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Adaptive Servoventilation in Diastolic Heart Failure and Cheyne-Stokes Respiration

Thomas Bitter, MD[1], Nina Westerheide[2], Lothar Faber, MD, FESC, FACC[1], Detlef Hering, MD[1], Christian Prinz, MD[1], Christoph Langer, MD[1], Dieter Horstkotte, MD, PhD, FESC, FACCP[1], Olaf Oldenburg, MD, PhD[1]

[1] Dept. of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany

[2] Department of Business Administration and Economics, Chair of Statistics, University of Bielefeld, Germany

Corresponding Author

Thomas Bitter, MD

Dept. of Cardiology

Heart and Diabetes Center NRW

Ruhr University Bochum

Georgstasse 11

D – 32545 Bad Oeynhausen

Germany

Email: akleemeyer@hdz-nrw.de

Phone: +495731-97-1258

Fax: +495731-97-2194

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Abstract

A high prevalence of nocturnal Cheyne-Stokes respiration (CSR) has been documented in patients with heart failure with normal left ventricular ejection fraction (HFNEF). Aim of this study was to investigate effects of adaptive servoventilation (ASV) for treatment of CSR in these patients.

In 60 patients with HFNEF defined according to current ESC guidelines, CSR was documented by polysomnography (apnoea-hypopnoea-index (AHI) >15/h). ASV treatment was offered to all patients; 21 rejected treatment initially, withdrew treatment or presented noncompliant during follow-up (controls) whereas ongoing ASV therapy was initiated in 39 patients (ASV group). Echocardiography, cardiopulmonary exercise testing (CPX) and measurement of NT-proBNP were performed at baseline and follow-up (11.6 $\pm$ 3 months).

ASV-therapy led to a significant reduction in AHI, longest apnoea- and hypopnoea lengths, maximum and mean oxygen desaturation, percentage of study time below 90% oxygen saturation, and arousal index. In addition, significant positive effects on peak oxygen consumption (VO_2-peak), predicted $V0_2$-peak, oxygen consumption at individual aerobic-anaerobic threshold, O_2-pulse, as well as left atrial size, and transmitral flow patterns (e´, E/e) could be confirmed.

ASV effectively attenuates CSR in patients with HFNEF, improves heart failure symptoms, and cardiac function. Whether this is accompanied by an improved prognosis needs to be determined.

Introduction

Heart failure with normal left ventricular ejection fraction (HFNEF) is a clinical entity that embodies symptoms of heart failure in presence of preserved systolic function of the left ventricle. In patients 60 years and older prevalence reaches that of heart failure with reduced left ventricular ejection fraction (HFREF) and by the eights decade it is more frequent than in HFREF. Thus, it is a disease of the older in specific. (1) Main pathophysiological correlate is an impaired left ventricular filling resulting in diastolic dysfunction with increased left ventricular enddiastolic pressures (LVEDP) with consequent pulmonary congestion, increased stimulation of pulmonary vagal irritant receptors (J-Receptors) and an enhanced chemosensitivity of central and peripheral CO_2 receptors. This predisposes to respiratory instability, which may cause nocturnal a major pathophysiologic cause for Cheyne-Stokes respiration (CSR). (2, 3) In a recent study we were able to demonstrate a prevalence of CSR in about 30% in HFNEF patients. (4) In addition, CSR itself is accompanied by recurrent hypoxaemias and phases of hyperventilation that may lead to several haemodynamic systemic changes and worsen HFNEF.

Adaptive Servoventilation (ASV) has been introduced as a novel ventilatory support device in patients with CSR, which in analogue to continuous airway pressure (CPAP) increases overnight pCO_2. (5) A superiority concerning suppression of hypopnoea and apnoea events in comparison to oxygen, CPAP and bilevel positive airway pressure support has been demonstrated. (5-8) While in patients with HFNEF and co-existing obstructive sleep apnoea (OSA) positive effects of CPAP are well investigated (9-12), data on therapeutic approaches on patients with HFNEF and CSR are lacking.

Aim of this study was the investigation of ASV effects on clinical and functional parameters in patients with HFNEF compared to a control group of patients who rejected therapy for various reasons.

Patients and Methods

Patients:

We included sixty patients with HFNEF defined according to current ESC-guidelines (13) and moderate to severe Cheyne-Stokes-Respiration and an apnoea-hypopnoea-index (AHI) >15/h and a proportion of >50% of CSR. All patients had to be in stable clinical condition of NYHA-class II-III. Prior to inclusion evidence of diastolic dysfunction was obtained invasively (LVEDP > 20mmHg) and patients had to be on stable medication for at least four weeks. In order to exclude patients with a significant obstructive and/or restrictive pulmonary disease spirometry testing was performed. Other exclusion criteria were reduced systolic LV-function, significant valvular heart disease, a history of SDB or ongoing treatment of SDB, a proportion of <50% of CSR, evidence of pulmonary disease, hypercapnia (pCO_2 > 45mmHg) in capillary blood gas samples, pregnancy, acute coronary syndrome or acute cardiac decompensation.

This study represents a prospective trial that was initiated in July 2006, lasting until December 2008. We invited all patients included in the study to re-attend to the Sleep-Lab of the Department of Cardiology every three month either for measurement of cardiac function (Echocardiography, Cardiopulmonary Exercise Testing, measurement of NT-proBNP and blood gas testing) and sleep studies (therapy group) or for measurement of cardiac function only (control group). Individual endpoint data from every patient (mean 11.6 $\pm$ 3 months, range 3 to 24 months) formed the basis of this study. During follow up, patients undergoing invasive procedures (e.g. percutanous coronary intervention) were excluded from the study. Although the European Society of Cardiolgy does not recommend any specific

pharmacological treatement in HFNEF patients (14), we excluded patients with changes in heart failure medication (except for dosage changes). The study has been approved by the local institutional review board of the Ruhr University Bochum.

Sleep studies:

Sleep studies were performed by full in-hospital polysomnography (N7000/S7000, Embla, The Netherlands). Electroencephalographic data were collected from central and auricular positions according to Rechtschaffen and Kales. (15) Eye movements as well as mandibular and tibial muscle efforts, nasal air flow (pressure), chest and abdominal effort, pulse oxymetry, and body position were recorded continuously. In addition patients were observed by video. Analyses were performed by Somnologica Studio 5^{TM} software (Medcare, Embla, The Netherlands) and reviewed by two independent SDB specialists not involved in patients' treatment.

Hypopnoea was defined as ≥ 30% reduction in airflow in combination with an oxygen desaturation of at least 3%. Apnoea was defined as a cessation of airflow ≥ 10 seconds. There had to be at least three cycles of crescendo and decrescendo change in breathing amplitude and five or more central sleep apnoeas or hypopnoeas per hour of sleep to be scored as Cheyne–Stokes respiration. (16) Automatic data from treatment devices were visualised with Res Scan^{TM} software (ResMed, Australia).

Adaptive Servoventilation:

Adaptive Servoventilation (AutoSet CS^{TM}2, ResMed, Australia) was introduced to 51 patients. ASV represents a bi-level ventilation system with automatic, anti-cyclic adaption of pressure support. Individual pressure support was introduced during

wakefulness under continuous blood pressure monitoring and adjusted according to nocturnal measurements. At therapy introduction 31 patients were not willing to receive therapy or rejected therapy after 1 introduction night. In addition 8 patients withdrew therapy during follow up due to unspecific personal reasons (n=2, all within 3 months) or due to lacking compliance (average daily use <4 h, n=6, 5 within 3 months, 1 within 6 months). For balancing group sizes and due to the fact that in heart failure patients a lacking compliance with ventilation therapy is associated with poorer outcome (17), these patients were regarded as untreated, thus being added to the control-group. After follow-up period 39 patients under ASV-therapy and 21 patients without ASV-therapy (12 due to non-specific reasons (e.g. personal lifestyle, sense of shame), 5 due mask intolerance, 4 due to subjective intolerance to positive airway pressure ventilation) were capable to finish the study. Study flow chart is given in figure 1. In the control-group sleep studies were performed at baseline only.

Echocardiography:

Diameters and dimensions of the left atrium (LA) and left ventricle were measured by M-mode following American Society of Echocardiography guidelines. (18) Since multiple echocardiography parameters are available to assess diastolic function, a comprehensive approach has been used in this study. Transmitral Doppler flow, supplying peak early (E) and peak atrial (A) Doppler mitral inflow velocities, the ratio of peak early and peak atrial Doppler mitral inflow velocity (E/A), and deceleration time (DT) of early Doppler mitral inflow velocity were used as traditional markers with limited validity due to load dependence. New methods, such as speckle tracking imaging provides accurate, well validated data regarding diastolic properties and

filling pressures of the left ventricle. Using speckle tracking technology offline evaluation, mean early diastolic (e`) lengthening velocities were obtained from different segments of the mitral anulus in 4, 3 and 2-chamber-view. Left ventricular filling pressure was determined from the ratio of early mitral valve flow velocity and early diastolic lengthening velocities (E/e´).

Cardiopulmonary exercise testing (CPX):

Symptom-limited bicycle cardiopulmonary exercise testing (ZAN Ferraris, Germany) starting with 10 watts and an increase of 10 watts per minute was performed at baseline and during follow-up. Oxygen uptake (O_2), carbon dioxide output (CO_2), instantaneous expiratory gas concentrations throughout the respiratory cycle, and minute ventilation (E) were measured continuously on a breath-by-breath basis. Heart rate and blood pressure (by sphygmomanometer) were measured at rest, during each stage of exercise, and at peak exercise. Peak oxygen consumption (VO_2-peak), oxygen consumption at the individual aerobic-anaerobic threshold (VO_2-AT), and relationship of minute ventilation and carbon dioxide production (VE/VCO_2) as well as maximum workload and total exercise time were recorded. Predicted VO_2-peak was calculated automatically taking patients´ gender and age into account.

VO_2-AT was defined as 1) the point at which the ventilatory equivalent for O_2 (VE/VO_2) was minimal followed by a progressive increase; 2) the point after which the respiratory gas exchange ratio consistently exceeded the resting respiratory gas exchange ratio; and 3) the VO_2 after which a nonlinear increase in minute ventilation occurred relative to VO_2. VO_2-peak was defined as the highest 30-second average of oxygen uptake in the last minute of exercise.

Left heart catheterization:

Left heart angiography was performed with a 5F pigtail catheter (Cordis, Langenfeld, Germany) for acquisition of the left ventricular ejection fraction (LVEF) and end-diastolic pressure (LVEDP).

Capillary Blood Gas Analysis:

Partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2) and capillary oxygen saturation were measured using ABL 330 (Radiometer, Copenhagen, Denmark).

NT-proBNP:

N-terminal pro – brain natriuretic peptide (NT-proBNP) was used as an additional marker of HFNEF severity. Analyses were performed using the Elecsys 2010 analyzer (Roche, Basel, Switzerland).

Pulmonary Function Test

In order to exclude patients with significant pulmonary disease pulmonary function test was performed. Spirometry and body plethysmography were performed with the use of a constant volume body plethysmograph (ZAN Ferraris, Germany). Vital capacity, forced vital capacity, the ratio of forced expiratory 1-second volume to forced vital capacity, peak expiratory flow, midexpiratory flow when 25%, 50%, or 75% of forced vital capacity remains in the lung, airway resistance, total lung capacity, and the ratio of residual volume to total lung capacity were used for the final analysis. The single-breath technique using carbon monoxide (CO) was used for the measurement of diffusion capacity. For final analysis, haemoglobin corrected

lung transfer factor for carbon monoxide (TLCO) and the carbon monoxide transfer coefficient (KCO, as transfer factor for CO/alveolar volume [VA]; TLCO/VA) in mmol · min^{-1} · kPa^{-1} (1 kPa=7.502 mm Hg) were selected.

Statistics:

Analysis of Covariance (ANCOVA), t-tests, and Wilcoxon-tests were applied for statistical analyses. Using the ANCOVA, the follow-up value of each reviewed variable was used as response variable and the associated baseline value of the corresponding variable and the two-level factor ASV-therapy/no ASV-therapy were used as explanatory variables. The first step of our analysis was to fit the full model, consisting of different slopes and intercepts for each level of the factor. Subsequently the model was simplified to find the minimal adequate model by removing all non-significant terms until reaching a model with significant terms only. Model simplifications were justified by the explanatory power of the model. The simpler model was preferred as long as it did not explain significantly less than the more complex model (alpha=0.05). Hence, the full model with interaction was checked for significance and compared to the simplified model without interaction. In case the full model was preferred, which indicates a significant interaction; further analyses have not been continued. Significant interaction was found by models using the variables $VE/VC0_2$, O_2 pulse, A, E/A-ratio E/e‘ and E. Unless the simpler model was preferred, the interaction could be neglected and it was checked if the two-level factor is significant. For this purpose the model without interaction was checked for significance and compared to a model without interaction and the two-level factor (alpha=0.05). Provided that the simpler model of these two was preferred, the two-level factor ASV-therapy/no ASV-therapy is not significant and the resulting model

does not include the categorial variable. Whenever the model without interaction - consisting of a common slope and different intercepts- was preferred, the two-level factor is significant and this model is the minimal adequate model. Differences between the groups were compared by the unpaired t-test. Weight changes, NYHA-class (non categorical parameter, which could not be included into ANCOVA analysis) and changes of sleep study results from baseline to follow-up analysed using paired t-test if normality test (Kolmogorov-Smirnov) passed and with help of Wilcoxon-test, if normality test failed. A value of $p<0.05$ was considered significant for all comparisons. Data are given as mean +- SD unless stated otherwise. Due to partly missing value of observations less than the 60 individuals were used in the different analyses. Statistical analyses were performed using the open source software R 2.6.2, see http://www.R- project.org.

Results

We included 60 patients into this study, all suffering from HFNEF and CSA with an AHI >15/h. While 39 patients received ASV-therapy, 21 formed the control-group due to rejecting therapy for different reasons (figure 1). Underlying cardiac disease in the treatment group were hypertensive heart disease in 16 cases (41%) coronary artery disease in 16 (41%) and cardiomyopathies (6 hypertrophic, 1 restrictive) in 7 (18%) patients. In the control group 12 patients (57%) presented with coronary artery disease, 5 (24%) with hypertensive heart disease and 4 (19%) with cardiomyopathies (all hypertrophic). According to echocardiographic assessment patients undergoing ASV-therapy had a pseudonormal left ventricular filling pattern in 20 cases (51%), an impaired relaxation filling pattern was present in 14 (36%) and a restrictive filling pattern in 5 patients (13%). In the control group 10 (48%) patients presented with a pseudonormal filling pattern, 7 (33%) with an impaired relaxation and 4 (19%) with a restrictive. Demographic and clinical data are given in table 1. The group who did not receive ASV-therapy presented with a higher LVEDP while the treatment group had larger left atria diameters. Patients undergoing ASV-therapy re-attended our hospital 2.8 ± 0.5 times, patients in the control group 1.3 ± 0.3 times, mainly for planned follow-up investigations. Six patients in the therapy-group and eight patients in the control group were re-admitted to hospital for any intervention or acute worsening of cardiac status leading to any change in heart failure medication, thus being considered as study drop-outs (figure 1). In the course of the study there was no significant change in patients weight, neither in the ASV-therapy group (89.9 ± 17.0kg to 89.3 ± 17.9kg, p=0.33) nor in the control group (90.7 ± 15.3kg to 91.0 ± 16.0kg, p=0.45).

Sleep study results

Sleep study results at baseline are presented in table 1. ASV-therapy led to a significant reduction in AHI (43.5 ± 14.7 h^{-1} to 3.5 ± 1.7 h^{-1}, $p<0.001$), longest apnoea- (32.3 ± 24.7 seconds to 19.3 ± 16.8 seconds, $p<0.001$) and hypopnoea (37.9 ± 10.6 seconds to 23.7 ± 13.1 seconds, $p<0.01$) periods, maximum desaturations (82.8 ± 4.8% to 88.1 ± 3.7%, $p<0.01$), percentage of study time below 90% oxygen saturation (7.6 ± 12.8 to 1.1 ± 3.2 %, $p<0.01$), arousal index (30.7 ± 6.4 h^{-1} to 17.5 ± 8.8 h^{-1}, $p<0.01$) as well as mean oxygen desaturation (5.6 ± 2.0% to 3.4 ± 1.6%, $p<0.01$). Total sleep time (359 ± 23min to 344 ± 26min, $p=0.17$, REM-sleep/total sleep time (13.1 ± 8.1% to 15.4 ± 8.4%, $p=0.10$) and mean oxygen saturation (92.5 ± 2.3% to 92.8 ± 2.5%, $p=0.32$) remained unchanged. Device based data analysis illustrated a mean usage >4 hours per day in 64.0 ± 30.4% of all possible treatment nights with an average use of 5.3 ± 2.1 hours per day, AHI for the entire treatment period was 4.2 ± 4.5 h^{-1} and apnoea-index was 0.2 ± 0.4 h^{-1}. Noncompliant patients presented with a mean usage >4h per day in 10.1 ± 14.4% of all possible treatment nights with an average use of 0.8 ± 1.4 hours per day. In these patients AHI was 3.8 ± 6.9 h^{-1} and apnoea-index was 0.2 ± 0.8 h^{-1}

NYHA class

There was a significant reduction of NYHA-class in both, the ASV treatment group (2.4 ± 0.6 to 2.0 ± 0.8, $p<0.001$) as well as the control group (2.5 ± 0.5 to 2.2 ± 0.4, $p<0.01$).

NT-proBNP

Reductions in NT-proBNP concentrations were documented in ASV treated patients and controls; however these changes were not different between groups (table 2).

Cardiopulmonary exercise testing

CPX testing results are presented in table 2. ASV-therapy led to a significant increase in VO_2-AT, $V0_2$ peak, predicted $V0_2$ peak and O_2 pulse. VE/VCO_2 as well as exercise duration tended to improve without reaching a level of significance.

Echocardiography

ASV treatment led to a significant decrease in LA and E/A as well as a significant increase of A, e´and E/e´. Additional findings are presented in table 2.

Discussion

This is the first study evaluating the effect of Adaptive Servoventilation in patients with heart failure despite normal left ventricular ejection fraction and moderate to severe Cheyne-Stokes-Respiration. The main finding of this study is that ASV not only improves CSA with a reduction of AHI and other sleep study parameters but also has a positive effect on cardiopulmonary exercise capacity, left atrial diameter, and echochocardiographic measures of diastolic ventricular performance in comparison to an untreated control group.

Sleep disordered breathing is common in patients with HFNEF. (4) Focussing on obstructive sleep apnoea in HFNEF, Arias et al. investigated 15 patients of whom 11 presented with an impaired relaxation filling pattern and 4 with a pseudonormal filling pattern. After 12 weeks of nocturnal application of continuous airway pressure (CPAP) in contrast to previously applied sham-CPAP echocardiographic parameters of diastolic dysfunction improved, suggesting that CPAP-therapy could prevent the progression of diastolic abnormalities in these patients, and might reverse alterations. (9) Similar results were presented in three other studies, all observing an improvement in various parameters of diastolic dysfunction. (10-12)

As described previously, CSR arises from a different pathophysiological mechanism: enhanced pulmonary capillary wedge pressure leads to a stimulation of pulmonary vagal irritant receptors (J-Receptors) and enhances chemosensitivity of central CO_2-receptors, resulting in hyperventilation. This in turn leads to a consecutive decrease in pCO_2 below the apnoea threshold with consecutive apnoeas. (2, 3, 19)

In patients with HFNEF and CSR effects of CPAP-therapy has not yet been investigated. The CANPAP trial investigated 258 heart failure patients with reduced left ventricular ejection fraction and CSR. (20) 128 were randomized to receive CPAP therapy whereas the remaining 130 did not. The authors could not find a superiority of the treatment group with respect to the primary endpoint survival after 24 months. A post-hoc analysis highlighted the major problem of this study, namely a decrease of AHI from 40 $\pm$ 16/h by -21 $\pm$ 16/h only, while a prognostic benefit could only be demonstrated for patients with an AHI <15/h. (21)

ASV offers ventilatory support with reduced pressure in phases of normo- and hyperventilation and does not potentiate loss of CO_2 as a trigger for central apnoea. Beside effectively attenuating hypopnoea and apnoea events in HFREF, positive effects on symptoms, neurohormonal activation, left ventricular functional parameters and cardiopulmonary exercise tolerance have been published recently. (5-8, 22)

In analogue to patients with HFREF and CSR our study presents similar findings in those with normal left ventricular ejection fraction. Explanations for this are rarely investigated, yet. Nevertheless it has been shown that sleep disordered breathing goes parallel with several systemic changes. Hypoxaemia in patients with obstructive sleep apnoea leads to vast sympathetic activation. (23) Even though hypoxaemic events are less extensive in patients with CSR a similar mechanism in CSR is plausible. In addition, CSR goes along with periods of hyperventilation that are likely accompanied by excessive sympathetic activation as well. (24) Consequences that

emerge from this are e.g. enhanced blood pressure (25), activation of the renin-angiotensin-aldosterone-system (RAAS) (26), and increased levels of vasoconstrictive factors such as circulating norepinephrine and endothelin. (27, 28) This again may stimulate fibrogenesis with an increased myocardial collagen turnover (29) and a shift in protein expression (upregulated expression of procollagen type I and type III, matrix metalloproteinase and a less compliant isoform of titin) (29-31) resulting in increased myocardial stiffness and increased matrix degradation. Reducing these stress factors may result in a positive (reverse-) remodelling in analogue to medical inhibition of the RAAS. Furthermore, vasoconstriction (as well as hypertension) itself increases afterload, left ventricular enddiastolic pressure and consecutive structural myocardial changes. (32) Another pathophysiologic explanation might be inflammatory reaction induced by the apnoea and/or hyperventilation. Proven for OSA patients, this goes along with increased serum levels of cytokines and acute-phase-proteins such as amyloid A which itself could predispose for diastolic dysfunction. (33)

Controlling CSR-induced systemic consequences by ASV could be the key to success of this non-medical therapeutic approach.

Potential limitations

There are some potential limitations of this study. Treatment allocation was not randomized and blinded to patients and physicians. Even though groups were similar with respect to measured baseline variables, due to the lack of a randomisation however, groups may differ in factors that cannot be measured. In addition the lacking randomisation may have caused a selection bias: patients who comply to

ASV-therapy may also present with a superior compliance to the rest of the heart failure treatment. In a recent study for instance, it was shown that disease management programs as one method of improving patients´ therapy compliance leads to a superior survival in systolic heart failure. (34) Another possible limitation is the echocardiographic evaluation of early diastolic lengthening velocity (e´) by speckle tracking. Even though early diastolic lengthening velocity derived from speckle tracking shows significantly lower velocities than tissue Doppler, speckle tracking derived E/e´ is at least equal to tissue Doppler E/e´ for the prediction of elevated LV filling pressures. (35) In addition we focussed on intraindividual changes that are independent from evaluation method. Finally, the study group consisted of patients with HFNEF due to different aetiologies. Due to this small number of patients we were unable to perform a subgroup analysis to clarify the impact of different aetiologies of HFNEF on the outcome.

Summary

In patients with heart failure with normal left ventricular ejection fraction and Cheyne-Stokes respiration Adaptive Servoventilation not only improves CSR with a reduction of the AHI and other sleep study parameters but also has a positive effect on cardiopulmonary exercise capacity and echochocardiographic parameters of diastolic function in comparison to an untreated group. This effect may be mediated by eliminating the adverse CSR-associated systemic consequences by controlling nocturnal CSR with ASV. Nevertheless end points triggered, randomised and blinded studies are necessary for further evaluation of this therapeutic approach.

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Table 1: Demographic and clinical data of the study population

	ASV-Therapy	Control group	Significance (p)
N	39	21	
Male, n (%)	33 (84.6%)	18 (85.7)	0.76
Age, years	67.4 ± 8.5	69.7 ± 7.9	0.61
Weight, kg	89.9 ± 17.0	90.7 ± 15.3	0.86
Height, cm	170 ± 29	174.1 ± 8.7	0.57
BMI	28.5 ± 6.7	29.8 ± 4.2	0.41
NYHA-class	2.4 ± 0.6	2.5 ± 0.5	0.85
NT-proBNP (pg/ml)	1480 ± 1630	1673 ± 1965	0.11
Heart rate at rest	74.3 ± 13.1	71.1± 8.2	0.43
Hypertension, n (%)	36 (92.3)	18 (85.7)	0.45
Diabetes, n (%)	15 (38.5)	7 (33.3)	0.78
Atrial fibrillation, n (%)	9 (23.1)	4 (19.0)	0.38
Cerebrovascular disease, n (%)	5 (12.8)	3 (14.2)	0.49
Medication, n (%)			
Beta-blockers	33 (84.6)	19 (90.4)	0.51
ACE/AT1-inhibitors	36 (92.3)	18 (85.7)	0.45
Calcium-channel-blockers	15 (38.5)	11 (52.3)	0.20
Nitrates	11 (28.2)	5 (23.8)	0.68
Digitalis glycosides	6 (15.4)	3 (14.2)	0.88
Diuretics	29 (74.3)	19 (90.4)	0.13
Blood gas analysis			
pCO_2, mmHg	35.9 ± 3.3	35.7 ± 4.0	0.44
pO_2, mmHg	76.7 ± 8.4	74.6 ± 10.7	0.44
Sleep study results			
Total sleep time, min	359 ± 23	345 ± 19	0.31
REM/total sleep time, %	13.1 ± 8.1	12.7 ± 7.6	0.54
AHI, h^{-1}	43.5 ± 14.7	39.8 ± 20.9	0.41
average oxygen saturation, %	92.5 ± 2.3	92.0 ± 2.5	0.42
lowest oxygen saturation, %	82.8 ± 4.8	83.2 ± 4.4	0.71
mean desaturation, %	5.6 ± 2.0	5.3 ± 1.3	0.66
longest apnoea period, s	32.3 ± 24.7	29.4 ± 11.5	0.61
longest hyponoea period, s	37.9 ± 10.6	42.5 ± 18.1	0.23
study time below 90% oxygen saturation, %	7.6 ± 12.8	7.1 ± 13.1	0.43
Arousal index	30.7 ± 6.4	29.9 ± 7.8	0.33
Invasive hemodynamic measuerement			
PAP, mmHg	33.5 ± 8.9	29.5 ± 6.5	0.12

PCWP, mmHg	22.7 ± 4.5	22.0 ± 3.7	0.64
LVEDP, mmHg	23.5 ± 5.4	25.4 ± 9.3	0.046
Pulmonary function testing			
FVC, l	3.3 ± 0.9	3.1 ± 0.9	0.68
FEV1, l	2.9 ± 0.9	2.7 ± 0.8	0.55
FEV1/FVC, %	87.9 ± 6.3	85.3 ± 4.9	0.63
TLC, l	6.4 ± 1.9	6.5 ± 1.3	0.83
TLC, %	90.1 ± 20.6	95.8 ± 13.9	0.46
TGV, l	3.5 ± 1.1	3.8 ± 1.1	0.56
TGV, %	93.8 ± 29.4	98.6 ± 24.4	0.53
KCO (Hb), mmol/kPa/min/l	1.3 ± 0.5	1.3 ± 0.4	0.79
KCO (Hb), %	102.6 ± 40.1	99.8 ± 26.3	0.85
Echocardiography			
E (m/s)	0.8 ± 0.3	0.8 ± 0.3	0.88
A (m/s)	0.7 ± 0.2	0.6 ± 0.3	0.30
DT (ms)	215± 78	215 ± 78	0.80
LAD (mm)	52.0 ± 5.5	48.2 ± 6.1	0.02
E/A	1.4± 1.0	1.4± 1.1	0.36
e´ (m/s)	3.8 ± 1.4	4.5 ± 1.6	0.08
E/e´	22.2 ± 9.7	19.2 ± 7.8	0.11
Cardiopulmonary exercise testing			
VO_2 AT (ml/min/kg)	12.9 ± 3.6	14.1 ± 3.9	0.29
VO_2 peak (ml/min/kg)	14.9 ± 4.7	16.3 ± 4.3	0.17
VO_2 peak (%)	64.8 ± 18.3	75.6 ± 17.6	0.10
Workload (Watts)	94.7 ± 37.9	87.6 ± 37.0	0.59
Duration (min)	10.4 ± 3.0	9.1 ± 3.0	0.21
VE/VCO_2	33.0 ± 5.2	35.3 ± 4.9	0.18
HRR	47.5 ± 28.4	52.4 ± 22.6	0.54
O_2 pulse	13.6 ± 3.1	13.7 ± 3.1	0.34
O_2 pulse (%)	78.6 ± 23.0	88.1 ± 18.0	0.51

Table 2: Follow-up results of measurement of NT-proBNP, echocardiography, and standardised cardiopulmonary exercise testing

	ASV-therapy	Control group	p
Heart rate at rest	68.1 ± 11.3	67.8 ± 7.5	0.92
NT-proBNP (pg/ml)	740 ± 1110	1480 ± 890	0.10
Echocardiography			
E (m/s)	0.7 ± 0.3	0.8 ± 0.3	0.73
A (m/s)	0.8 ± 0.2	0.7 ± 0.2	0.04
DT (ms)	229 ± 53	235 ± 91	0.72
LAD (mm)	49.8 ± 7.4	51.1 ± 5.8	<0.01
E/A	1.1 ± 0.6	1.2 ± 0.6	<0.01
e´ (m/s)	4.3 ± 1.0	4.3 ± 1.5	<0.01
E/e´	17.9 ± 7.0	21.7 ± 14.7	0.03
Cardiopulmonary exercise testing			
VO_2 AT (ml/min/kg)	15.7± 4.3	12.7 ± 2.8	0.01
VO_2 peak (ml/min/kg)	17.8 ± 5.5	15.2 ± 4.1	<0.01
VO_2 peak (%)	78.4 ± 22.2	69.1 ± 19.7	<0.01
Workload (Watts)	102.1 ± 36.8	95.0 ± 38.4	0.61
Duration (min)	11.1 ± 3.0	8.9 ± 2.5	0.06
VE/VCO_2	31.1 ± 4.9	34.1 ± 5.6	0.07
HRR	52.7 ± 24.3	58.1 ± 19.8	0.25
O_2 pulse	15.8 ± 3.6	13.5 ± 3.7	<0.01
O_2 pulse (%)	97.8 ± 29.0	84.1 ± 23.8	0.13

Figure legend

Figure 1: Study flow chart