid eye movement sleep. *Figure 1.5 column fitting*

Table 1 Baseline Characteristics

	Control N=31	ASV N=32	p-value
Age, years	65±9	64±10	0.636
Male, n (%)	28 (90)	30 (94)	0.615
BMI, kg/m ²	32±5	29±4	0.026
Glomerular Filtration Rate, ml/min/1.73m ²	68±22	67±19	0.859
NT-pro BNP, ng/ml	1259±1430	1050±1084	0.517
Left ventricular ejection fraction, %	29±6	29±7	0.971
NYHA-Class II, n (%)	25 (81)	24 (75)	0.590
NYHA-Class III, n (%)	6 (19)	8(25)	
Cause of Heart Failure			0.163
Ischaemic, n (%)	19 (61)	16 (50)	
Idiopathic, n (%)	10 (32)	16 (50)	
Hypertensive, n (%)	2 (7)	0 (0)	
Rhythm & Pacing			0.277
History of Atrial Fibrillation, n (%)	6 (19)	6 (19)	
Bi-ventricular Pacemaker, n (%)	5 (16)	2 (6)	
Implanted Cardiac Defibrillator, n (%)	15 (48)	16 (50)	0.898
Medication			0.010
Loop diuretic, n (%)	28 (90)	20 (63)	
Spironolactone, n (%)	15 (48)	16 (50)	
ACE-inhibitor, n (%)	20 (65)	24 (75)	
AT-receptor blocker, n (%)	9 (29)	10 (31)	
Beta-receptor blocker, n (%)	28 (90)	25 (78)	0.185

Data are presented as mean±SD unless otherwise stated. ASV – Auto-Servo Ventilation; n - number;

BMI - Body Mass Index; NT-pro BNP – N Terminal-pro B-type natriuretic peptide, NYHA – New

York Heart Association; ACE - Angiotensin-Converting Enzyme; AT - Angiotensin.

Table 2 Outcome measures polysomnography

	Control N=31	ASV N=32	ANCOVA

Polysomnography	baseline	12 weeks	p-value	baseline	12 weeks	p-value	p-value*
Sleep onset latency (min)	21±19	18±17	0.353	18±16	13±11	0.132	0.244
Time In Bed (min)	474±53	474±41	0.937	464±39	460±60	0.701	0.427
Total Sleep Time (TST, min)	327±92	327±78	0.998	376±59	374±77	0.907	0.711
Apnea-Hypopnea Index (AHI, /h)	46±19	47±22	0.814	50±18	10±10	< 0.001	< 0.001
Central AHI (/h)	19±15	20±15	0.651	21±16	5±5	< 0.001	< 0.001
Cheyne Stokes Respiration (min)	62±51	60±58	0.702	74±77	16±18	< 0.001	< 0.001
Total Arousal Index (/h)	41±17	41±20	0.824	45±16	29±18	< 0.001	0.002
Sleep efficiency (%)	68±15	69±15	0.823	74±10	75±12	0.933	0.687
Sleep Stage N1 (% TST)	21±16	23±20	0.337	23±13	14±8	0.001	0.002
Sleep Stage N2 (% TST)	65±13	63±17	0.671	62±12	69±9	0.016	0.058
Sleep Stage N3 (% TST)	3±6	2±6	0.323	0.3±0.8	0.9±3.3	0.306	0.502
Rapid Eye Movement Sleep (REM, % TST)	12±9	11±8	0.696	15±6	16±8	0.273	0.057

Data is presented as mean±SD. *P-value for the between group differences, adjusted for baseline differences using analysis of covariance (ANCOVA)

Table 3 Effect of ASV on arousals from sleep*

	Control N=10			ASV N=8			ANCOVA
Polysomnography	baseline	12 weeks	p-value	baseline	12 weeks	p-value	p-value[†]
Respiratory Arousal Index (/h)	28±14	27±23	0.825	35±13	6±7	<0.001	0.001
Movement Arousals Index (/h)	0.3±0.6	0.4±0.5	0.891	2±5	5±7	0.308	0.143
Spontaneous Arousals Index (/h)	14±5	17±9	0.299	12±7	16±5	0.193	0.752
Total Arousals Index (/h)	42±13	45±26	0.705	50±16	26±14	0.001	0.013

*Classification of arousals in respiratory, movement and spontaneous arousals were available from one study site (n=18).

[†]P-value for the between group differences, adjusted for baseline differences using analysis of covariance (ANCOVA).

Table 4 Outcome measures actigraphy

	Control N=31	ASV N=32	ANCOVA

Actigraphy	baseline	12 weeks	p-value	baseline	12 weeks	p-value	p-value*
Sleep Latency (min)	32±33	39±40	0.092	29±28	26±18	0.606	0.080
Time In Bed (min)	527±68	539±74	0.139	522±78	510±78	0.281	0.053
Total Sleep Time (min)	372±57	368±60	0.651	390±84	393±67	0.844	0.265
Sleep Fragmentation Index (/h)	46±15	50±19	0.104	46±21	38±14	0.012	0.001
Sleep Efficiency (%)	71±10	69±11	0.118	75±12	77±9	0.211	0.005

Data are presented as mean±SD. *P-value for the between group differences, adjusted for baseline differences using analysis of covariance (ANCOVA)

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