# Mortality and Compliance

# in Adaptive Servo-Ventilation Treatment for patients with Sleep Apnea

Syventävä opinnäytetyö

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Tämän opinnäytteen alkuperäisyys on tarkastettu Turnitin OriginalityCheck-ohjelmalla Tampereen yliopiston laatujärjestelmän mukaisesti.

## Tausta

Unenaikaiset hengityshäiriöt ovat yleisiä sydämen vajaatoimintaa sairastavilla potilailla (1) ja jopa 70 prosentilla sydämen vajaatoiminta –potilaista on joko obstruktiivinen tai sentraalinen uniapnea (2-5). Sentraalisen uniapean esiintyvyys on alle prosentti terveessä väestössä (1), mutta sydämen vajaatoimintaa sairastavilla potilailla se on yleinen sairaus ja jopa 50 prosentilla näistä potilaista todetaan sentraalinen uniapnea (1,3,6). Sentraalisen uniapnean syytä ei tarkkaan tunneta, mutta sen on ajateltu johtuvan lähinnä erityisesti sydämen vajaatoiminnassa esiintyvästä elimistön lisääntyneestä reaktiosta hiilidioksidin osapaineelle verenkierrossa sekä verenkierron muutoksista alentuneeseen sydämen minuuttitilavuuteen liittyen. (1,2,5-9)

Adaptiivinen servo-ventilaatio (ASV) on ei-invasiivinen ventilaatiohoito, joka on suunniteltu hoitamaan sekä obstruktiivista uniapneaa jatkuvalla positiivisella painetuella, että sentraalista uniapneaa vaihtelevalla hengityksen painetuella (2,3,6,9,10). SERVE-HF –tutkimus (11) oli ensimmäinen laaja monikansallinen tutkimus, joka tutki ASV-hoidon etuja sydämen vajaatoimintaa sekä sentraalista uniapneaa sairastavilla potilailla. Keväällä 2015 julkaistujen tutkimustulosten mukaan ASV-hoito lisäsi kuolleisuutta tässä potilasryhmässä potilailla, joilla sydämen vasemman kammion ejektiofraktio (LVEF) oli alle 45%.

Tampereen yliopistollisen sairaalan uniyksikkö on hoitanut kaiken kaikkiaan 50 potilasta ASV-hoidolla. Tätä potilasryhmää ja hoidon etuja ei ole aiemmin tutkittu Tampereen yliopistossa. Suunnittelimme ja toteutimme retrospektiivisen tutkimuksen real life –tutkimusasetelmassa näistä 50 hoitoa saaneesta potilaasta. Tutkimme ASV-hoidon etuja, hoidon aloittamisen indikaatioita sekä hoitoa saanutta potilasryhmää.

**Metodit**

Kävimme läpi kaikki Tampereen yliopistollisen sairaalan uniyksiköstä vuosina 2002 – 2016 ASV-hoitoa saaneiden potilaiden potilaskertomukset ja keräsimme tiedot potilaiden demografiikasta, ASV-hoidon aloituksen indikaatioista, lopettamisen syistä, hoitomyöntyvyydestä, hoidon onnistumisesta ja kuolleisuudesta seuranta-aikana.

**Tulokset**

Pää-indikaatio ASV-hoidon aloittamiselle oli sekamuotoinen obstruktiivinen ja sentraalinen uniapnea. Hoitomyöntyvyys oli hyvä; keskimääräinen käyttöaika yössä oli lähes kuusi tuntia ja yli 65 prosenttia potilasta oli tyytyväisiä hoitoon. Yli 61 prosentilla potilaista oli sydämen vajaatoiminta ja näillä potilailla EF alentui lievästi lähes kuuden vuoden seuranta-aikana (50.9% seurannan alussa, 46.1% viimeisin tulos seurannan aikana, P = 0,25). Unen laatu parani lievästi ja päivänaikainen väsymys lievittyi Epworth Sleepiness Scale –kyselyllä mitattuna (ESS, 8.1 pistettä alussa, 6.7 pistettä viimeisin mittaus seurannan aikana, P = 0.036). Apnea-hypokapnea-indeksi parani huomattavasti ja merkitsevästi ASV-hoidolla (49.6 ennen hoitoa, 4.9 viimeisin mittaus hoidon aikana, P = .000). Kuolleisuus oli 8 prosenttia lähes kuuden vuoden seuranta-aikana.

**Johtopäätös**

Real life –tutkimusasetelmassa sydämen vajaatoimintaa ja sentraalista uniapneaa sairastavilla potilailla, joilla EF oli vähintään 45%, ASV-hoito näyttää parantavan apnea-hypokapnea-indeksiä, parantavan unenlaatua sekä vähentävän päivänaikaista väsymystä. Hoitomyöntyvyys on hyvä ja kuolleisuus matala.

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# Mortality and Compliance

# in Adaptive Servo-Ventilation Treatment for patients with Sleep Apnea

A Real Life Retrospective Study

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MK Pelkonen conducted data collection and prepared the manuscript. All the authors contributed to literature search, study design, analysis of data and review of the manuscript.

The study was conducted at Sleep Unit of the Department of Respiratory Medicine, Tampere University Hospital, Tampere, Finland. The results have not been presented previously. The authors have no conflicts of interest.

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**ABSTRACT**

**Introduction.** Adaptive servo-ventilation (ASV) is designed to treat both obstructive sleep apnea (OSA) with continuous pressure support and central sleep apnea (CSA) with varying inspiratory pressure support. A recent multinational trial to study the benefits of ASV treatment in subjects with heart failure (HF) and CSA showed increased mortality with ASV treatment in subjects with ejection fraction (EF) ≤ 45%. Our aim was to conduct a real-life retrospective analysis on the benefits, compliance and mortality among subjects with CSA treated with ASV where the treatment had been discontinued in subjects with EF < 45 %.

**Methods.** Medical records of all 50 subjects treated with ASV in Tampere University Hospital Sleep Unit during years 2002 - 2016 were reviewed and data of subject characteristics, ASV-treatment details and outcomes were collected.

**Results.** Main reason for prescribing ASV-treatment was OSA-CSA. Compliance for treatment was good. Over 61% of the subjects had HF and for those there was a slight but not significant impairment in EF (50.9 to 46.1, P = 0,25) during almost six years of follow up. There was a mild improvement in quality of sleep and daytime fatigue measured with the Epworth Sleepiness Scale (ESS, 8.1 to 6.7, P = 0.036). Apnea - hypocapnea (AH) -index improved extensively and significantly with ASV treatment (49.6 to 4.9, P = .000). Mortality was 8% during almost six years follow up.

**Conclusion.** In a real life setting in subjects with HF and CSA-CSR with an EF of at least 45% ASV treatment seems to be improving AHI, quality of sleep and decreasing daytime fatigue. The compliance for treatment is good and mortality is low.

**Keywords**

Sleep Apnea, Central Sleep Apnea, Heart Failure, Noninvasive Ventilation, Adaptive Servo-Ventilation, Mortality, Compliance

## Introduction

Sleep disordered breathing (SDB) is a common syndrome in patients with heart failure (HF) (1) and even up to 70 % of the HF patients have either obstructive sleep apnea (OSA) or central sleep apnea – Cheyne–Stokes respiration (CSA-CSR) (2-5). The incidence of CSA-CSR is under 1% in healthy population (1), but amongst HF patients with more severe disease (NYHA III-IV) CSA-CSR is a common condition with 21 - 50% suffering from it (1,3,6). HF itself can cause similar symptoms as SDB (2,5,6), but there is also a hypothesis that CSA-CSR might even be a compensatory mechanism in severe HF (7-9). The severity of HF correlates to the severity of CSA-CSR, but on the other hand CSA-CSR accelerates the progression of HF, decreases the time to heart transplantation, and increases mortality (5,6,8,9). CSA-CSR and OSA are conditions highly underdiagnosed among patients with HF (2,5,6). The presence of SDB with HF is associated with worsened prognosis and increased mortality (10).

The pathophysiology causing CSA-CSR is still somewhat unknown. It seems to be mainly caused by the body's increased reaction to partial pressure of $CO_2$ and changes in circulation because of decreased cardiac output in HF. Lung to brain circulatory delay is prolonged in HF and the chemical regulation, caused by the partial pressure of $CO_2$ in blood affecting the baroreceptors in chest and brain, is secondarily delayed. The partial pressure of carbon dioxide may fluctuate during sleep. In HF the increased sympathetic activity is responsible for the increased sensitivity of chemoreceptors to $PaCO_2$. In this case the negative-feedback system, that controls breathing, elicits a large ventilatory response when the partial pressure of carbon dioxide rises. The consequent hyperventilation drives the partial pressure of carbon dioxide below the apneic threshold resulting in central apnea. As a result of the apnea, the partial pressure of carbon dioxide rises again, which leads to an increased ventilation. In this way cycles of central apnea and hyperventilation recur during sleep. (1-3,5-7,9)

The treatment of SDB in patients with HF has been shown to increase the time to heart transplantation and improve NYHA functional class (11) but the treatment of CSA-CSR is still controversial. Since CSA-CSR is a result of HF or even compensatory to it, the optimal treatment of HF is essential in treating CSA-CSR (12). Adaptive servo-ventilation (ASV) is a non-invasive ventilation therapy designed mainly to treat CSA-CSR

(9). ASV delivers a baseline continuous positive airway pressure and variable increase in inspiratory pressure. ASV devices are equipped with sensors that can detect central apneas and the algorithm used by these machines assesses the amplitude and frequency in airflow and compares these with the target values determined to match the patient's minute ventilation during stable breathing. The goal of ASV therapy is to break the periodic breathing cycle. (2,3,6,9,13) Multiple studies have suggested ASV as a beneficial treatment for symptoms of CSA-CSR, but none have proved it to be curative. Studies show improvements in quality of life, EF, oxygen uptake, 6-min walking distance –test, AHI-index, sleep fragmentation and sleep efficiency. ASV has been shown to moderate the sympathetic adrenergic tone by decreasing natriuretic peptide concentration, urinary metadrenaline excretion and ventricular premature complexes. There are results in decreasing daytime sleepiness and heart failure symptoms, reducing hospital admissions and increasing oxygen saturation. (10,14-24)

The SERVE-HF trial (25), sponsored by ResMed, was the first large multinational trial to study the benefits of ASV treatment. After a 12-months follow-up the results showed that all-cause and cardiovascular mortality were both increased with this therapy. ASV had no significant effect on the primary end point (death from any cause, lifesaving cardiovascular intervention e.g. cardiac transplantation, resuscitation after sudden cardiac arrest, unplanned hospitalization for worsening HF) in subjects who had HF with reduced EF and predominantly CSA. After the SERVE-HF report several institutes cancelled trials studying ASV in treating CSA-CSR. A Field Safety Notice (26) was issued by ResMed in 2015 stating that ASV therapy is contraindicated with HF patients with a reduced EF. A secondary multistate modelling analysis of SERVE-HF data (8) showed an increased risk of both cardiovascular death without previous hospital admission and cardiovascular death after a life-saving event in the group receiving ASV versus the control group. Updated Adaptive Servo-Ventilation Recommendations for the 2012 AASM Guideline were released based on meta-analyses in May 2016 (27). A Standard level recommendation against the use of ASV to treat subjects suffering from congestive HF and CSA-CSR with a EF of $\leq 45\%$ was suggested.

Tampere University Hospital Sleep Unit has been treating a total of 50 subjects with Adaptive Servo-Ventilators. After the Field Safety Notice and the new AASM recommendations were released a cardiologist

was consulted with all the subjects suffering from HF and treated with ASV in Tampere University Hospital. ASV-treatment was discontinued and replaced with more suitable treatment such as CPAP with subjects suffering from severe HF (EF ≤ 45%). So far the subjects using and the benefits of ASV-treatment have not been studied in Tampere University Hospital. A retrospective study of the 50 subjects using or having used the ASV-treatment was conducted to describe the indications for prescribing ASV treatment and the subject group using this treatment, and to evaluate the benefits of ASV in treating CSA-CSR and HF.

## Methods

A retrospective study of all the subjects using or having used the ASV-treatment (BiPAP AutoSV Philips Respironics, © Murrysville Pennsylvania U.S. or AutoSet CS-A Resmed, © Resmed Australia) in Tampere University Hospital Sleep Unit was conducted. Medical records of all 50 subjects treated with ASV during years 2002 - 2016 were reviewed. The study was approved by the ethics committee of Tampere University Hospital. The basic demographics and comorbidities of the subjects were collected from the medical records. A starting date and a reason for initiating ASV-treatment and possible end date with a reason for ending ASV-treatment were recorded. Compliance for the treatment was studied with analyzing the length of ASV treatment, nightly hours of using the ventilator and also personal experience of satisfaction with the treatment. The benefits of ASV treatment considering the quality of sleep and daytime fatigue were studied with obtaining the result of Epworth Sleepiness Scale (ESS) (28) questionnaire before ASV-treatment and latest result during treatment. Information of AH-index before treatment, during possible CPAP treatment before ASV-treatment and during ASV-treatment was obtained to study the effects of the treatment for decreasing central apneas and breaking the crescendo-cycle of breathing. The results are presented as mean (SD) or n (%) where appropriate.

Statistical analyses of the data were done using the SPSS V23.0 software package (SPSS Inc.). Differences in parameters before and during treatment considering the efficiency of ASV-treatment were analyzed using the Related-Samples Wilcoxon Signed Rank Test. p Value of $< 0.05$ was considered significant.

## Results

Altogether 50 subjects had been treated with ASV. One subject was excluded from the analysis due to insufficient medical record data. Most of the ASV-treated subjects were male, elderly and obese (Table 1). Over 61% of the subjects had HF, atrial fibrillation or atrial hypertension and over 30% had type II diabetes or coronary arterial disease.

Details of ASV-treatment are presented in Table 2. Main reason for prescribing the treatment was OSA-CSA and almost 70% of the subjects were treated with a trial of CPAP-treatment before ASV-treatment. The mean duration of follow-up was almost six years. Compliance for treatment was good: mean nightly use was almost six hours and over 65 percent of the subjects were satisfied with the treatment. ASV-treatment was discontinued during follow up most frequently because of no compliance to treatment or HF. Mortality during study was as low as 8.2%.

The outcome measures related to ASV-treatment are presented in Table 3. AHI was quite high before any treatment (49.6/h) and there was a significant but only partial alleviation in those subjects who had been treated with a trial of CPAP (28.0/h). However, after treatment with ASV there was an even more profound decrease in AHI to normal level. The improvement in ESS-points before treatment and latest results during follow up was mild but statistically significant (P = 0.04, Wilcoxon test). The impairment in EF in patients with HF from before treatment to latest result during follow up was not significant (P = 0,25, Wilcoxon test).

**TABLE 1 SUBJECT CHARACTERISTICS OF THE 49 PATIENTS INCLUDED**

| | mean (sd) | n (%) | Data available n (%) |
|---|---|---|---|
| **MALES/FEMALES** | | 42 (85.7) / 7 (14.3) | 49 (100) |
| **AGE** | 67.1 years (12.7) | | 49 (100.0) |
| **BMI** | 32.1 (5.6) | | 47 (96) |
| **CURRENT SMOKERS** | | 8 (16.3) | |
| **FORMER SMOKERS** | | 10 (20.4) | |
| **NO MENTION OF SMOKING IN PATIENT RECORDS** | | 31 (63.3) | |
| **PACK YEARS AMONGST CURRENT AND EX SMOKERS** | 23.5 years (15.9) | | 15 (30.6) |
| **COMORBIDIES** | | | |
| HEART FAILURE | | 30 (61.2) | |
| ATRIAL FIBRILLATION | | 28 (57.1) | |
| STROKE | | 9 (18.4) | |
| DIABETES MELLITUS TYPE II | | 15 (30.6) | |
| CORONARY ARTERY DISEASE | | 15 (30.6) | |
| ARTERIAL HYPERTENSION | | 29 (59.2) | |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | 3 (6.1) | |
| ASTHMA | | 3 (6.1) | |

**TABLE 2 DETAILS OF ASV-TREATMENT**

| | mean (sd) | N, total = 49 (%) | Data aivailable, n (%) |
|---|---|---|---|
| **DURATION OF FOLLOW UP** | 5.9 years (16.2) | | 49 (100.0) |
| **REASON FOR TREATMENT** | | | 49 (100.0) |
| OSA-CSA | | 39 (79.6) | |
| CSA | | 5 (10.2) | |
| OSA | | 3 (6.1) | |
| OTHER SLEEPING DISORDER | | 2 (4.1) | |
| **CPAP-TREATMENT BEFORE ASV-TREATMENT** | | 34 (69.4) | |
| **NIGHTLY USE** | 5.8 hours (2.0) | | 39 (79.6) |
| **SUBJECTIVE EXPERIENCE OF TREATMENT:** | | | 45 (76) |
| SATISFIED | | 33 (67.3) | |
| DISSATISFIED | | 9 (18.4) | |
| NO DIFFERENCE | | 3 (6.1) | |
| **ASV-TREATMENT DISCONTINUED DURING FOLLOW UP** | | 15 (30.6) | |
| **REASON FOR TREATMENT DISCONTINUATION:** | | | |
| NO COMPLIANCE | | 5 (10.2) | |
| HEART FAILURE | | 4 (8.2) | |
| NO NEED TO TREAT | | 2 (4.1) | |
| NO EFFECT | | 1 (2.0) | |
| **MORTALITY** | | 4 (8.2) | |

**TABLE 3 OUTCOME MEASURES OF ASV TREATMENT**

| | Before treatment | During CPAP-treatment | During ASV-treatment, latest result | P-value (before treatment vs. durin Cpap) | P-value (during cpap vs. during asv) | P-value (before treatment vs. during ASV) |
|---|---|---|---|---|---|---|
| **AHI AVAILABLE N (%)** | 43 (87.8) | 32 (65.3) | 44 (89.8) | | | |
| **AHI MEAN (SD)** | 49.6 (19.7) | 28.0 (16.0) | 4.9 (4.95) | .000 | .000 | .000 |
| **EF AVILABLE N (%)** | 27.0 (55.1) | | 23 (46.9) | | | |
| **EF MEAN (SD)** | 50.9 (12.4) | | 46.1 (15.6) | | | .25 |
| **ESS AVAILABLE N (%)** | 26.0 (53.1) | | | | | |
| **ESS MEAN (SD)** | 8.1 (3.96) | | 6.7 (4.8) | | | .04 |

AHI, apnea hypopnea index
EF, ejection fraction
ESS, Epworth Sleepiness scale

## Discussion

In this retrospective study we found that the main reason for prescribing ASV-treatment was OSA-CSA and over 70% of the subjects were treated with trial of CPAP-treatment before ASV-treatment. Compliance for treatment was good. Over 61% of the subjects had HF and for those there was a slight but not significant impairment in EF during almost 6 years of follow up. There was a mild improvement in quality of sleep and daytime fatigue measured with the ESS-questionnaire. AH-index improved extensively and significantly with ASV treatment. Mortality was fairly low for an elderly subject group with several comorbidities.

The results of this study must be reflected in the light of the SERVE-HF –study (25). The subjects in our study were dominantly male and elderly like in the SERVE-HF and the follow up time was similar, almost six years. Comorbidities existed equally. In the ASV group of SERVE-HF study HF was more severe (mean EF = 32.2) compared to our subject group (mean EF during treatment = 46.1). According to the most recent studies (8,9) CSA is a compensatory mechanism in severe HF rather than a mediator in disease progression. SERVE-HF multistate modelling analysis (27) showed that in subjects with EF less than or equal to 30%, use of ASV markedly increased the risk of cardiovascular death. The more severe state of HF in SERVE-HF ASV group might be one explanation to the higher mortality rate in SERVE-HF ASV group (34.8%) compared to the mortality (8.2%) in this study. Also during the follow up ASV treatment was discontinued with 8% of the subjects due to severe HF and EF $\leq$ 45%, which might have affected the low mortality rate found in this study. Over two thirds of subjects were treated with a trial of CPAP before ASV and for these subjects AH-index decreased significantly treating with ASV compared CPAP. This might indicate to treatment emerged CSA, which means that treatment of OSA or sleep apnea in general with CPAP reveals a central component. This has been seen in other studies as well (9). The improvement in AHI is aligned with other ASV-study results (9). This is to be expected since ASV-devices treat both OSA with continuous pressure support and CSA with varying inspiratory pressure support, breaking the crescendo-cycle of breathing and in this way diminishing apneas and hypopneas. Improvement in ESS points was also seen in SERVE-HF-study (25). Daytime fatigue and quality of sleep have shown improvement in several studies with ASV-treatment (9,17).

It is still unknown whether CSA-CSR is a marker or in fact a mediator in the progress of HF and so according to the recent studies and this retrospective report it remains unclear how ASV treatment affects the progress of HF (8,9). In another Scandinavian retrospective study (29) 18 months of ASV treatment did not significantly affect cardiovascular death, combined cardiovascular death or hospital admissions in subjects with CSA and HF, but there was a trend towards better combined outcome. In the recent CAT-HF-trial (30) in hospitalized HF patients with moderate-to-severe sleep apnea, adding ASV to optimal medical treatment did not improve 6-month cardiovascular outcomes, but according to pre-specified subgroup analysis a positive effect of ASV in preserving EF for subjects with HF was suggested. More data on prognostic relevance of CSA-CSR, changes in cardiac parameters during ASV treatment and indication for treatment is needed. The ongoing ADVENT-HF trial (31) is looking whether ASV can reduce the rate of cardiovascular hospitalizations and death in subjects with HF and sleep apnea. So far, no effective alternative treatment to CSA for patients with HF and EF $\leq$ 45% is available. Unilateral phrenic nerve stimulation that improves CSA, daytime fatigue and sleep quality might be a promising treatment alternative. However, studies of phrenic nerve stimulation and cardiovascular outcomes are still missing (32).

The study being a retrospective analysis causes limitations. The subjects were not examined and interviewed with a similar standardized manner but the data was collected from medical records manually. The clinical findings such as EF and AHI were not measured at every visit or in the same stage of treatment for every subject. Sample size in our study was small, only 50 subjects were treated with ASV and included in the study. However, this was a real life –study without exclusion criteria, describing the use of ASV-treatment in subjects using it at home during almost six years of follow up, which can be considered as a strength for the study.

In conclusion in a real life setting, the results of ASV treatment in subjects with HF and CSA-CSR with an EF of at least 45% are quite satisfying: for these subjects ASV treatment seems to be improving AHI, quality of sleep and decreasing daytime fatigue. The compliance for treatment is good and mortality is low.

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